Adverse drug events in hospitals: a systematic review

Eventos adversos a medicamentos em hospitais: uma revisão sistemática

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Abstract

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The objective of this study was to evaluate studies on the occurrence of adverse drug events (ADEs) in hospitals in order to learn about their frequency and characteristics, comparing the methods for identifying them and the various definitions. A search was conducted on MEDLINE and identified studies published from 2000 to 2009. Inclusion criteria were: studies in populations not selected for specific diseases or drugs and ADEs that occurred during hospitalization. Twenty-nine studies were selected, displaying multiple sources of heterogeneity, including differences in the study populations, surveillance techniques, definitions of ADEs, and indicators. The proportion of patients with ADEs ranged from 1.6% to 41.4% of inpatients and the rates ranged from 1.7 to 51.8 events/100 admissions. A considerable share of these events could have been avoided. The findings show that ADEs in inpatients are a public health problem. However, further studies are needed to monitor these adverse events in order to effectively promote safe drug use.

Drug Monitoring; Drug Therapy; Pharmacoepidemiology

Introduction

Drugs currently represent an important therapeutic strategy and are widely used, especially in the hospital setting. However, there are inherent risks in their pharmacological action or related to their use, which can lead to the development of adverse drug events (ADEs), otherwise known as adverse drug reactions (ADRs).

In order to guarantee the safe use of medicines, it is necessary to monitor the occurrence of post-registration/post-marketing ADEs, a process known as pharmacovigilance. This strategy aims to assist regulatory activities in the patient safety area.

A pioneering initiative in monitoring adverse drug reactions in inpatients was the Boston Collaborative Drug Surveillance Program (BDSCP), launched in 1966, which conducted an active search for events and collected data on 35,000 patients in ten years [1]. In another study, Seidl et al. [2] conducted an active search for events and estimated their frequency at 13.6% among inpatients. Since then, numerous studies have been published, although with widely varying estimates of frequency.

In 1998, a meta-analysis estimated the incidence of severe ADRs at 6.7% (5.2%-8.2%) [3], but this finding should be interpreted with caution due to various sources of heterogeneity among the studies [4].

The early 1990s witnessed a new stage in the issue of drug safety, which in addition to recognizing the production of adverse events, even when drugs are used appropriately, also identifies the possibility that drugs can cause harmful effects due to flaws or errors during the complex process of their clinical utilization [5].

In this context, the aim of the current review was to evaluate studies on the occurrence of ADEs in the hospital setting in order to determine their frequency and characteristics, comparing the techniques for their identification and the concepts used to describe them.

Method

This was a systematic literature review with a search for articles published from 2000 to August 2009.

The electronic search strategy included the MEDLINE database, using the PubMed interface. The search equation consisted of the descriptors "*adverse drug reaction reporting systems*", "*drug therapy/adverse effects*", and "*pharmaceutical preparations/adverse effects*" to retrieve studies on adverse events. Added to these were either the descriptors "*hospitals*", "*hospitals, veterans*", "*hospitalization*", "*inpatients*", "*pharmacy service, hospital*", "*hospital units*", and "*medication systems, hospital*" or the terms "*hospital**" and "*inpatient**" in the title and abstract. The limits on the search strategy were the period of publication (January 1, 2000, to August 24, 2009), type of population (humans), and type of study (excluding editorials, letters, reviews, and cases). We also excluded articles whose titles included the terms "*child*", "*children*", "*pediatric*", or "*emergency*".

The articles retrieved through the electronic search were submitted to exclusion criteria in order to select those that captured the variety of events occurring in patients admitted to general hospitals. This selection process followed the stages described below.

First, the articles' titles were evaluated independently by the authors, considering the exclusion of studies focusing on: events associated with specific drugs, organs, or systems, and events occurring in hospitals or clinics involving clinical specialties, outpatient services, intensive care units, emergency departments, community care, or nursing home. We also excluded studies that only evaluated ADEs that led to hospitalization or that occurred after discharge, plus those that only approached elderly or pediatric populations.

Next, the same exclusion criteria were applied to the article abstracts, also excluding those

that only approached serious events, those that produced sequelae or were fatal, or exclusively focused on medication errors. We did not include studies that specifically approached the utilization of medicines and pharmaceutical care, health professionals' or patients' opinions, or presentation of programs to improve ADE detection systems, since they failed to provide relevant data for our purposes. We only included full texts available in English, Portuguese, Spanish, or French. Occasional disagreements between the two reviewers were resolved by discussion until reaching a consensus.

The complete texts of the remaining articles (plus those that lacked abstracts) were read in full. During this stage, exclusions were performed according to the previously mentioned criteria or when the articles presented prevalence data on sub-samples of studies already included in the review. Articles that only identified events by means of spontaneous reporting were excluded, because the latter method underreports the events and thus hinders comparison with other studies.

The same inclusion and exclusion criteria were used to select the studies retrieved by manual search in the bibliographic references of the selected articles. The search strategy was also performed in the LILACS database, but detected no additional articles for inclusion.

The expression "adverse drug event" is used throughout the text to characterize harm caused by the use of medicines.

Data collection used a standardized form that was pretested with three data. Article extraction was performed by F.G.C. and reviewed by S.R.

The EndNote software (Thomson Reuters; http://www.endnote.com) was used to organize the bibliographic references.
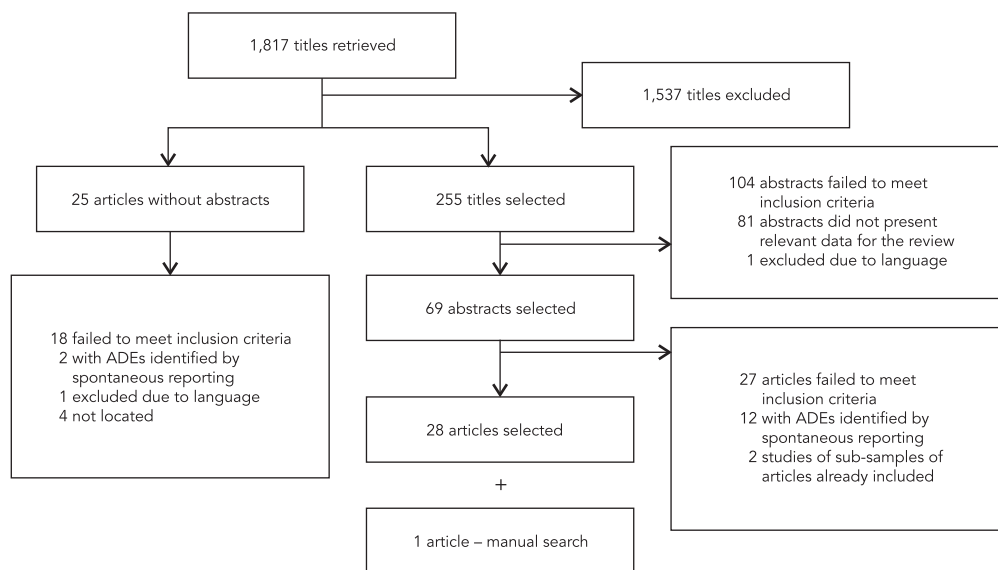
Results

The search strategy retrieved 1,817 articles, and Figure 1 shows the selection stages with the results of the application of the inclusion and exclusion criteria. Twenty-eight articles remained [6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33] for evaluation, plus one more article retrieved by manual search [34].

Table 1 describes the studies, conducted in 13 countries from North America, Europe, South America, and Asia. Ten studies [8,9,15,16,18,19,22,23,24,28] (34.5%) were conducted in the United States and two (6.9%) in Brazil [20,29].

Most of the studies were performed in one hospital (19/29) [7,8,12,13,15,16,17,18,19,20,21,25,26,27,28,31,32,33,34]. Six were multi-center [6,9,22,23,24,29] and

Figure 1

Flowchart of systematic article search and selection on in-hospital adverse drug events.

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    │ 25 articles without      │     │   255 titles selected    │────▶│ 104 abstracts failed to meet     │
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                 │                                │                    │     relevant data for the review │
                 ▼                                ▼                    │   1 excluded due to language     │
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    │ 18 failed to meet        │     │  69 abstracts selected   │
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    │    reporting             │                 │                    │    inclusion criteria            │
    │  1 excluded due to       │                 ▼                    │ 12 with ADEs identified by       │
    │    language              │     ┌──────────────────────────┐     │    spontaneous reporting         │
    │  4 not located           │     │  28 articles selected    │     │  2 studies of sub-samples of     │
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four [10,11,14,30] did not provide information on the place where they were performed. Interestingly, 62.1% of the studies (18/29) [6,7,8,9,12,13,15,16,19,20,21, 22,25,26,27,31,33,34] involved university, academic, or teaching hospitals, i.e., presumably large-scale, high-complexity hospital units.

Forty-eight percent of the studies (14/29) [6,8, 9,14,18,19,22,23,24,25,28,29,30,31] used a retrospective approach, i.e., the presence of ADEs was analyzed after the patient was discharged; 48.3% of the studies (14/29) [7,11,12,13,15,16,17,20,21,26,27,32,33,34] used a prospective approach, whereby the ADEs were identified during the hospital stay; and one study [10] was cross-sectional, where ADEs were identified using a survey. Among the studies with a prospective approach, two used retrospective strategies to complement the evaluation, based on an analysis of hospital discharge forms [16,21].

All the studies described the target population's size. Only 41.4% (12/29) [6,7,10,11,12,20,21,26,27, 28,29,33] provided information about age, and 24.1% (7/29) [6,7,10,20,26,27,33] on gender. As for the unit of analysis, 62.1% (18/29) [6,7,10,11,12,15,18,20,21,24,25,26, 27,30,31,32,33,34] used the number of patients or patient charts, 48.3% (14/29) [6,8,9,12,14,16,17,20,22,23,25, 28,29,33] the number of admissions or discharges, and 24.1% (7/29) [13,16,17,19,31,32,34] the number of patient-days.

As for the technique used to identify ADEs, 55.2% of the studies (16/29) [6,7,8,9,11,13,15,16,17,19, 21,24,25,26,27,33] used a combination of strategies to capture the events. The most widely used techniques included monitoring with screening criteria, review of patient charts, and use of the International Classification of Diseases (ICD) associated with ADEs. Monitoring with screening criteria related to the events was performed by 34.5% of the studies (10/29) [7,9,13,15,18,19,22,26,28,31], either alone (3/29) [18,22,28] or in association (7/29) [7,9,13,15,19,26,31]. The filters consisted basically of rescue drugs, altered laboratory findings, or signs and symptoms related to adverse events. Thirty-eight per cent (11/29) [8,9,13,14,15,17,19,24,30,31,33] of the studies used patient chart review, while in four of these [12,14,30,31] the patient charts were only reviewed to confirm the events. Twenty-eight per cent (8/29) [6,14,21,23,24,25,29,30] of the studies identified the ICD codes related to the events, of which four studies used ICD-9 [14,21,23,30], three ICD-10 [6,25,29], and one the clinically modified ICD-9 [24].

Other techniques included spontaneous reporting, stimulated reporting, review of lists of interventions recorded by staff pharmacists, staff interviews, and medical and pharmaceutical visits.

Table 1

Characteristics of studies on adverse drug events (ADEs) among patients in general hospitals.

Reference	Country/Year	Hospital's characteristic	Design	Population's characteristics	Techniques for identification of ADEs	Frequency
Lagnaoui et al. [34]	France/2000	University hospital	Prospective	N = 444 patients; 2,569 patient-days	Medical and pharmaceutical visit	4.7% of patients with ADEs; 10.1 ADEs per 1,000 patient-days; 5.9 ADEs per 100 hospitalizations
Fattinger et al. [6]	Switzerland/2000	2 teaching hospitals (one tertiary, one secondary)	Retrospective	N = 3,624 patients; 4,331 hospitalizations Age: median female 64 (46-71), median male 59 (46-77) Males 40.6%	Monitoring using computerized database – drugs, clinical events, lab results, ICD-10, and physician evaluation	48% of hospitalizations with events possibly related to drug; 41% of hospitalizations with events possibly related to drugs, not related to the disease
Dormann et al. [7]	Germany/2000	University hospital (9 beds)	Prospective	N = 379 patients Mean age 50.8 (17-88) Males 6.7%	Stimulated spontaneous reporting and screening criteria (lab data)	11.8% of patients with ADEs
Suh et al. [8]	USA/2000	University hospital	Retrospective	N = 9,311 hospitalizations	Spontaneous reporting and review of patient charts	1.6% of hospitalizations with ADEs *
Senst et al. [9]	USA/2001	1 University hospital; 3 hospitals (mental health and pediatrics)	Retrospective	N = 3,187 hospitalizations	Screening criterion (medication, lab data, and combination of data), review of pharmaceutical and medical records and patient chart sample	4.2 ADEs per 100 hospitalizations **
Baune et al. [10]	France/2003	NS	Cross-sectional	N = 902 patients Mean age 61years Males 48.8%	Staff survey	6.3% (4.7%-7.9%) of patients with ADEs
Ramesh et al. [11]	India/2003	NS	Prospective	N = 3,717 patients Age: children 22.8%, adults 44.3%, elderly 32.9%	Spontaneous reporting and stimulated by pharmacist	3.7% of patients with ADEs **
Dormann et al. [12]	Germany/2004	University hospital	Prospective	N = 630 patients; 844 hospitalizations Median age 57 (18-97)	Patient monitoring with patient chart review (signs and symptoms, lab data)	15.2% of hospitalizations with ADEs; 23.3 ADEs per 100 hospitalizations
Forster et al. [13]	Canada/2004	Academic hospital (30 beds)	Prospective	N = 543 patient-days	Patient monitoring: staff interview, patient chart review, screening criteria, and review of spontaneous reporting of errors	4.4 ADEs per 100 patient-days
Corral Baena [14]	Spain/2004	NS	Retrospective	N = 32,253 discharges	Secondary database of discharge forms – use of ICD-9 with patient chart review	2.15% of discharge forms with ADEs ***
Weingart et al. [15]	USA/2004	Teaching hospital (40 beds)	Prospective	N = 209 patients	Spontaneous reporting, review of intervention of pharmacists staff, reports with confidential staff interviews, screening criteria	5.3% of patients with ADEs; 7.7% of patients with "close calls"

(continues)

Table 1 (continued)

Reference	Country/Year	Hospital's characteristic	Design	Population's characteristics	Techniques for identification of ADEs	Frequency
Nebeker et al. [16]	USA/2005	Teaching hospital, tertiary	Prospective	N = 937 hospitalizations; 6,856 patient-days	Patient monitoring: review of notes, prescription, results of lab tests, and discharge summary	70 ADEs per 1,000 patient-days; 52 ADEs per 100 hospitalizations; 25% of patients with ADEs
Al-Tajir & Kelly [17]	United Arab Emirates/2005	Tertiary hospital	Prospective	N = 5,235 hospitalizations; 37,360 patient-days	Spontaneous reporting Monitoring: lab data, nursing notes, patient chart review, and spontaneous reporting	0.07ADEs per 100 patient-days (spontaneous reporting) ***; 3.59 ADEs per 100 patient-days (monitoring) ***
Cohen et al. [18]	USA/2005	Community hospital	Retrospective	N = 120 patient charts (baseline), 90 patient charts (transition), and 370 patient charts (post-intervention)	Screening criteria	Baseline: median 5.07 (3.79-6.02) ADEs per 1,000 patient-days *** Transition: median 3.19 (0.58-5.03) ADEs per 1,000 patient-days *** Post-intervention: median 1.30 (0.87-1.71) ADEs per 1,000 patient-days ***
Mycyk et al. [19]	USA/2005	Academic hospital, tertiary	Retrospective	N = 150,973 patient-days # (pre-intervention), 160,748 patient-days # (post-intervention)	Electronic database: screening criteria (medication and lab results), spontaneous reporting and patient chart review	Pre-intervention: 1.3 ADEs per 1,000 patient-days *** Post-intervention: 1.1 ADEs per 1,000 patient-days ***
Camargo et al. [20]	Brazil/2006	University hospital	Prospective	N = 333 patients; 335 hospitalizations Mean age 52.3 (SD = 17.85) Males 45.1%	Intensive monitoring: use of patient chart as source of information	25.9% (21.0%-30.7%) of patients with ADEs ##
Otero-Lopez et al. [21]	Spain/2006	University hospital	Prospective ###	N = 2,643 patients Mean age 71.7 (18-93)	Discharge forms: use of ICD-9 in secondary diagnosis and review of clinical history. Stimulated reporting	7.2% (6.2%-8.2%) of patients with ADEs
Kilbridge et al. [22]	USA/2006	1 community and 1 university hospital	Retrospective	N = 25,177 hospitalizations (university hospital), 8,029 hospitalizations (community hospital)	Electronic database: screening criteria	University hospital: 4.4 ADEs per 100 hospitalizations *** Community hospital: 6.2 ADEs per 100 hospitalizations ***
Bond & Raehl [23]	USA/2006	3,328 hospitals	Retrospective	N = 8,067,562 hospitalizations	Secondary database of discharge forms: use of ICD-9	1.7% of hospitalizations with ADEs ***
Hougland et al. [24]	USA/2006	41 acute care hospitals	Retrospective	N = 1,961 patient charts	Discharge forms: use of ICD-9-CM in secondary diagnosis and E-code with patient chart review	3.6 ADEs per 100 patient charts §
Lugardon et al. [25]	France/2006	Teaching hospital	Retrospective	N = 27,426 patients; 39,441 hospitalizations	Spontaneous reporting and secondary database of discharge forms: use of ICD-10; capture/ recapture	2.9% (2.3%-3.5%) of ADEs in patients ***; 2% (1.6%-2.4%) of ADEs in hospitalizations ***

(continues)

Table 1 (continued)

Reference	Country/Year	Hospital's characteristic	Design	Population's characteristics	Techniques for identification of ADEs	Frequency
Davies et al. [26]	England/2006	University hospital	Prospective	N = 125 patients Median age (patients with ADEs) 69.5 (52-79); median (patients without ADEs) 61 (45-78) Males 51.2%	Pharmaceutical visit: screening criteria (medication), spontaneous reporting and evaluation of new symptoms	19.2% (12%-26%) of patients with ADEs
Tribino et al. [27]	Colombia/2006	University hospital, tertiary (42 beds)	Prospective	N = 836 patients Mean age 58.9 (SD 0.67) Males 54%	Spontaneous reporting and review of clinical history (signs and symptoms, physical examination, and patient interview, confirmed by clinician)	25.1% of patients with ADEs; 32 ADEs per 100 patients
Schade et al. [28]	USA/2006	Rural acute care hospital	Retrospective	N = 3,572 discharges Age > 18 years	Screening criterion (rescue drugs)	1.73% of discharges with ADEs §§
Rozenfeld [29]	Brazil/2007	Hospitals accredited by SUS in Rio de Janeiro	Retrospective	N = 1,898,676 discharges Age ≥ 20 years	Secondary database of discharge forms: use of ICD-10	1.8 cases per 1,000 hospitalizations ***
Sanchez-Muñoz, et al. [30]	Spain/2007	NS	Retrospective	N = 3,983 patients	Secondary database of discharge forms: use of ICD-9 with patient chart review	2.2% of patients with ADEs
Hwang et al. [31]	South Korea/2008	Teaching hospital, tertiary	Retrospective	N = 598 patients; 6,578 patient-days	Screening criteria with patient chart reviews	31.3% ADEs in patients ***; 28.4 ADEs per 1,000 patient-days ***
Pourseyed et al. [32]	Iran/2009	General hospital (35 beds)	Prospective	N =400 patients; 3,276 patient-days Mean age 60.41 (SD 16.97) Males 50.8%	Intensive monitoring: daily patient follow-up until discharge	10% of patients with ADEs
Davis et al. [33]	England/2009	University hospital	Prospective	N = 3,322 patients; 3,695 hospitalizations	Pharmaceutical visit: patient chart review, medical and nursing notes, lab data, and direct information from staff and patient	15.8% of patients with ADEs; 14.7% (13.3%-15.9%) of hospitalizations with ADEs

ICD-9: International Classification of Diseases – 9th revision; ICD-9-CM: International Classification of Diseases – 9th revision, clinically modified; ICD-10: International Classification of Diseases – 10th revision; SD: standard deviation; NS: not specified; SUS: Unified National Health System (Brazil).

* Rate of patients with events was calculated by dividing the number of patients with ADEs by the number of hospitalizations;

** Rate includes pediatric patients;

*** Does not distinguish between events that occurred before or during hospitalization;

Number of patient-days was calculated by multiplying the ADE rate by the number of events;

Event occurred before or during the hospitalization;

Prospective approaches retrieved 182 events and retrospective approaches 9 events. Eight events were retrieved by both approaches;

§ Rate was calculated by dividing the number of events by the number of patient charts reviewed;

§§ Frequency of discharges with ADEs was calculated by dividing the number of discharges with at least one ADE by the number of discharges.

As for the estimates of frequency of events, the indicators varied. In addition, ten studies [14,17,18,19,20,22,23,25,29,31] did not present estimates that differentiated between events leading to hospital admission and those that occurred before or during hospitalization. One study [29] called attention to the fact that such differentiation was impossible, due to the method used to identify events. Table 2 lists the studies that focused on events that occurred during hospitalization, with the respective frequency estimates. The events estimator is the proportion of patients or hospitalizations with ADEs. Readmissions were considered independent events, based on Dormann et al. [12], whose findings showed that the occurrence of an adverse drug event in one hospitalization is not a predictive factor for readmission. Another estimator is the rate of events per 100

Table 2

Characteristics of studies that evaluated adverse drug events (ADEs) that occurred exclusively during stay in general hospitals.

Reference/Year	Techniques for identification of ADEs	Proportion of patients or hospitalizations (%)	ADEs/100 patients or hospitalizations	ADEs/100 patient-days	Severity	Avoidability
Lagnaoui et al. [34]/2000	Physician and pharmacist visit	4.7	10.1	5.9	Serious 7.7%	Avoidable 50%
Fattinger et al. [6]/2000	Monitoring using electronic database: drugs, clinical events, lab results, ICD-10, and evaluation by clinician	41.4	NS	NS	NS	NS
Dormann et al. [7]/2000	Stimulated spontaneous reporting and screening criteria (lab data)	11.8	12.1	NS	Mild 48%; moderate 46%; serious 6%	NS
Suh et al. [8]/2000	Spontaneous reporting and patient chart review	1.6	NS	NS	Mild 30%; moderate 53%; serious 17%	NS
Senst et al. [9]/2001	Screening criterion (medication, lab data, and combination of data), review of pharmaceutical and medical records, and review of sample of patient charts	NS	4.2	NS	Significant 36%; serious 45%; life-threatening 36%	Avoidable 14.8%
Baune et al. [10]/2003	Staff interview	6.3	NS	NS	Serious or severe 73%	Avoidable 25%
Ramesh et al. [11]/2003	Spontaneous reporting, and stimulated by pharmacist	3.7	NS	NS	NS	NS
Dormann et al. [12]/2004	Patient monitoring and patient chart review (signs and symptoms, lab data)	15.2	23.3	NS	NS	NS
Forster et al. [13]/2004	Patient monitoring: staff interview, patient chart review, screening criteria, and review of spontaneous reporting of errors	NS	NS	4.4	Significant 42%; serious 46%; life-threatening 13%	Avoidable 2.6 ADEs/100 patient-days
Weingart et al. [15]/2004	Spontaneous reporting, review of intervention of pharmacists staff, reports with confidential staff interviews, screening criteria	5.3	NS	NS	Significant 54.5%; serious 27.3%; life-threatening 18.2%	Probably avoidable 27.3%
Nebeker et al. [16]/2005	Patient monitoring: review of notes, prescription, results of lab tests, and discharge summary	25.7	51.5	7.0	Moderate 91%; serious 9%; level E 87% *; level F 4% *; level G < 1% *; level H 3% *; level I 6% *	NS
Otero-Lopez et al. [21]/2006	Discharge forms: use of ICD-9 in secondary diagnosis and review of clinical history. Stimulated reporting	7.2	NS	NS	Mild 63.3%; moderate 30.4%; serious 6.3%	Avoidable 19.9%
Hougland et al. [24]/2006	Discharge forms: use of ICD-9-CM in secondary diagnosis and E-code with patient chart reviews	NS	3.6	NS	NS	NS
Davies et al. [26]/2006	Screening criteria (medication), spontaneous reporting and evaluation of new symptoms	19.2	NS	NS	Level 3 66.6% **; level 4 26% **; level 7a 7.4% **	Possible avoidable 48%; definitely avoidable 11%

(continues)

Table 2 (continued)

Reference/Year	Techniques for identification of ADEs	Proportion of patients or hospitalizations (%)	ADEs/100 patients or hospitalizations	ADEs/100 patient-days	Severity	Avoidability
Tribino et al. [27]/2006	Spontaneous reporting and review of clinical history (signs and symptoms, physical examination, and patient interview, confirmed by clinician)	25.1	32.1	NS	Mild 13.4%; moderate 81.3%; serious 4.1%; fatal 1.1%	NS
Schade et al. [28]/2006	Screening criterion (rescue drugs)	NS	1.7	NS	NS	Avoidable 25.8%
Sanchez-Muñoz et al. [30]/2007	Secondary database of discharge forms: use of ICD-9 with patient chart review	2.2	NS	NS	Mild 38.6%; moderate 58%; serious 3.4%	Avoidable 52.1%
Pourseyed et al. [32]/2008	Intensive monitoring: daily patient follow-up until discharge	10%	NS	NS	NS	NS
Davies et al. [33]/2009	Pharmaceutical visit: patient chart review, medical and nursing notes, lab data, and direct information from staff and patient	15.8	NS	NS	Level 1 0.1% **; level 2 20.6% **; level 3 56.3% **; level 4 20.7% **; level 5 0.1% **; level 7a 1.9% **; level 7b 0.1% **	Possibly avoidable 46.9%; definitely avoidable 6.4%

ICD-9: International Classification of Diseases – 9th revision; ICD-9-CM: International Classification of Diseases – 9th revision, clinically modified; ICD-10: International Classification of Diseases – 10th revision; NS: not specified.

* The severity of the event increases from level E to I, where level I is the patient's death;

** The severity of the event increases from level 1 to 7b, where events classified as 7b are those directly related to the patient's death.

patients or admissions, or the rate of events per 100 patient-days.

The proportion of patients or admissions with ADEs during hospitalization (Table 2) varied from 1.6 to 41.4%, and the rates ranged from 1.7 to 51.5 events per 100 hospitalizations and from 4.4 to 7.0 events per 100 patient-days.

Of the 19 studies, 68.4% (13/19) [7,8,9,10,13,15,16,21,26,27,30,33,34] classified the events according to severity. There was a predominance of less serious events, mostly classified as mild or moderate (more than 80% of total), regardless of the classification used for severity. Fifty-three per cent of the studies (10/19) [9,10,13,15,21,26,28,30,33,34] assessed avoidability. Events were considered avoidable when the authors classified them as avoidable or possibly, definitely, or probably avoidable. The frequency of these events varied from 14.8% to 59%.

As for the drug classes involved, only eight studies (8/19) [6,7,8,9,16,21,27,30] conducted this analysis. Of the five classes most commonly involved, anti-infective agents were the most frequent, with 8 to 39% of the reported events. Another class that called attention was cardiovascular agents, related to 25.3% of the events. Antineoplastics agents were among the five drug classes most frequently related to ADEs and can be attributable in up to 30.7% of events.

Discussion

The estimates found in the studies show that medicines used during hospitalization can frequently lead to ADEs, and that a considerable proportion of such events are avoidable.

Variability of studies and the impact on estimates

This systematic literature review included studies that evaluated ADEs occurring during hospitalization, excluding studies that only used spontaneous reporting as the method for identifying ADEs, in addition to a series of other factors in order to allow analysis of homogeneous studies. Even so, there was a wide range in the frequency of events, which could be explained by the numerous factors related to the studies' characteristics, despite the similar profile of hospitals, patients, medicines prescribed, and disease severity.

The variability hindered obtaining a summary measure for frequency of ADEs. In addition, nine studies did not differentiate between events that occurred during hospitalization and those occurring prior to it. The disease conditions, drug use pattern, and type of care in and out of hospital differed considerable, which made it impossible to consider events that occurred before or during hospitalization in the same group. Even among the studies that only evaluate events that occur during hospitalization, three distinct event estimators were identified, thus hindering comparison of the studies.

Concepts and definitions

The definitions used to characterize drug-related harm varied, thus impacting measurement and hamper comparisons between studies. Rissato et al. [35] discuss the need for standardized terminology in their review of terms and concepts used to characterize the harm caused to patients by medicines. Obviously, although the definitions vary widely, they have in common their central focus on drug-related harm.

Historically, in 1966 the World Health Organization (WHO) defined the term "adverse drug reaction" any response to a drug which is noxious, unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease. In 1972, WHO added the phrase "or for modification of physiological function" to the end of this definition. The two definitions were used by 37.9% (11/29) of the studies [7,8,10,11,12,17,18,20,25,27,32].

Seven studies used the term "adverse drug event" [9,14,19,21,23,30,31], while two used "adverse drug reaction" [26,33], based on the concept of harm caused to the patient due to use of the drug in the therapeutic context, while four [9,14,21,30] defined the event as any injury, large or small, caused by the therapeutic use (including non-use) of a drug. Non-use involves other situations, namely, problems with access to the drug, adherence, or the fact that the drug was not prescribed, although necessary.

Six studies [13,15,16,28,29,34] presented a broader definition of ADEs, including in their context the harm caused to patients by non-therapeutic use of the drug. Two of these studies used the term adverse drug event [22,24] and one used adverse drug reaction [6], but without defining them.

Neither the terminology nor the concepts were homogeneous across the studies. Sixteen studies used the term adverse drug event, of which two used the WHO definition for adverse drug reaction [17,18]. Nine studies used the term adverse drug reaction, and one [29] used the term injury, including cases of self-inflicted lesions and poisonings.

According to Rissato et al. [35], the lack of standardization in the concepts and terms allows confusing the notion of adverse drug reaction with other types of events that occur under distinct circumstances from those in which use of the drug occurs at the normally recommended doses.

Three studies [9,13,15] defined and evaluated potential ADEs, considering errors that could have led to harm but were avoided by interception or chance. Detection of such cases is important, because the triggering mechanism is frequently similar to that of the incidents that lead to harm [36] and is thus related to weaknesses in the quality of prescribing and dispensing process.

Identification technique

One factor that appears to directly impact the estimates is the technique used to capture the events. Al-Tajir & Kelly [17] demonstrated the complementary nature of the techniques used to identify events, as did Otero-Lopez et al. [21]. Sixteen studies (55.2%) used a combination of strategies to identify events.

Studies that used the International Classification of Diseases (ICD) to capture events from information contained in secondary databases showed the lowest frequencies of events, 2.2% [30] and 1.8 per 1,000 hospitalizations [29].

Four studies identified the codes related to the events using information from secondary databases. These databases contain a considerable volume of data that are easy to access electronically, with a wide coverage. This technique thus proved more useful for detecting events that led to the hospital admission as compared to those that occurred during the hospital stay [14,30].

The most widely used techniques to identify adverse drug events was monitoring by screening criteria. This technique is based on the hypothesis that the occurrence of criteria is closely related to the harm [37]. Data are collected with the aid of screening criteria that can be automated, with the screening performed electronically [19,22]. The screening criteria are used as filters for a preliminary analysis of the information recorded on the patient, thereby providing a more objective and viable alternative to traditional patient chart reviews.

Causality

Another factor that can impact estimates of ADEs is the way the association between the drug's use and patient harm is measured. Cause-effect di-

agnosis for ADEs is a complex issue. Most events are nonspecific and can be confused with clinical manifestations of the disease under treatment [38]. Algorithms and decision tables, when adequately applied, allow greater objectivity in establishing the causal relationship.

Eleven studies did not use scales or algorithms to assess causality [9,14,15,18,23,24,25,28,29,30,34]. The others used five distinct classifications. Among the most widely used strategies are the Naranjo algorithm, the Karch & Lasagna criteria, and the WHO criteria. In relation to the diversity of strategies for determining causality, Thürmann [39] reports that distinct algorithms and the way they are applied are the main sources of discrepancies between studies.

This fact can be observed in the current review. Even the ten studies that used the Naranjo algorithm did not use its proposed categories (definite, probable, possible, or doubtful) in the same way. Thus, six studies [7,12,20,26,27,33] only included definite, probable, and possible events. One study [22] only considered definite and probable events. Another [17] considered definite, probable, possible, and doubtful events, thereby overestimating ADEs as compared to the other studies. Two studies [8,19] failed to specify the categories they included.

Although algorithms may allow greater objectivity in assessing the causal relationship between use of medicines and adverse effects, some clinical judgment persists, for example, when the algorithm involves the following question: are there alternative causes (other than the medication) which could cause the effects by themselves? Reliability studies could provide useful information on the measures' robustness, indicating to what extent repeated evaluations of the same patient chart (or clinical case) would produce the same results. However, none of the studies identified here examined this issue.

Characteristics of the study population

Although population differences could explain the variability in the frequency of ADEs, the selected studies mainly focused on overall estimates rather than associations between the events and the populations' characteristics. Still, some studies demonstrated that certain more susceptible age brackets [40,41,42] and female gender could be risk factors for ADEs [43].

Characterization of the populations in terms of race and socioeconomic status was virtually nonexistent in the studies. Physicians' perceptions of patients can vary systematically according to the patient's race, socioeconomic status, and other demographic characteristics, and this difference in perception can influence the treatment options for patients and thus their quality of care [44]. Extrapolating these findings to studies on adverse drug events raises the hypothesis that race and socioeconomic status could influence the degree of susceptibility to the occurrence of avoidable events, since these characteristics could impact the quality of care provided.

Furthermore, in a systematic review, MacDowell et al. [45] demonstrated that different ethnic groups display distinct risks for developing adverse drug reactions in cardiovascular diseases. For example, black patients present a relative risk of 1.5 (95%CI: 1.2-1.9) of intracranial hemorrhage triggered by antithrombotics, when compared to non-black patients.

Other possible predictive factors for the variability in estimates, like diagnoses, prescription pattern, and number of drugs used, could not be considered in the analysis, since they were not reported homogeneously and constantly.

Characteristics of events during hospitalization

The review covered information on severity, avoidability, and the drugs attributable in adverse events that occurred during hospitalization.

The proportion of avoidable events varied from 14.8% to 59%. Despite the variability, avoidable events accounted for an important share of the total, and better knowledge of them could help develop preventive strategies and improve the quality of patient care.

As for the drugs involved, the most frequently reported classes were anti-infective, cardiovascular, and antineoplastics agents. Importantly, three drug groups alone may account for more than 50% of the adverse events, thus potentially signaling a field for intervention and prevention of ADEs.

Study limitations

This study's findings should be interpreted with its limitations in mind. First, the articles included in the review were mainly retrieved through a search in the MEDLINE database, which includes more American than European journals. This could explain the larger number of studies performed in the United States; on the other hand, the United States is obviously one of the pioneers in research on ADEs. Secondly, we did not conduct any article search in the gray literature or address any direct requests to authors for unpublished data.

As for the review's external validity, we focused on studies in general hospitals and high-complexity hospitals, 61.5% of which were university, academic, or teaching institutions. Since the nature of the clientele affects the prescription patterns and thus the frequency of events, high-complexity hospitals could increase the risk of ADEs.

Final remarks

Adverse drug events in inpatients are not unpredictable or incomprehensible accidents, but events that should be monitored and followed in order to understand where and why they occur. The literature is extensive, but highly diversified as to concepts, objectives, methods, and techniques. Estimates of frequency vary widely, thereby demanding additional effort at in-depth and critical analysis.

The fact that a considerable share of the events are classified as avoidable and mostly related to a limited set of drug classes emphasizes importance of hospitals knowing the pattern of events that occur during hospitalization in order to orient preventive strategies.

There is an evident need for standardization of concepts and definitions for describing the harm caused by the use of medicines, as well as for the development of study protocols for ADEs. Standardized approaches would allow comparison of indicators from different hospitals and improve our understanding of the magnitude of the problem.

Resumo

O objetivo foi avaliar estudos sobre a ocorrência de eventos adversos a medicamentos (EAM) em hospitais para conhecer as suas freqüências e características, comparando os métodos de identificação e as definições utilizadas para caracterizá-los. A busca foi realizada no MEDLINE e identificou estudos publicados entre 2000 e 2009. Os critérios de inclusão foram estudos em população não selecionada por patologias ou medicamentos específicos e os EAM ocorridos durante a internação. Foram selecionados 29 estudos e encontradas múltiplas fontes de heterogeneidade entre eles, incluindo diferenças nas populações estudadas, nas técnicas de vigilância, nas definições de EAM e nos indicadores. A freqüência de pacientes com EAM está entre 1,6% e 41,4% dos pacientes internados e as taxas entre 1,7 e 51,8 eventos/100 internações. Uma parte considerável desses eventos poderia ter sido evitada. Os resultados mostram que EAM em pacientes internados são um problema de saúde pública. Entretanto, são necessários novos estudos de monitoramento desses eventos adversos para a efetiva promoção do uso seguro dos medicamentos.

Monitoramento de Medicamentos; Quimioterapia; Farmacoepidemiologia

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