Confounding Variables and the Performance of Triggers in Detecting Unreported Adverse Drug Reactions

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ABSTRACT

Purpose: This study explored the performance of trigger in detecting adverse drug reactions (ADRs), the confounding variables impairing the causal association of the ADRs, and the underreporting rate by hospital health professionals.

Methods: A 6-month cross-sectional study was conducted in a public general hospital. Data collection was conducted in 2 stages: (1) screening of patient hospitalizations to identify suspected ADRs with 9 triggers developed by the Institute of Healthcare Improvement; and (2) chart review to perform the causality assessment of the suspected ADRs identified, to describe the confounding variables associated with detection of suspected ADRs that were not drug induced, and to analyze the positive predictive value of triggers in recognizing ADRs. To estimate the underreporting rate, ADRs detected by using the tool were compared with ADRs reported by health professionals during the same period.

Findings: During the study period, 3318 hospitalizations were analyzed. A total of 837 suspected ADRs were identified. However, after causality assessment, 356 were definite ADRs. Confounding variables associated with the detection-suspected ADRs were related to the clinical conditions of inpatients. The use of triggers contributed to increased ADR detection by 10.5%. The performance ranged from 0.00 to 0.75, with an overall positive predictive value of 0.43. Six ADRs were spontaneously reported, of which just 1 was also detected by using the trigger tool. Only 1 of 356 potential ADRs was reported by health professionals.

Implications: Findings show that the use of triggers contributes to detecting ADRs underreported by health professionals. However, confounding variables impaired the performance of the tool because they underestimated the causal association. Furthermore, both methods are complementary to early recognition of drug-induced harm and should be applied together in health institutions to contribute to policies of risk management, drug safety, and optimization of pharmacotherapy. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮)

Key words: pharmacovigilance, product surveillance postmarketing, risk assessment, drug therapy, hospitalization, healthcare.

INTRODUCTION

A systematic review found that only 6% of adverse drug reactions (ADRs) are spontaneously reported.[1] This rate is a small percentage of the harm experienced by patients and is not representative of the total possibilities of occurrence of drug-induced harm.[2] Spontaneous reporting depends on the motivation of the reporters[3];

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however, poor information[4–6] and the presence of confounding variables[7] also hinder causality assessment. Thus, risk communication related to drug use is ineffective.[8]

Several strategies have been developed to improve the detection of medication-related harm.[3,9–11] One approach, the use of triggers, has shown promise in improving the identification of drug safety problems. Classen et al[12] noted that the use of the tool increased ADR detection by 10-fold. However, varying performances have been observed,[13–19] as well as poor sensitivity, compared with case note review for the identification of preventable ADRs.[17]

The wide range of performance is not directly related to safety barriers, but it is instead due to the characteristics of hospitals,[15] the design and aims of studies, the sample enrolled, settings,[18] and the presence of confounding variables. Confounding occurs when the estimate of association between drug exposure and health status is distorted by the effect of one or several other variables that are also risk factors for the outcome of interest.[20] Because confounding variables are a source of bias,[21] it is critical to consider confounding variables when designing, analyzing, and interpreting studies intended to estimate causal effects. Confounding variables associated with poor performance of triggers are still unknown.

The intent of the present study was to explore and describe the relevant confounding variables, aiming to optimize the risk management of drugs in hospitals, as well as to improve safety care. Therefore, the objective of this study was as follows: to explore the performance of trigger tools in ADR; to identify the confounding variables associated with the detection of suspected ADRs that were not drug induced; and to estimate the underreporting rate by hospital health professionals.

PATIENTS AND METHODS

Study Design, Setting, and Population

A cross-sectional study was performed in a medium-complexity public, nonteaching hospital; the hospital has 30 clinical and surgical specialties and 94 beds. The study was conducted over a period of 6 months. The institution has an electronic charts system (prescription, clinical outcomes, and laboratory parameters), in which all health professionals register their assessments. In 2012, a risk management policy was implemented, including an institutional program of pharmacovigilance.

Inclusion criteria comprised all inpatients aged ≥18 years who had been hospitalized from November 2011 to January 2012 and from May to July 2012. The exclusion criteria included inpatients whose charts were incomplete or unavailable for consultation.

Variables

The primary outcome was the sensitivity of each trigger for ADRs. This study aimed to evaluate the association between the ADRs identified according to the trigger tool and the demographic characteristics of the inpatients enrolled (age and sex); ADR causality assessment; seriousness of ADRs; and the presence of confounding variables related to the activation of triggers.

The number of definite ADRs detected by using the trigger tool was compared with the number of ADRs reported by health professionals to estimate the percentage of improvement in safety reporting.

Data Sources/Measurement

Data were extracted from a local electronic system. Nine triggers from the list developed by the Institute of Healthcare Improvement were applied to perform the active search of ADRs (Figure).[11] Only 1 trigger ("rising serum creatinine") was adapted (to "serum creatinine >1.2 mg/dL").

Data collection occurred in 2 stages (Figure) and was performed with the aid of an instrument developed to guide the ADR evaluation process. The instrument had 5 sections with the following information: (1) reference ranges of laboratory parameters; (2) drugs associated with changes in laboratory parameters; (2) synonyms of triggers related to clinical conditions (rash, fall, lethargy, and somnolence); (3) brand names of sodium polystyrene; (4) clinical manifestations related to hyperkalemia, hypoglycemia, and renal failure; and (5) events that could have activated the triggers whose etiology was not related to the drug use.

The first stage of data collection corresponded to the screening of patient charts with the 9 triggers. When at least 1 trigger was identified, the second phase of data collection (close chart review and analysis) was conducted to verify the causal association between the suspected ADR and the drug used (Figure).

The causality assessment was performed by using clinical judgment. The clinical pharmacist of the hospital

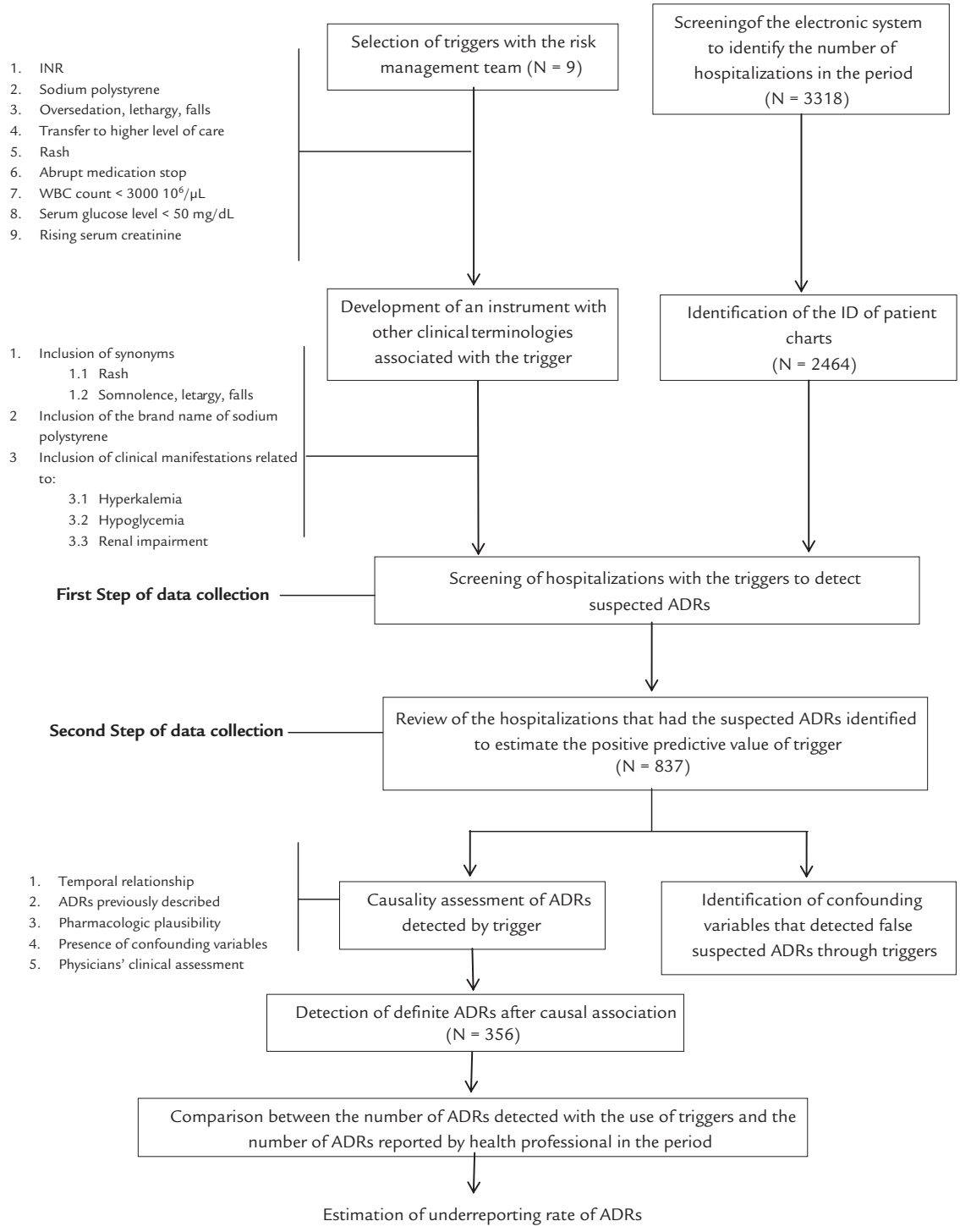

Figure. Flowchart of data collection. ADRs = adverse drug reactions; INR = international normalized ratio; WBC = white blood cell.

supervised the team responsible for ADR imputation. The judges were pharmacy undergraduate students who were previously trained to standardize the analysis of causal association. The training took into account the classes of triggers, with emphasis on drugs and health conditions that could be associated with them, as well as practical classes about causality assessment, with analysis of fictitious ADRs to be imputed.

Clinical judgment of suspected ADRs considered: (1) the temporal relationship between the occurrence of the event and drug use; (2) ADRs previously described in the scientific literature (UpToDate and Micromedex databases); (3) the pharmacologic plausibility (whether the mechanism of action of the drug may produce the event); (4) exclusion of confounding variables that may explain the case (clinical condition of the patient and other drug-related problems); and (5) objective and subjective impressions of physicians about the case.

Chart review ~~a~~nd periodic discussions among the judges, clinical pharmacists, and physicians were conducted until consensus was achieved on causal association. The confounding variables were described for each trigger related to suspected ADRs that were not considered drug related according to clinical judgment. The confounding variables were described when the causality association was not observed.

The ADRs identified were reported to the department of risk management because it was considered they had the potential to be reported by health professionals. The risk manager reported the ADRs to the Brazilian Sanitary Agency (ANVISA).

We used the World Health Organization definition of ADR,[22] which is any noxious, unintended, or undesired effect of a drug occurring at doses used in humans for prophylaxis, diagnosis, or therapy. The concept of harm used was a temporary or permanent disorder in the physical or psychological functioning or structure of the human body.[16] An abrupt stop in medication was considered as the unexpected discontinuation of a drug, excluding: replacement of a drug for another of the same chemical group with similar pharmacokinetic or pharmacodynamic properties; prescriptions to take "if necessary"; and drugs not administered due to administrative reasons,[16] such as drugs not dispensed due to shortages or that were nonstandardized in the hospital.

Serious adverse effects were considered as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening.[23]

Bias

Causality assessment was performed by using a chart review. The possible lack of information in patient charts may impair determination of causal associations and underestimate the detection of definite ADRs.

Study Size

All hospitalizations (100.0%) were analyzed during the study period to verify the contribution of triggers in enhancing detection of ADRs.

Quantitative Variables

An inpatient may have been hospitalized more than once in the period of study. Therefore, chart review of all hospitalizations was conducted to estimate the prevalence of ADRs detected by using the trigger tools and to compare that with the number of ADRs reported by health professionals in the same period.

Analytical Methods

Data obtained from the likelihood of causality assessment, the presence of confounding variables, and demographic characteristics (sex and age) of hospitalizations with and without ADRs identified were expressed as frequencies and subjected to an analysis of descriptive statistics. The χ^2 test was applied to the dichotomous variables age (elderly or nonelderly) and sex, to reveal statistically significant differences between overall hospitalizations; hospitalizations with suspected ADRs; and hospitalizations with definite ADRs. Patients aged ≥ 65 years were considered "elderly." Odds ratios were calculated to analyze the association between dichotomous variables and the occurrence of ADRs.

After detection of ADRs, the positive predictive value (PPV) of each trigger was evaluated. PPV is the proportion of positive results in statistics and diagnostic tests that are true positive results.[24] ADR prevalence was detected by close review and analysis. Calculations were performed according to the following formulas:

$$\mathrm{PPV}_{\mathrm{trigger}} = \frac{(\text{no. of ADRs detected by triggers in the period})}{(\text{no. of triggers detected in the period})}$$

$$\mathrm{Prevalence}_{\mathrm{ADR\text{-}trigger}} = \frac{(\text{no. of ADRs detected by triggers in the period})}{(\text{no. of hospitalizations in the period})} \times 100\%$$

Moreover, ADR prevalence detected according to spontaneous report was also estimated, while taking into account all ADRs reported by health professionals in the same period of data collection. The calculation was performed by using the following expression:

$$\text{Prevalence}_{\text{ADR reporting}} = \frac{(\text{no. of ADRs reported in the period})}{(\text{no. of hospitalizations in the period})} \times 100\%$$

A comparison between ADR prevalence estimated by using the trigger tools and by spontaneous reporting was performed to verify ADR underreporting rate according to the follow expression:

$$\text{ADR}_{\text{underreporting rate}} = \frac{(\text{no. of ADRs detected by triggers} - \text{no. of ADR reports})}{(\text{no. of hospitalizations in the period})} \times 100\%$$

Approval by Ethics Committee Research

The study (protocol E-015/10) was approved by the Ethics Committee in Research of the Instituto Lauro de Souza Lima.

RESULTS

Participants

In the study period, there were 3318 hospitalizations, which corresponded to 2464 inpatients (the same patient could have been hospitalized more than once).

Descriptive Data

According to the demographic characteristics, 67.9% of overall hospitalizations involved nonelderly people (aged <65 years) and women (59.1%) ($P < 0.0001$) (Table I) who were hospitalized due to infectious diseases (pneumonia) and with prescription of polypharmacy. At the first stage of data collection (screening of patient charts), 837 triggers were activated. Suspected ADRs were detected in most hospitalizations of men (59.3%) and elderly subjects (55.4%), although the differences were not statistically significant.

There was no difference in ADR detection with triggers between each period evaluated. Furthermore, ADRs identified were considered as expected.

Outcome Data

After causality assessment, of the 837 suspected ADRs, 356 (42.5%) were classified as definite, 328 (39.2%) as possible or probable, and 153 (18.3%) were improbable. None of the definite ADRs met the criteria of seriousness. Findings showed that nonelderly people (52.0%) and men (55.9%) were the

Table I. Demographic characteristics of overall hospitalizations, according to sex, age, presence of suspected adverse drug reactions (ADRs), and definite ADRs.

Hospitalizations	Female Patients, No. (%)	Male Patients, No. (%)	Total, No. (%)	Statistical Analysis	
				OR (95%) CI	*P*
Overall					
Elderly	557 (28.4)	509 (37.6)	1066 (32.1)	1.5 (1.3–1.7)	<.0001
Nonelderly	1406 (71.6)	846 (62.4)	2252 (67.9)		
Total, no. (%)	1963 (100.0)	1355 (100.0)	3318 (100.0)		
Suspected ADR					
Elderly	177 (51.9)	287 (57.9)	464 (55.4)	1.2 (0.9–1.6)	0.09
Nonelderly	164 (48.1)	209 (42.1)	373 (44.6)		
Total, no. (%)	341 (100.0)	496 (100.0)	837 (100.0)		
Definite ADR					
Elderly	68 (43.3)	103 (51.8)	171 (48.0)	1.4 (0.9–2.1)	0.11
Nonelderly	89 (56.7)	96 (48.2)	185 (52.0)		
Total, no. (%)	157 (100.0)	199 (100.0)	356 (100.0)		

OR = odds ratio.

Table II. Positive predictive value (PPV) (effectiveness) of the triggers applied to identify adverse drug reactions (ADRs) in patient records of hospitalized patients.

Trigger	No. of Times the Trigger Was Detected	No. of Times the Trigger Was Associated With an ADR	PPV
INR >6	12	9	0.75
Abrupt medication stop	271	201	0.74
Serum glucose <50 mg/dL	29	21	0.72
Sodium polystyrene	28	18	0.64
Rash	33	18	0.55
Fall, lethargy, somnolence	97	50	0.52
WBC count <3000/mL	21	10	0.48
Creatinine >1.2 mg/dL	291	29	0.10
Transfer to higher level of care	55	0	0.00
Total	837	356	0.43

INR = international normalized ratio; WBC = white blood cell.

most susceptible for occurrence of ADRs (Table I). However, there was no statistically significant difference. A total of 220 inpatients developed the 356 definite ADRs identified. A total of 128 had 1 occurrence; 63 had 2 occurrences; 19 had 3 occurrences; and 10 had >3 occurrences.

The prevalence of ADRs estimated according to triggers was 10.7% (356 of 3318). The overall performance of the triggers was 0.43, as the PPV of each trigger ranged widely from 0.00 to 0.75 (Table II).

The drug classes and confounding variables mainly associated with the 9 triggers are described in Table III.

Other Analysis

Regarding the spontaneous reporting, 6 ADRs were reported by the risk management of the hospital in the period analyzed. Only 1 ADR was also detected by using the triggers; this ADR was related to cutaneous rash and was possibly caused by clindamycin or ciprofloxacin. The 5 other ADRs reported were phlebitis (n = 3), whose causal relationship was mainly associated with the use of antibiotics (azithromycin, ceftriaxone, and meropenem), and dyspnea (n = 2), arising from azithromycin (unlikely) and formoterol. The ADR prevalence estimated by the spontaneous reporting was therefore 0.2% (6 of 3318).

Considering the ADR underreporting rate, it was noted that only 1 of 356 ADRs with the potential to be reported by health professionals was actually reported. Therefore, the use of triggers contributed to increasing ADR detection by 10.5% in the hospital under study.

DISCUSSION

Key Results

Our study is the first to illustrate the confounding variables associated with different performances of triggers in detecting ADR. Most of them are related to clinical conditions of inpatients. Nevertheless, triggers enhanced the detection of definite ADRs that were not reported by health professionals. The improvement observed may support indicators of risk management of health care to contribute to polices of patient safety; communication of harm drug-induced and contribution of safe pharmacotherapy.

Limitations

Data collection was conducted in a general, public, nonteaching hospital. The data may therefore not be generalizable to other types of institutions. Moreover, differences between the definitions of ADR used while developing the triggers and those used in our

Table III. Drug classes and main confounding variables associated with each of the 9 triggers used in the study.

Trigger	Drug Classes Mainly Associated	Confounding Variables
INR >6	Anticoagulants: warfarin, enoxaparin, heparin	Clinical conditions: hepatic impairment (n = 2) Laboratory test errors (n = 1)
Sodium polystyrene	ACE inhibitors: enalapril Anticoagulants: heparin, enoxaparin, warfarin Potassium-sparing diuretics: spironolactone Cardiotonics: digoxin	Clinical condition: hyperkalemia secondary to renal impairment (n = 10)
Fall, lethargy, somnolence	Drugs that act in the nervous system, with severely enhanced sedation after associated with drugs such as: Neuroleptics: haloperidol, risperidone Anxiolytics: lorazepam, diazepam Hypno-analgesics: morphine	Secondary to worsening patient conditions (n = 40) Sedation scheme (n = 7)
Transfer to a higher level of care	–	Worsening of clinical conditions (n = 55)
Rash	Antibiotics: amoxicillin, azithromycin, clindamycin; pyrazinamide, ciprofloxacin	Mechanical or bacterial phlebitis (n = 3) Clinical conditions (n = 8) Skin infections (n = 4)
Abrupt medication stop	Psychotropic medication Insulin Diuretics: furosemide and spironolactone ACE inhibitors: enalapril Anticoagulants: heparin, enoxaparin, warfarin Antibiotics	Improvement of clinical condition/clinical observation (n = 52) Absence of benefit (n = 18)
WBC <3000 × 10^6/μL	Antivirals: aciclovir	Clinical conditions (n = 11)
Serum glucose <50 mg/dL	Insulin: intermediate-acting, fast-acting, regular	Prolonged fastening (n = 5) Clinical conditions (n = 3)
Serum creatinine >1.2 mg/dL	ACE inhibitors: captopril, enalapril Diuretics: furosemide	Acute renal failure with a prerenal component (n = 253) Acute renal failure with a postrenal component (n = 9)

ACE = angiotensin-converting enzyme; INR = international normalized ratio.

study may have contributed to the wide range of sensitivity found.

Data may also be underestimated because causality assessments were conducted by using chart review and clinical judgment. This approach could hinder the identification of potential confounding variables that were not described in patient charts, and results may change according to the complexity of the hospital, the judges who perform the causal association, and the design of the study (prospective or retrospective).

Interpretation

According to a meta-analysis by Miguel et al,[25] ADRs could occur in 16.8% of patients during hospitalization. Methods applied to recognition of ADRs were: spontaneous reporting, solicited reporting, close review and

analysis, prospective monitoring, computerized system with investigation of every alert to validate ADRs, codification/codes, and chart review. Angamo et al[26] observed that the prevalence of ADR-related hospitalizations in developed and developing countries was 6.3% and 5.5%, respectively. Consequently, to detect and manage drug-induced harm arising from primary health care is still a challenge to hospitals.

The recognition of ADRs according to triggers revealed a prevalence of 13.2%[27] and 14.6%[14] in hospitals of North and South America, respectively. Our data corroborate these findings. Furthermore,[29] Classen et al[12] suggest that triggers increase 10 times the identification of adverse events in hospitals. Considering that the development of pharmacovigilance is recent in Latin America, many challenges need to be addressed[28] to increase the recognition of ADRs, as South American countries have the lowest ADR reporting rates.[29]

Therefore, the close review and analysis with triggers is feasible to target this obstacle, once it is an efficient, robust method.[8] In addition, this method is practical and less laborious[11,30] compared with retrospective analysis of patient chrts.[14]

Regarding risk factors, studies show that nonelderly subjects and men often tend to be affected by ADRs detected by using triggers.[14,27] Varallo et al[31] found that age is a protective factor for the occurrence of drug-induced harm. The investigators suggest that older people now receive greater care and health assistance, due to the physiological changes related to the aging process, which may favor the development of adverse effects. This scenario may explain why they had a lower frequency of ADRs in the present study.

A systematic review has shown that there may be differences between men and women in the occurrence of ADRs, depending on the therapeutic regimen used.[32] However, when using triggers for the detection of ADRs, no statistical differences were observed for these variables,[14,27] as confirmed in the present study.

Concerning causality assessment, Sam et al[33] conducted a screening of charts with triggers and found that 61% of the ADRs detected were classified as possible or probable after being imputed with the World Health Organization–Uppsala Monitoring Centre algorithm. In our study, the active participation of risk management in the selection of triggers and the assessment according to clinical judgment might explain the higher frequency of ADRs obtained as definite. We suggest therefore that choosing triggers in accordance with the epidemiologic/nosologic profile is an effective strategy to increase signal detection, improve risk communication, and contribute to patient safety.

Another advantage of the application of triggers rises from their ability to recognize multiple ADRs in a single patient. These tools can therefore be used to prevent iatrogenic events. However, it is necessary to know the confounding variables that can activate these triggers and that hinder causal association, to enhance and improve their performance in the early identification of ADRs.

We observed that confounding variables are generally related to the clinical condition of inpatients, which comprise the same limitations described for causal assessment related to spontaneous reporting.[7] Poor-quality information in patient charts then decreases the benefit of trigger tools and hinders the recognition of confounding variables. As a consequence, safety report and causality assessment will be impaired.[7] Health professionals should be encouraged to report ADRs to increase the detection of harm associated with drug use, as well as to identify risk factors to prevent them.

The wide PPV range of triggers demonstrated in several studies[13–19] also might be explained by retrospective chart review in addition to the epidemiology profile of the institution, as well as the patient's characteristics, the specialty of the wards, the drugs standardized in the hospital, and the method applied to ADR detection.[17,18] Therefore, knowing confounding variables may improve strategies to conduct prospective follow-up of inpatients, preventing negative clinical outcomes in real time, and contributing to patient safety and institutional policies of risk management, as well as optimizing the effectiveness and safety of pharmacotherapy.

Safety indicators associated with triggers state that they should not be used as a benchmarking tool at the tertiary health care level.[11] We suggest that each health institution should select the most appropriate triggers to identify drug-induced harm. For example, our data showed that patient transfers to higher health care levels or institutions were ineffective triggers for identifying ADRs in the hospital under study. This fact can be explained by the complexity of the

institution (medium complexity), which does not provide clinical care for serious conditions that require the most advanced health technologies.

Regarding the events related to creatinine levels >1.2 mg/mL, an important limitation should be considered: acute kidney failure was considered when an increase of 0.5 mg/dL was observed in 2 subsequent measurements of creatinine levels.[34] Therefore, rising creatinine levels, rather than creatinine levels >1.2 mg/mL, should be considered as a trigger when evaluating acute renal failure associated with drugs, even when a patient's creatinine level is <1.2 mg/mL. In fact, the original trigger tool, which was adapted in our study, listed a trigger of rising creatinine level.[11] Furthermore, although creatinine levels >1.2 mg/mL could be activated by several confounding factors, as observed in our study, it is an important indicator for clinical assessment.

An international normalized ratio (INR) >6 demonstrated the best PPV. However, our finding may be underestimated, because in the sample analyzed, side effects related to anticoagulant drugs appeared with INR measurements <6. In several cases, physicians discontinued the treatment when INR was extrapolated over the therapeutic range of warfarin (2.0–4.0) due to the higher risk of bleeding and to avoid drug-related problems. Therefore, the customization of the trigger list should be considered, while mainly taking into account the nosology profile of the institution and the characteristics of the patient population in the hospital. In the hospital under study, a better parameter for the recognition of ADRs related to anticoagulant drugs could be INR >3.5.

Abrupt medication stops (PPV, 0.74) were usually detected in association with other triggers. The most frequent cases identified during the study were: (1) somnolence (discontinuation of psychotropic medications or insulin treatment); (2) worsening of kidney function (discontinuing diuretics and angiotensin-converting enzyme inhibitors); (3) changes in INR and clinical conditions related to bleeding (discontinuing heparin, enoxaparin, and warfarin); and (4) rash, which could characterize allergic cutaneous reactions (discontinuation of antibiotics, which were replaced by another different therapeutic class).

We noted that for patients with leukopenia (white blood cell count $<3000 \times 10^6/\mu L$), the drugs responsible for the decrease in white blood cell count were not suspended, such as: acyclovir (n = 5), antiretroviral therapy (n = 2), prednisone (n = 1), azathioprine (n = 1), and azithromycin (n = 1). The discontinuation of antiretroviral therapy would only be justified by considering the CD4 lymphocyte count, which requires the association of antibiotic prophylaxis with sulfamethoxazole and trimethoprim.

Because 5 ADRs reported by health professionals were not detected with the trigger tool screening, the spontaneous reporting and close review and analysis with triggers are complementary. Therefore, both of them should be used in association, as recommended by the World Health Organization,[3] to improve risk communication. According to del Campo et al,[35] the active search of ADR encourages the interaction with other hospital services and promotes a habit of reporting among health professionals. Furthermore, spontaneous reporting is a more specific method to detect ADRs because it enables the imputation of a high degree of causality.

Strategies to encourage the reporting of drug-related problems by health professionals are needed to change their attitudes regarding postmarketing surveillance.[10] Furthermore, it is important to know the confounding variables that may decrease the performance of trigger tools to optimize and improve the search strategy of drug-related problems according to the needs of health care, to contribute to patient safety, and to optimize policies of risk management and safety issues. Advanced multiprofessional collaboration, effective communication, adequate skills, and more systematic medication processes to increase medication safety should then be addressed in health care institutions.[36]

CONCLUSIONS

Close review and analysis with triggers improved risk communication in pharmacovigilance, even when confounding variables for trigger detection were excluded, with only 1 of 356 potential ADRs once having been spontaneously reported. The data suggest that assessment of the performance of each trigger should be conducted to: (1) determine the confounding variables related to the method; (2) select the most effective trigger in ADR detection within different institutions; and (3) establish new parameters (customization of trigger list) to optimize the use of this tool in detecting and preventing drug-related problems.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

AUTHOR CONTRIBUTION

Fabiana Rossi Varallo contributed to data collection, figure creation, literature search, data collection, data interpretation and writting. Caroline Pagotto contributed to data collection and literature seach. Tales Rubens de Nadai contributed to data interpretation. Carolina Dagli-Hernandez contributed to data interpretation, figure creation and writting. Maria Teresa Herdeiro contributed to interpretation and writting. Patricia de Carvalho Mastroianni contributed to study design, literature search, interpretation and writting.

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