Use of triggers tools to search for adverse drug reactions in the elderly admitted to emergency departments

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Abstract *Adverse drug reactions (ADRs) can cause illness, disability or death, especially in the elderly. An active search for suspected ADRs was carried out using triggers, which motivated the search of elderly people under care in adult emergency departments (ED). It was a cross-sectional and retrospective study that used an adaptation of the Institute of Health Care Improvement triggers. A total of 287 medical records were analyzed and 38 triggers were found, identifying 7 suspected ADRs. One was found without the use of triggers. Thus, in total, 8 ADRs (2.79%) were found, of which 6 were considered serious. There was a higher prevalence of ADRs in females (62.5%) and in those over 80 years of age (50%). The medications most implicated were those for alimentary tract and metabolism and cardiovascular system. Of the triggers tested, some are essential for use at EDs, such as those that indicate problems with anticoagulants, hypoglycemic agents and antihypertensives. Triggers have proved useful for an active search for suspected ADRs at EDs, including severe ones, identifying problems occurring outside hospital settings and signaling medications that pose an increased risk to the elderly.*
Key words *Drug-related side effects and adverse reactions, Pharmaceutical preparations, Emergency medical services, Aged*

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Introduction

Medications are used to bring benefits. However, some adverse drug reactions (ADRs) can cause illness, disability or death[1]. In addition, when occurring in patients hospitalized, they increase hospitalization time, interrupt treatments and increase hospital expenses[2]. A recent review conducted with European studies has found that 10.1% of patients have experienced an ADR during hospitalization[3]. This figure reached 16.8% in a meta-analysis that estimated the occurrence of ADRs during hospitalization[4]. In addition, another meta-analysis indicated that ADRs are among the 4th and 6th leading causes of death in the United States in the inpatient population, with an estimated incidence of 0.23 to 0.41%[5]. Magnitude of ADRs may vary due to the heterogeneity of the population studied, the methodology used for their detection and the type of institution involved[4]. These data reveal that ADRs may have an impact on patients' health status as well as costs to health systems.

In addition, a systematic review has shown that ADRs have been identified as causes of hospital admission with a frequency between 0.16% and 15.7%, depending on the patients' age. In the elderly, for example, the mean frequency was 10.7%[6]. Meta-analysis has shown that the chance of hospitalization due to suspected ADRs in elderly patients is four times higher than in non-elderly patients[7]. This can be explained by the physiological changes that occur in the organism caused by aging, such as in pharmacokinetics and pharmacodynamics, which influence the metabolism and elimination of medications by the organism, making the elderly more susceptible to ADRs, but can also occur because elderly patients, in general, receive multiple medications for chronic diseases[8].

Despite the importance of detecting ADRs in a hospital environment, few studies have been carried out in adult Emergency Departments (ED) units. However, some studies show a significant admission rate due to medications used in the patient's home[9,10]. Among the factors for this occurrence is self-medication since, according to a meta-analysis performed in the country, one third of the Brazilian adult population (18 to 65 years old) self-medicates[11]. In addition, overuse of medications and their irrational use increase the likelihood of an event occurring, resulting in unnecessary and avoidable expenditure of public health resources[8].

In order to search for such events in patients hospitalized, a methodology based on the use of triggers was used, which can be found from the review of the patients' medical record. Its presence allows directing the investigation to determine the occurrence and measurement of the event. Triggers may be (a) medications prescribed to treat a possible event, (b) laboratory test results, and (c) procedures and interventions by health workers or even abrupt medication withdrawal[12].

Thus, the objective of this study was to conduct an active search for suspected ADRs that motivated the search for elderly under care at an ED using the trigger methodology and to discuss its use in this care unit.

Methods

This is a retrospective cross-sectional study carried out at an ED at a university hospital of medium complexity located in the Brazilian municipality of São Paulo. It is a public hospital that serves students, staff (and their dependents) at the Brazilian university *Universidade de São Paulo* (USP), residents of the sub-district of *Butantã* and some patients from outside the community in cases of emergency. In the period from 2013 to 2014, the hospital had 280 beds, of which 12 were for the ED.

In the study, patients aged 60 years or older were included, who entered the ED during the periods defined for the research. In order to obtain a heterogeneous sample of ED care, the middle of each season of the year was chosen to avoid seasonal bias. Thus, the data collection was based on an interval of 28 days divided during the year in 4 periods: July 20-26, 2013, October 20-26, 2013, January 20-26, 2014, and April 20-26, 2014.

Patients whose medical records or medical files at the ED were not available in the Medical and Statistical Archive Service (SAME, in the Portuguese abbreviation) were excluded from the study.

The Information Technology department of the hospital made available the patients registered and served at the ED during the period defined for the study. Using inclusion and exclusion criteria, the patients were randomly selected from this list. Medical records were requested from SAME for searching the triggers, which was carried out from reading the notes by doctors and a multidisciplinary team (nursing, physiotherapy, occupational therapy and speech-language therapy), as well as the analysis of the prescriptions. The results of the examinations and

the respective reference values used in the hospital were consulted in the institution's internal electronic system.

Triggers were based on the study by the Institute for Health Care Improvement (IHI)[13], which has developed a list of global triggers that can measure adverse events and can be used in any health service. They were not specific for ED, but their applicability was analyzed in this study, since they are the most frequently cited in the literature and easy to use.

For this study, only suspected ADRs were investigated, which are defined as "any harmful and unintentional event caused by medications in doses usually used for prophylactic, therapeutic or diagnostic purposes"[14]. It is a particular type of adverse drug event (ADE), since ADE is a broader term, defined as "any unfavorable medical occurrence that may occur during medication treatment that does not necessarily have a causal relationship with such treatment"[14]. Thus, medication errors, poisoning, off-label use and technical complaints were not investigated.

As the suspected ADRs were addressed rather than the totality of adverse events, such as IHI proposes, only the triggers presented in the Medicines Module[13] were used. The IHI list was adapted, since the reference value adopted by the Clinical Laboratory of the hospital studied for the laboratory examinations was used. The list of triggers is shown in Chart 1. With the results obtained, a descriptive analysis was carried out by means of relative frequencies on the patient with suspected ADR, the characterization of the suspected ADR and the medications involved.

For the characterization of the medications involved, the 1st and 5th levels of the Anatomical Therapeutic Chemical (ATC)[15] classification were used. The dosage used and the time-window were also recorded, which verify the consistency between the time of administration of the medications and the time of initiation of ADR.

Suspected ADRs were classified according to the World Health Organization – Adverse Drug Reaction Terminology (WHO-ART), which presents classification levels. The SOC (System, Organ, Class) level was used[16]. Thus, it was possible to analyze which systems and organs were affected by the ADRs.

The severity of the ADRs was defined by the criteria contained in the "Guidelines for Risk Management in Pharmacovigilance" of ANVISA [Brazilian government *Agência Nacional de Vigilância Sanitária* (National Health Surveillance Agency)], according to which the ADR is considered serious when there are: "Death, life threat, hospitalization or prolongation of hospitalization, persistent or significant disability, congenital anomaly and a clinically significant event (need for medical intervention in order to avoid death, life-threat or hospital care)"[17].

As for the causality analysis, it was performed using the Naranjo algorithm, which evaluates the probability that a suspected ADR is a consequence of the medication use. The categories of causality are: definite, probable, possible and doubtful[18].

The ADR outcome was related to the patient's evolution in relation to the suspected ADR presented: they were treated and discharged, had to be hospitalized, evolved to death or evaded the hospital. All suspected ADRs found in this study were discussed with the pharmacovigilance group of the hospital under study for a more accurate analysis of the case and its notification to ANVISA, if indicated.

The project was approved by the Ethics Committees of the University Hospital (number 1194139) and by the Faculty of Pharmaceutical Sciences of Universidade de São Paulo (USP).

Results

During the 28-day study period, 2,326 patients aged 60 years or older were treated at the hospital's ED. Of these patients, 828 elderly people who had only one medical record in the file were excluded. Of the remaining 1,498, 475 medical records were requested from SAME at random. It was not possible to find the medical file in all medical records, since some had been lost and others did not exist due to patients' evasion after the medical records were entered and before care by a health professional. Figure 1 shows the results of the study.

In total, 8 suspected ADRs were observed as a reason for ED admission after analysis of 287 medical records, which is equivalent to a prevalence of 2.79% of ADRs. Chart 2 shows the suspected ADRs found.

The demographic profile of patients with suspected ADRs is shown in Table 1.

Suspected ADRs, according to WHO-ART, were classified as 0800 (metabolic and nutritional disorders), 0410 (central and peripheral nervous system disorders), 0600 (disorders of the gastrointestinal system), and 0431 (visual disorders). All suspected ADRs were treated at the ED and patients were discharged on the same day.

Chart 1. Triggers* for suspected adverse drug reactions in elderly people at an adult emergency department, São Paulo – 2013-2014.

Trigger	Meaning
M1. Positive stool culture for Clostridium difficile.	Trigger for adverse reaction to antimicrobials.
M2. Partial thromboplastin time (PTT) greater than 100 seconds.	Increased values occur in the use of heparin. In order to characterize the suspected ADR, it is necessary to check for bleeding, hematomas or reduction in hemoglobin and/or hematocrit values, in addition to the PTT.
M3. International Normalized Ratio (INR) greater than 6	Check for the presence of bleeding together with INR changed to indicate a suspected ADR.
M4. Glucose levels less than 50 mg/dL	Check if the patient has lethargy or tremors or if glucose administration has been prescribed. The presence of these factors may be indicative of ADR due to the use of insulin or hypoglycemic agents.
M5. Blood Urea Nitrogen (BUN) greater than 49 mg/dL or serum creatinine greater than 1.30 in men and 1.10 in women	Check patient history to rule out other causes of kidney change such as preexisting kidney disease or diabetes.
M6. Vitamin K administration	**If it is given because of prolonged INR, check the medical record for evidence of bleeding.**
M7. Administration of antihistamines	They are often used for allergic reactions to medications but also for other procedures, as a medication adjuvant or for seasonal allergies. Review medical records to determine reason for use.
M8. Administration of flumazenil	May indicate hyper sedation or benzodiazepine overdose.
M9. Administration of naloxone:	May indicate hyper sedation, respiratory depression, overdose or chest stiffness by opioid-derived medicinal products.
M10. Administration of antiemetic	Nausea and vomiting are commonly the result of medication administration. Check whether they are due to the medication or the patient's condition.
M11. Super sedation/hypotension	Check for signs of super sedation and lethargy. Analyze vital signs notes and graphs for signs of hypotension related to the administration of sedation, analgesics, or muscle relaxants.
M12. Abrupt interruption of medication	May indicate the medication suspected of causing the adverse event. It should not be considered as a trigger when the suspension was by treatment terminated.
M13. Other	Use it when an ADR is detected but is not related to any of the triggers in this list.

*Adapted from Medication Module Trigger do Institute for Health Care Improvement[13].

Only constipation and diplopia were considered as non-serious. In all cases, the time-window between the suspected ADR and the use of the medication was in agreement with that described in the literature. When carrying out the analysis of causality by Naranjo, all were considered possible.

Only metformin and glibenclamide were used in the medical records, which were being correctly used. As for the other medications, it was not possible to confirm the dosages prescribed due to the lack of information in the medical records.

In total, 38 triggers were found in the 287 cases studied, which are shown in Table 2.

Triggers M1, M2, M3, M6, M8, and M9 were not found. Triggers M5, M7, and M10, were found but they were not related to any suspected ADR. Only triggers M4 and M11 were related to the suspected ADR. For M13 there is the suggestion of 2 triggers: serum sodium level and constipation. A suspected ADR (diplopia) was found without the presence of any trigger. Diplopia was not considered a useful trigger suggestion to appear in M13 since it was only possible to verify
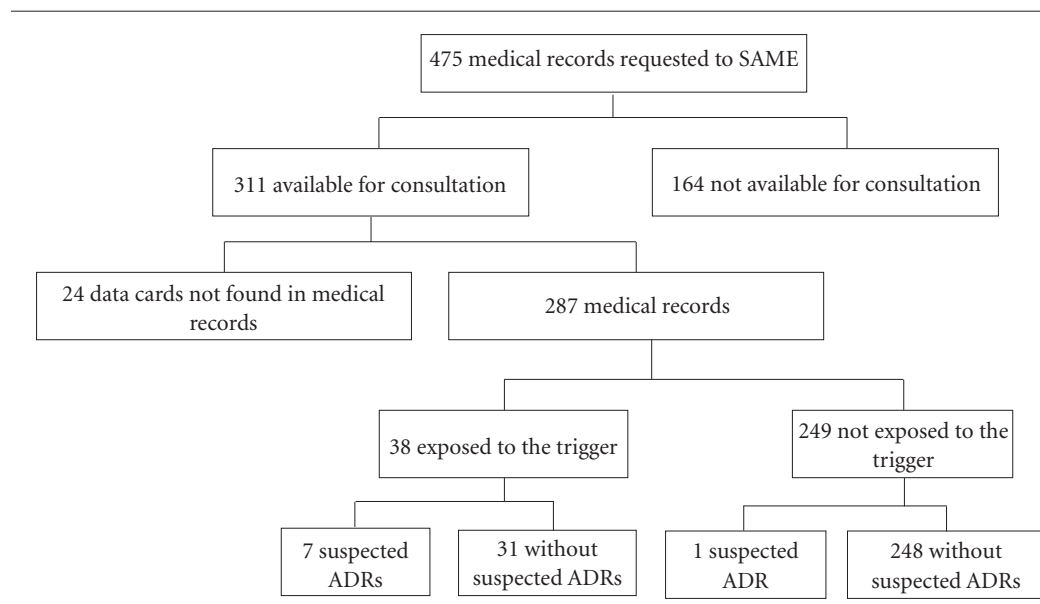
Figure 1. Distribution of medical records and suspected ADRs.

Chart 2. Description of medication triggers suspected of adverse reactions in elderly served at an emergency department, São Paulo – 2013-2014.

Suspected	Triggers	Suspected medications (ATC)*
Hyponatremia	M13 (Other): Serum sodium level < 136 mEq/L	Hydrochlorothiazide (C)
Hypoglycemia	M4 (Glucose < 100)	Glibenclamide (A)
Hypoglycemia	M4 (Glucose < 100)	Metformin (A), Glibenclamide (A)
Postural hypotension	M11 (hypotension)	Captopril (C), Furosemide (C)
Postural hypotension	M11 (hypotension)	Losartan (C), Hydralazine (C), Amiodarone (C)
Constipation	M13 (Other): Constipation	Codeine (N)
Constipation	M13 (Other): Constipation	Calcium polystyrene sulfonate (V)
Diplopia	–	Timolol eye drops (S)

*The groups in parentheses represent the 1st level of the Anatomical Therapeutic Chemical (ATC) classification.

the suspected ADR due to the doctor's report in the medical record.

Discussion

In this study, it was verified that 2.79% of the cases of ED visits by the elderly were due to some suspected ADR. The literature presents quite different results. A systematic review that analyzed only prospective studies found that the prevalence of ADRs in hospital admissions ranged from 0.16% to 15.7%, with an average of 5.3% for all ages, and 10.7% for the elderly[6]. A study carried out in a tertiary-level hospital in Barcelo-

Table 1. Demographic characteristics of elderly with suspected adverse drug reactions at an adult emergency department, São Paulo – 2013-2014.

Features	Medical records analyzed (%)	Patients with suspected ADR (%)
Genre		
Female	167 (58)	5 (62.5)
Male	120 (42)	3 (37.5)
Age (years)		
60 – 70	126 (44)	3 (37.5)
71 – 80	102 (35)	1 (12.5)
> 80	59 (21)	4 (50.0)

Table 2. Distribution of triggers indicative of suspected adverse drug reactions in medical records of the elderly at an adult emergency department, São Paulo – 2013-2014.

Triggers	Present in the medical records	Which have indicated ADR
M1 (positive stool culture for Clostridium difficile)	0	0
M2 (PTT > 100)	0	0
M3 (INR > 6)	0	0
M4 (glucose < 100)	2	2
M5 (urea > 49 and/or altered creatinine)	21	0
M6 (vitamin K)	0	0
M7 (antihistaminic)	1	0
M8 (flumazenil)	0	0
M9 (naloxone)	0	0
M10 (anti-emetic)	9	0
M11 (hypotension/super sedation)	2	2
M12 (abrupt interruption of the medication)	0	0
M13 (other)*	3	3
Total	38	7

* Serum sodium level changed and constipation.

na, Spain, found that 3.3% of the elderly admitted to the ED had a suspected ADR as the reason for admission[19].

On the other hand, a study conducted in Ontario, Canada, evaluated the reason for admission at EDs of patients over 65 years of age and it was verified that 0.75% of the total annual care was due to ADRs. And among these patients, 21.7% needed hospital admission[9]. Another study, also conducted in Canada with patients over 65 years of age, found that 0.8% of the reasons for ED care were due to suspected ADRs, of which 21.5% required hospital admission[10]. As for the United States, a rate of 0.2% of patients over 65 years of age who entered EDs due to an ADR was found (a rate more than twice as high as in patients younger than 65 years)[20]. The last three studies referred to retrospective work performed in more than one hospital. The two Canadian studies were based on the International Classification of Diseases (ICD) that each patient presented as a reason for entering the ED and the United States study was based on the national database of adverse events. All were passive search studies[9,10,20]. This may have influenced the differences of results presented because in the current study an active search was performed on all the medical records without searching the entrance ICD.

In these other countries, the severity of ADRs was also higher, since two of them showed a hospitalization rate of approximately 21% among ADR patients as a reason for ED admission[9,10].

And in this study no patients needed hospitalization.

A Brazilian study has investigated problems related to medications leading to emergency departments care. In that study, the authors found that 9% of the problems occurred in individuals aged 65 years or more but they referred to indication, efficacy and safety and 29.2% were suspected ADRs. However, these patients' age groups were not specified, making difficult a comparison with the results of this study[21].

The differences in prevalence found in the different studies may have been a result of the different definitions used to designate an adverse reaction but they may also be due to the age used to consider a person an elderly since in Brazil persons aged 60 or older are considered as elderly. In developed countries, the elderly are individuals aged 65 or older[22]. Also the type of search used may influence the prevalence since studies in which there is a review of medical records combined with patient interviews report higher prevalence[6]. On the other hand, retrospective studies have lower prevalence rates[23]. The profile of the hospital in which the study was performed and even the duration of the study may also influence the results. In the latter case, there are authors who state that longer studies present lower prevalence than shorter studies[7].

It is not surprising that the medications most related to the suspected ADRs were those of class A (alimentary tract and metabolism) and C (car-

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diovascular system) since, according to data from the Department of Information Technology of Brazilian Unified Health System (SUS) (Data-SUS) related to the year 2013, chronic diseases such as hypertension, hypercholesterolemia and diabetes present high prevalence in the Brazilian elderly population, respectively, 50.6%, 24.3%, and 18.1%[24]. Also the review by Kongkaew et al. has shown that cardiovascular medications are among the most frequently associated with the elderlies' hospital admission[6]. As for the research carried out in Ontario, mental disorders due to psychotropics, opioids, sedatives and hypnotics were the most prevalent ADRs among the elderly and were equivalent to 25% of severe ADRs and 33% of moderate ADRs[9]. The other Canadian study showed that the medications most associated with ADRs were antibiotics (15.9%), anticoagulants (14.2%), antineoplastic agents (9.6%) and opioids (7.3%)[10]. As for the United States, the main ADR-related medications among the elderly were warfarin, digoxin, and insulin. These three medications were equivalent to one third of the causes of ADRs[20]. Although not found in this study, it is observed that most medications suspected of causing ADRs demand monitoring of pharmacotherapy, demonstrating the importance of monitoring the use of medications in outpatients to avoid the appearance of ADRs. As for the differences in medication classes, they may have occurred due to the epidemiological condition of the sites studied.

Many studies point to advanced age as a risk factor for the appearance of ADRs[7,9,25]. In this study, there was a slight predominance of suspected ADRs in patients over 80 years of age. It is possible that the elderly who are more advanced in age present more comorbidity and therefore use polypharmacy. In addition, the elderly in a more advanced age having comorbidities are excluded from clinical trials. Thus, the treatment choice for these patients derives from younger, healthier patients, increasing the risk of ADRs in patients over 80 years of age[26].

Some studies show a higher prevalence of ADRs in females, as observed in the aforementioned study in Canada, in which 60.7% of ADRs have occurred in women[9]. Research conducted in Germany has also shown a higher prevalence of ADR in females, especially in the age group of 55 to 76 years. Some explanations that justify this difference are physiological and hormonal aspects in women that influence medications pharmacokinetics and pharmacodynamics and the distinguished females' body constitution, which presents greater content of body fat, besides some studies indicating a difference of hepatic metabolism of medicaments[8,27]. In this study, the prevalence of ADRs was also higher in females (62.5%). However, it should also be taken into account that more medical records of female patients than of male patients were studied.

All suspected ADRs were found to be "possible," according to the Naranjo algorithm[18], because of the lack of information in the medical records, and it was not possible to answer all the questions proposed by the instrument. In the medical files there were few details regarding the medications the patient was using at home and there was no information either about the medical prescription on discharge of the patient. It was not possible either to know whether the patient had already been re-exposed or not to the medication and whether the ADR had occurred for the first time.

With the exception of common cold and diplopia, which did not fit ANVISA's severity criteria, the other suspected ADRs were classified as severe.

Below is a discussion on the use of triggers tested in adult emergency departments:

• Trigger M1 (*Clostridium difficile*) did not prove to be a good ED trigger since it is an exam that is not always available and, in addition, its result is not quickly released. In the hospital studied, this exam has not been performed either because of its low sensitivity. Thus, its use, prospectively, at an ED would be very difficult.

• Triggers M2 (PTT > 100), M3 (INR > 6), and M6 (vitamin K) were not found in the study population. However, the literature shows that many reasons for ED care are due to anticoagulants. Thus, they are important triggers in the search for suspected ADRs at an ED.

• Trigger M4 (glucose < 50) was found in two medical records and it is important in the detection of possible ADR at EDs, since many elderly people use insulin and/or oral hypoglycemic agents.

• The M5 trigger (creatinine and urea) has great applicability, since several medications are nephrotoxic. However, its presence requires a detailed evaluation of the case, since elderly patients' renal function is easily altered by the aging process and other comorbidities.

• The M7 (antihistaminic) trigger helps in the identification of hypersensitivity reactions, such as rash and exanthema. In the study population, these ADRs were not found. This may have occurred because when this type of mani-

festation is of lesser severity, it generally does not generate demand for ED care. Or else because, in these cases, the patient is not kept under observation. Even so, because they are common ADRs, it is an important trigger to use at an ED. In addition to antihistamines, rash and pruritus could be added as triggers to identify hypersensitivity ADRs.

• Triggers M8 (flumazenil) and M9 (naloxone) do not present great applicability as triggers at EDs. As they are antagonists of benzodiazepine and opioids, they are more important in hospitalization and for identification of poisoning.

• Trigger M10 (antiemetic) in this study was considered when the antiemetic was administered at the beginning of the patient's ED care and could therefore indicate a relationship with an ADR of a medication that the patient would be using at home. Nausea and vomiting are common symptoms in various diseases and are ADRs of various medications. This way, it is a trigger that requires attention at the time of analysis.

• Trigger M11 (hypotension/super sedation) is essential for use in ED since antihypertensive medications are commonly used by the elderly. This study has identified two suspected ADRs.

• Trigger M12 (abrupt interruption of the medication) is difficult to use in a retrospective study because it is not possible to know if the interruption was really abrupt since the way the patient used the medication is not known. In addition, without information on patient discharge it is not possible to know whether or not the medication was continued after ED care. However, it is an applicable trigger for prospective studies.

• Trigger M13 (other): in the search for active ADRs, two more important triggers for EDs were found: constipation and serum sodium level. Sodium is an important ADR trigger caused by diuretics.

One of the limitations of this study is that the sample surveyed is not representative of all the elderly attending the ED. Even though it was selected at random, it is a convenience sample used to verify and discuss the use of triggers in this service unit. Because this was a retrospective study, it has also presented as a limitation the lack of detailed information on the clinical and multiprofessional staff evolution in relation to the suspected ADRs and medications that the patient used prior to admission to the ED, in addition to the prescription originated in the visit to the ED. Medication dosage used at home was usually incomplete in the medical record and it was not possible to confirm this information with the patient. The lack of information in the medical records has limited the evaluation of ADRs. The lack of electronic records and prescriptions was also a major limitation for the retrospective work. Triggers performance for use at ED has not been investigated either since there was no pattern of ADRs that occurred in the service studied for the calculation of sensitivity and specificity. However, a study carried out in Canada has investigated these parameters and observed a low sensitivity, from 2.6 to 15.8%, depending on the trigger, but a high specificity. The authors suggest that more sensitive triggers can be developed using clinical decision-making methods, in which clinical judgment is initially used to define options as predictors[28].

Even with these limitations, it can be concluded that it is possible to search for adverse drug reactions at EDs using IHI triggers. Several of them were applicable, with some suggestions. Prospective studies also using the other trigger modules proposes by the IHI and with a larger number of people are suggested to consolidate the IHI trigger framework useful for each service and to calculate trigger performance in identifying suspected ADRs in the elderly seeking ED care. Thus, this study has allowed obtaining a profile of suspected ADRs that occur outside hospital environments, signaling for medications that may cause more common reactions in this population and who therefore need more attention to increase patients' safety in relation to the use of medications.

Collaborations

KL Nagai worked on the design of the research, on the collection and interpretation of the data and on the writing of the article. PSK Takahashi worked on research design, data interpretation, article writing, and critical review. LMO Pinto worked on critical review. NS Romano-Lieber worked on the design of the research, on the writing of the article and on its critical review.

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