THE PREVALENCE OF MEDICATION RELATED ADVERSE EVENTS IN INPATIENTS – A SYSTEMATIC REVIEW AND META-ANALYSIS

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1. ABSTRACT

Purpose: Adverse drug events (ADEs) have been internationally recognized as a major threat to patient safety. The purpose of this study was to conduct a meta-analysis focusing on inpatient ADEs in the Western World to provide better estimate of the current state of medication safety in these countries.

Methods: The studies for meta-analysis were identified through electronic search in Cochrane, Scopus, Medline and Web of science databases. Included articles focused on adult inpatient ADEs, had commonly accepted definition for ADE and were conducted between 2000 and 2016. Disease or ADE specific studies were excluded. Meta-analysis was conducted on the prevalence of inpatient ADEs and fatal adverse drug reactions (FADRs).

Results: The pooled estimate of the prevalence of inpatient ADEs was formed by 46 626 patient records included in 9 articles. Inpatient ADE prevalence was 19% and 32.3% of these ADEs were assessed preventable (MD 28.6%, SD 22.6%). Three articles including 3385 patients focused on inpatient FADRs, but the pooled estimate of this was disregarded due to low number and high heterogeneity of the included studies.

Conclusions: ADEs are estimated to affect 19% of inpatients during hospitalization. Most of the ADEs are moderate in severity causing no permanent harm to the patient. Only a small amount of ADEs cause inpatient deaths, but in this meta-analysis, however, we were unable to give direct estimate of the prevalence.

2. KEYWORDS

Adverse drug events, Drug safety, Clinical pharmacology, Pharmacoepidemiology

3. INTRODUCTION

Hospital-acquired adverse drug events (inpatient ADEs) have been a target of vast research during the past years [1-2]. It has been widely recognized that ADEs pose a major threat to patient safety increasing both patient morbidity and mortality [3]. In addition to health concerns, the economic burden related to ADEs has also gained much attention; it has been estimated, that the costs of ADEs exceed the cost of medications in certain countries [4]. In the United States it has been estimated that

ADEs cause $1.56 billion in direct costs and $136.8 billion in indirect costs in addition to being between the fourth and sixth leading causes of death amounting to 106 000 deaths annually [5-6].

The recent reviews focusing on hospital inpatient ADEs have all included articles from developing countries or have ruled out parts of the Western World. However, there are several differences in medical care between the developed and developing countries, e.g. in terms of access to innovative drugs. Furthermore, there are major differences in the structures of public and private health care highlighting the need to analyze medication related patient safety of these countries separately. While 40-50 novel drug agents are authorized by the FDA and EMA annually, the need for up-to-date analysis of ADEs in the Western countries is obvious.

The purpose of this review is to provide up-to-date information on inpatient ADEs in the Western World from 2000 to 2016, to determine a new reliable estimate of the total number of inpatient ADEs, and to evaluate the amount of fatal ADEs among inpatients during hospital treatment. The main objective is to provide information on the frequency and type of ADEs, as well as drugs most frequently involved with them.

4. METHODS

4.1 Data sources

This systematic review and meta-analysis was carried out according to the recommendations by the PRISMA statement. An electronic search was conducted between January 2000 and November 2016 from four databases (Cochrane database, MEDLINE, Web of Science, and Scopus). The search terms consisted of commonly used terminology on AEs (Online Resource 1). Where applicable, the reference lists of relevant studies were also manually cross-checked for identifying additional articles. The search was limited to studies written in English.

4.2 Study selection

After the removal of duplicates and clearly unsuitable studies according to the title, the selected articles were independently assessed for final inclusion by two researchers (OL and MT) according to predefined inclusion criteria. In this review ADE was defined as an injury resulting from medical intervention related to a drug [7]. Accordingly, ADEs can occur as untoward injuries or symptoms resulting from appropriate or inappropriate medication use and unintentional errors [8-10]. ADEs

therefore include both direct reactions (ADRs) and indirect events (MRAEs). Inpatient ADE was defined as an adverse drug event occurring in inpatient during hospital stay.

For inclusion in this review, studies had to use commonly accepted definition for the studied ADE or ADR (e.g. similar to WHO) or otherwise indicate (e.g. case examples) that the definition used coincides with general definition of ADE or ADR. Studies also had to report the frequency of ADEs or ADRs occurring in adult inpatients during hospital stay. Finally, studies had to be written in English and conducted during the selected time period in the Western World (Europe, North-America, Australia, New Zealand). Only original studies were included in this review.

Studies were excluded if they focused on a specific ADE or ADRs related to a specific drug. Studies identifying ADEs or ADRs exclusively through International Classification Disease codes (ICD-9 or ICD-10) were excluded as most ADEs and ADRs are known to stay undetected by this method. Furthermore, studies that focused on a specific age group or studies in which primary objective was not ADE or ADR identification were excluded.

4.3. Data extraction

From the included articles information on study design, data collection period, population characteristics as well as studied ADE or ADR and its definition was collected. One researcher (OL) extracted all data after which second reviewer (MT) independently assessed the accuracy of the data extract. Any disagreements were solved by consensus. Complementary information was requested from Hoonhout et al. (2011) concerning the amount of adult patients in their study. The authors estimated that the amount of adult patients was 98.8% of the total patient population which was then used in this review.

The number of ADEs or ADRs presented in the results in this review represent the sum of definite, probable, or possible identified ADEs or ADRs, as reported in the original studies. If the percentages of patients with ADEs or ADRs were not directly reported in the original studies, they were calculated by dividing the amount of AEs by the number of admissions or individual patients, which was then multiplied by 100 giving the frequency of ADEs or ADRs per patient or per 100 admissions. In independent articles sample size was described as number of admissions, patients, or patient records reviewed. It was not clear whether patient records referred to single admissions or single patients, and they were therefore not converted to either one for the final analysis.

4.4. Risk of bias

Two reviewers (OL and MT) assessed the quality of each included study during data extraction according to the predefined quality criteria (Online Resource 2). To minimize inconsistencies we required a generally approved definition for ADE or ADR (clear definition or case examples), and a distinctly described method for causality assessment in addition to more inclusive data sources than spontaneous reports or ICD-10 codes exclusively.

4.5. Statistical analyses

The results of the studies are presented with pooled descriptive statistics, i.e. mean (standard deviation, SD) values and medians of preventability and severity of ADEs or ADRs. For prevalence of inpatient ADEs and deaths due to ADRs, meta-analyses were performed using random effects model in STATA software version 13.1. The random effects model was selected due to the significant deviation in the results of independent articles. The meta-analyses were performed only on the prevalence of inpatient ADEs and deaths due to inpatient ADRs. The results are presented using forest plots. Heterogeneity was explored using I^2 statistics. Heterogeneity is described in percentages from 0-100%, where 0% indicates no heterogeneity and increasing percentage indicates increasing heterogeneity [11]. The statistical significance of I^2 was tested with Chi square test. P-value level < 0.05 was set as the level of statistical significance.

5. RESULTS

A total of 1611 citations were found from the electronic database search (fig. 1). After removal of duplicate records 1241 articles remained for the evaluation for inclusion according to the predefined criteria. The same criteria were used for the evaluation of the remaining 270 full text articles. The majority of exclusions were made due to studies not focusing on the prevalence of ADEs or ADRs, or because they were conducted outside the Western World. Finally, 14 articles were included in this review[12-25]. Of these articles, 12 were included in the meta-analysis [12-15, 18-25]. Nine of the articles focused on inpatient ADEs, 2 on inpatient ADRs and 3 on ADRs causing inpatient deaths (Fatal ADRs or FADRs).

5.1. Study characteristics

All included articles reported the incidence of ADEs, ADRs, or FADRs in patients during hospital admission. Of the articles reporting inpatient ADEs or ADRs, six were conducted in Europe, four in the United States, and one in New Zealand. All of the articles reporting FADRs were conducted in Europe. The data in these articles was collected between 2000 and 2011 and they focused on adults of all ages. Global Trigger Tool (GTT) was used as the ADE identification method in six studies. In each of these studies ADEs were reviewed by a panel of experts after GTT identification to determine whether or not drug related ADE had occurred. Study characteristics are presented more specifically in tables 1 and 2.

5.2. Severity and type of inpatient ADEs, ADRs, and FADRs

The severity of the reported inpatient ADEs and ADRs was regrouped into 4 categories; minor, moderate, severe, and life-threatening or fatal (table 1). Minor ADEs or ADRs included events where no harm was caused to the patient and therefore no intervention was necessary (e.g. Hartwig scale 1, NCCMERP scale A-D). In moderate ADEs or ADRs no permanent harm was caused to the patient but some intervention was required (e.g. Hartwig scale 2-3, NCCMERP E). In severe ADEs or ADRs patient suffered significant, immediate intervention was required, and the event prolonged the length of hospital stay (e.g. Hartwig scale 4-6, NCCMERP F-H). Life-threatening or fatal ADEs or ADRs either required intensive care or resulted in patient death (e.g. Hartwig scale 7a-7b, NCCMERP I). Six studies reported the severity of inpatient ADEs [12, 14, 15, 18, 21, 23]. Minor inpatient ADEs were detected in only one of these studies (71.1%). The mean number of moderate inpatient ADEs was 56.9% (MD 63.5, SD 25.2), severe ADEs 27.7% (MD 28.9, SD 15.1), and life-threatening or fatal ADEs 3.7% (MD 2.0, SD 4.9). Two studies reported the severity of inpatient ADRs. The mean numbers of the detected severities were 4.4%, 75.0%, 18.9%, and 1.8% for minor, moderate, severe, and life-threatening or fatal reactions, respectively [16,17].

The most common inpatient ADEs included dizziness, sedation, delirium (CNS events), electrolyte disturbances (renal dysfunction), hypo- and hyperglycemia (endocrine disorders), constipation (GI events) and bleeding (hematological events) (figure 2). Only one study had quantitative data on inpatient ADRs, with most common ADRs being GI events (diarrhea, nausea), hematological events (bleeding), skin reactions (rash, thrush), and CNS events (sedation, altered mental status) [17]. The most frequent FADRs were hematological events, renal dysfunction and cardiovascular events including intracranial bleeding, bleeding in GI tract, acute renal dysfunction, and arrhythmias, respectively.

5.3. Drugs involved in inpatient ADEs, ADRs, and FADRs

Of the 11 articles studying inpatient ADEs and ADRs, six reported the drugs involved in ADEs and two reported the drugs involved in inpatient ADRs [12, 14-17, 21, 22, 25]. All three articles focusing on inpatient death due to ADR reported drugs involved in the fatal ADRs (FADRs). The drugs involved in inpatient ADEs, ADRs, and FADRs are presented in figure 3 according to the Anatomical Therapeutic Chemical (ATC) classification.

When the ATC main codes were broken down into more specific classes, the drugs most frequently involved in inpatient ADEs were opioids (morphine, tramadol, oxycodone, codeine), antipsychotics (olanzapine, risperidone, haloperidol), and sedatives (clonazepam, lorazepam, zolpidem) from ATC class N, diuretics (furosemide), beta-blockers and antiarrythmics from ATC class C, anticoagulants and antiplatelet drugs (warfarin, acetylsalicylic acid, heparin, low molecular weight heparin) from ATC class B, and per oral and intravenous antibiotics (ceftriaxone, piperacillin/tazobactam, vancomycin, amoxicillin/clavulanic acid, fluoroquinolones) from the ATC class J. Similarly the drugs most involved in inpatient ADRs were from the ATC classes N, J, and B (morphine, tramadol, codeine, amoxicillin, levofloxacin, ceftriaxone, cefuroxime, warfarin, and low molecular weight heparins, respectively). The most common drugs of the three ATC classes most frequently involved in FADRs were antithrombotic and anticoagulant drugs (warfarin, low molecular weight heparins, clopidrogrel, acetylsalicylic acid) from ATC class B, opiates, antipsychotics and sedatives (olanzapine, clozapine, haloperidol, benzodiazepines) from ATC class N, and antineoplastics and immunosuppressants (rituximab, corticosteroids) from ATC class L.

5.4. Factors associated with inpatient ADEs, ADRs, and FADRs

Seven articles focusing on the prevalence of inpatient ADEs or ADRs reported factors associated with higher risk of experiencing an ADE or ADR during hospital stay [12, 14-17, 23, 25]. In four articles, a positive correlation was found between inpatient ADEs and increased length of stay (LOS), three articles reported positive correlation between ADEs and higher age, and in two articles polypharmacy, multimorbidity and cardiovascular comorbidities were found to increase the risk of inpatient ADEs. Other associated factors were vascular surgery, female gender, Caucasian race, decreased renal status, and any interaction in current medication. LOS, polypharmacy, higher age,

female gender, decreased renal status, and any interaction in current medication were also reported to increase the risk for inpatient ADR in two articles.

Two of the three studies reporting inpatient deaths due to ADRs reported factors associated with increased risk of FADRs [20, 24]. Both studies found a positive correlation between polypharmacy and FADRs. Other factors associated in these studies were multimorbidity and presence of NSAID or antiaggregants together or alone in patients' medication.

5.5. Meta-analysis of the prevalence of inpatient ADEs and FADRs

A total of 9 articles encompassing 46 626 patient visits to hospitals reported the prevalence of ADEs in inpatients. The mean prevalence of all inpatient ADEs was 21.6% (MD 19.7, SD 16.7) where the smallest prevalence was 1.9% and the highest 57.9%. The mean prevalence of preventable ADEs was 32.3% (MD 28.6, SD 22.6). The preventability reported by independent articles varied from 12.0% to 75.0%. Two articles encompassing 3727 patients reported the prevalence of inpatient ADRs with mean value of 23.4% (SD 10.8). Only one of these articles reported the amount of preventable ADRs (53.3%) [16].The three articles focusing on FADRs encompassed a total of 3385 patients. The mean prevalence of inpatient FADRs was 9.6% (SD 7.7) with the smallest prevalence being 4.5% and the largest 18.4%.

The pooled estimate of the prevalence of inpatient ADEs was 19% (95% CI 16 - 23%) (fig 4). There was, however, significant heterogeneity in the results of the articles (I^2 = 99.49%). The pooled estimate of FADRs was 10% (95% CI 1 – 19%) similarly with significant heterogeneity in the results of independent articles (I^2 = 98.65%) (Online Resource 3). This estimate was, however, overlooked due to considerably small number of studies included.

6. DISCUSSION

6.1. Main findings

We identified 9 articles reporting the frequency of ADEs during hospital stay and 3 articles reporting the number of inpatient FADRs. The estimate of the overall frequency of inpatient ADEs was 19% in this meta-analysis. The estimate of the prevalence of FADRs was overlooked due to high heterogeneity and low number of included studies. Inpatient ADRs were not involved in these meta-analyses.

The heterogeneity in the setting of both meta-analyses was considered to be caused by the combined effects of different ADE detection and causality assessment methods. The estimated amount of inpatient ADEs does not differ much from the results of recent reviews focusing on ADRs in the European setting (mean ADR occurrence rate in adult population 22.0%), indicating that ADEs in the Western World are highly common and that their appearance is similar regardless of which part of the Western World [26].

In this study, over one third 32.3% of inpatient ADEs were estimated preventable which is slightly less than the estimates in earlier reviews [1, 26]. However, significant variation was detected in the preventability results of separate articles, which was also considered to be a result of the use of different preventability measurement methods in independent studies. We were unable to assess the preventability of ADRs leading to inpatient deaths since it was not reported in any of the included studies.

The drugs most frequently involved in inpatient ADEs were from the ATC class N (Nervous system), whereas drugs most frequently associated with inpatient deaths were from the B (Blood and blood forming organs) class. More specifically, drugs from these classes involved in inpatient ADEs and FADRs were opioids, antipsychotics, sedatives, antithrombotics, and anticoagulants, respectively. These results are well in line with the other findings in this review, in which the majority of inpatient ADEs were CNS events, whereas the majority of inpatient deaths were due to hematological disorder. Similarly, drugs most frequently involved in inpatient ADRs were antiinfectives from the ATC class J and the most common adverse reactions detected were GI events.

The majority of the articles reporting factors associated with ADEs found LOS, higher age, and polypharmacy to increase the risk of inpatient ADE and ADR significantly. Furthermore, polypharmacy was also found increasing the risk for FADRs. The correlation between ADE and age and polypharmacy has been detected in previous research indicating that no significant change has occurred regarding these risk factors during recent years [28, 29]. In the future, recognizing specific risk factors among inpatients will have increasing significance as the population in the Western World ages [30,31]. The association between age and increasing number of regular medication has been widely recognized in recent years highlighting the need for better clinical tools for ADE detection and prevention [32-34].

6.2. Strengths and limitations

The articles included in this review were identified through electronic searches from four different databases. The search provided a high number of citations which, on the other hand, made study selection laborious and slow. An information specialist was consulted during the searches in order to ensure the search was as comprehensive as possible. We cannot, however, exclude the possibility of missing some relevant studies due to limiting the search to the English language, restrictions in ADE and ADR definitions, and excluded databases during the electronic search.

The risk of bias was taken into account by assessing and scoring each included study by two reviewers. The included studies were required to have commonly accepted definition of ADE or ADR to reduce definition heterogeneity of the articles. Studies involving ADE detection methods known for underestimating the ADE and ADR frequency were excluded to ensure an accurate estimate of the ADE or ADR frequency as much as possible. It was found that preventable ADEs were defined to be caused by medication error in a majority of the included articles, which may have overlooked the preventability of ADEs due to other reasons.

Considerable variability was detected in sample sizes, study settings and the types of ADEs as well as drugs responsible for ADEs reported in the included articles. Significant heterogeneity was also found in the reported frequencies of ADEs in inpatients of independent articles, which is clearly depicted by the high I^2 values. The differences between studies also made the estimation of the most frequent ADEs and the drugs most frequently related to ADEs problematic.

The heterogeneity seen in the results in this review and meta-analysis is largely due to the heterogeneity affecting the terminology and methodology in the field of drug safety research. Different definitions could be seen throughout the included articles in the basic terminology (e.g. ADE, ADR, severity, and preventability) as well as methods used to assess these, which not only made it difficult to assembly the review and meta-analysis data but also created a fair amount of uncertainty in the results. The heterogeneity in this study therefore reflects the current situation in which drug safety research is still lacking the unity critical to the reliability of the results in this type of research.

This review is the first review to assess the frequency of inpatient ADEs in the Western World setting. It therefore provides new and valuable information on ADEs presenting in inpatients during hospital stay. It enables us to critically assess the safety aspect of specialized medical care in the Western World since it only involves studies researching problems in medical care following the common practice of western medicine. The results also indicate that further real-world evidence and studies of ADEs are needed to establish better prospects in improving medication safety. In the future, more

emphasis is needed on unifying terminology used and improving classification methods to enable more accurate and pronounced methods for classification and evaluation of ADEs.

7. CONCLUSION

ADEs are highly common during hospitalization and are estimated to affect 19% of inpatients. The majority of ADEs are moderate in severity not causing patients any permanent harm but require some form of intervention. Only a small proportion of ADEs are life-threatening or fatal. In this review and meta-analysis, no consistent estimate of inpatient deaths due to ADRs could be made because of the small number and high heterogeneity of the included studies focusing on FADRs.

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9. CONFLICTS OF INTEREST

The authors declare no conflicts of interest. No funding was received for the conduct or for the preparation of this study.

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Fig. 1 PRISMA diagram of the selection process of all articles included in the systematic review

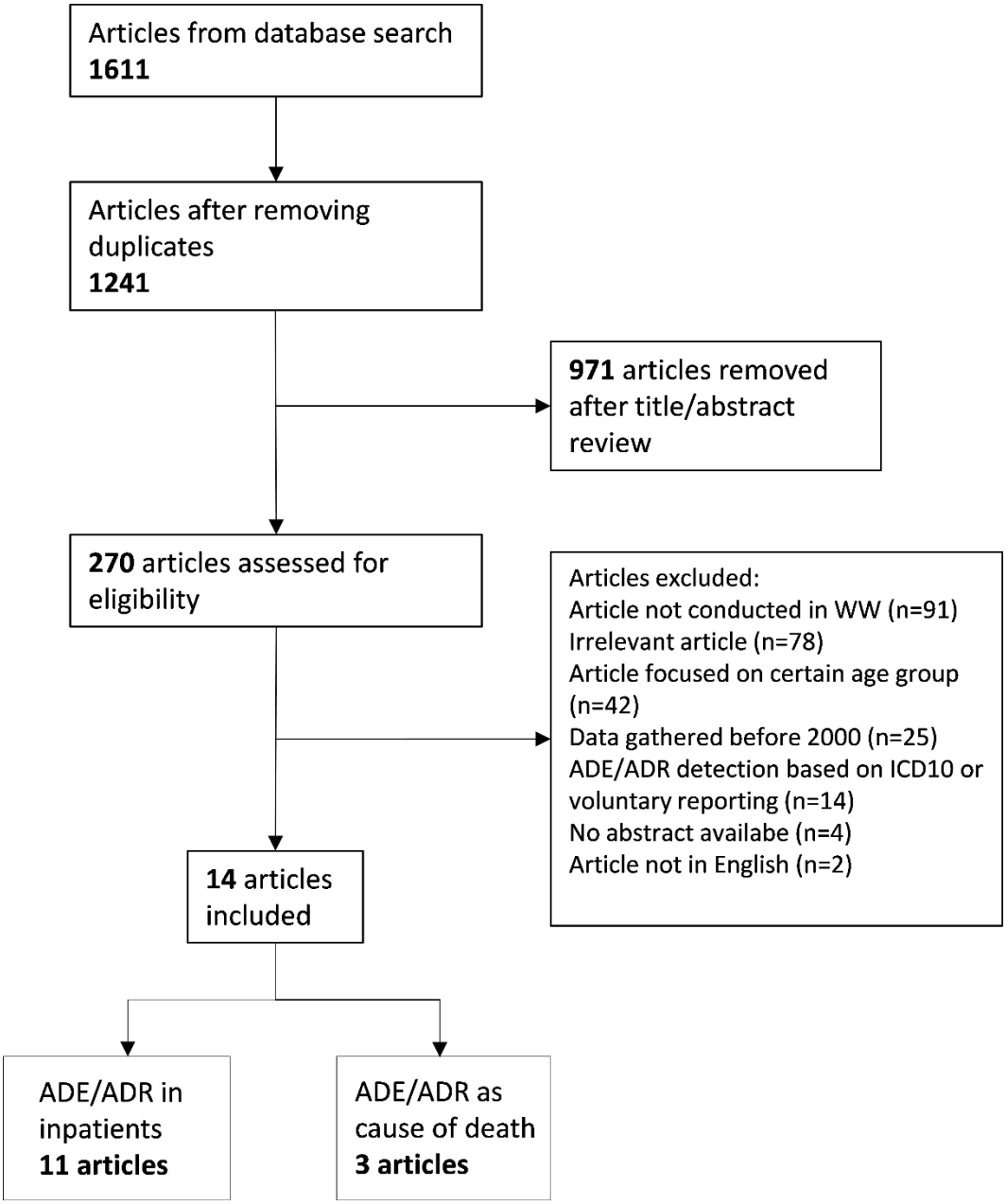


Fig. 2 Most frequent adverse drug events (ADEs), adverse drug reactions (ADRs), and fatal adverse drug reactions (FADRs) occurring in inpatients

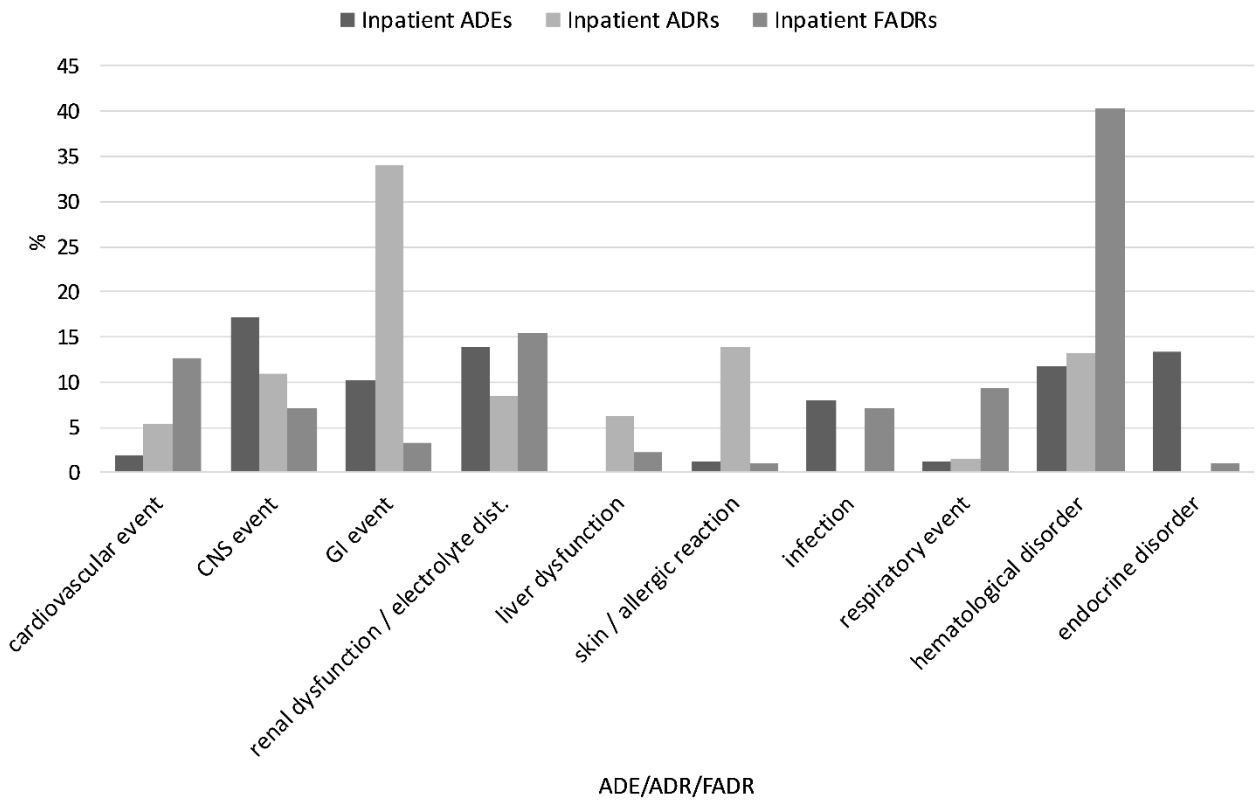
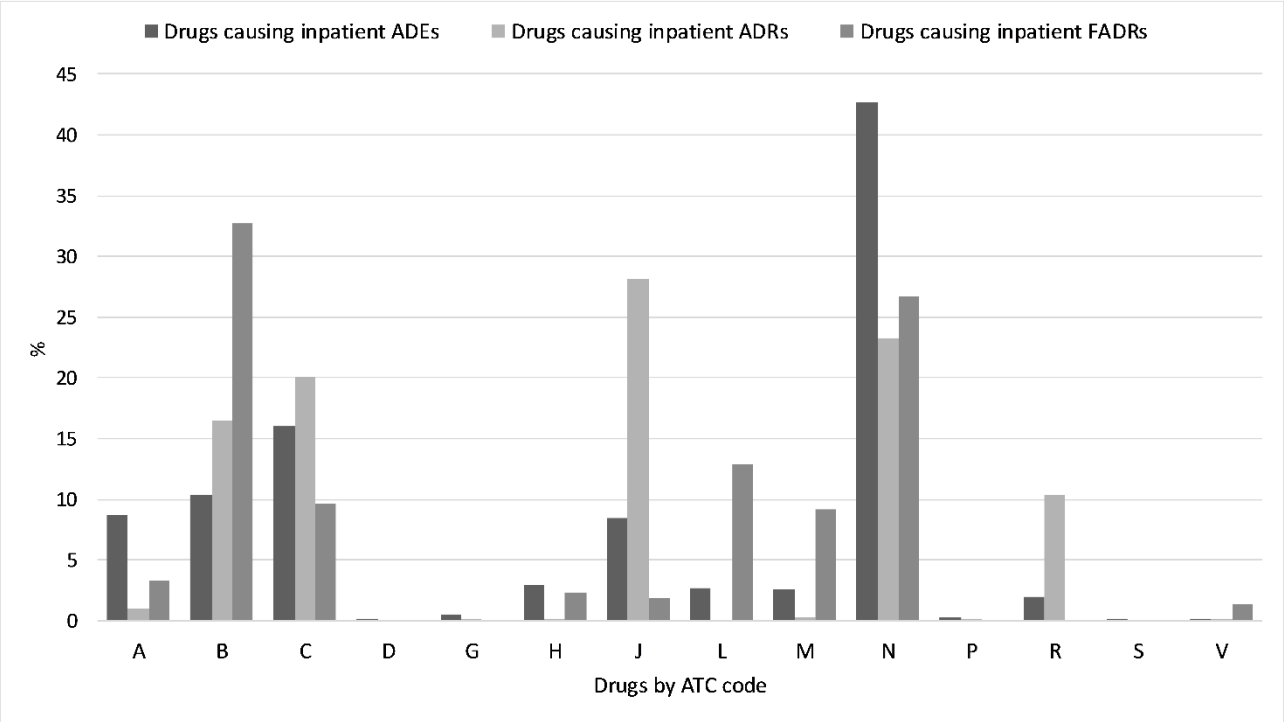


Fig. 3 Drugs most frequently involved in inpatient adverse drug events (ADEs), inpatient adverse drug reactions (ADRs), or fatal adverse drug reactions (FADR)



A= Alimentary tract and metabolism, B = Blood and blood forming organs, C = cardiovascular system, D = dermatological drugs, G = genitourinary system and reproductive hormones, H = systemic hormonal preparations excluding hormones and insulins, J = antiinfectives for systemic use, L = antineoplastic and immunomodulating agents, M = musculoskeletal system, N = nervous system, P = antiparasitic products, insecticides and repellents, R = respiratory system, S = sensory organs, V = various ATC structures

Fig. 4 The percentage of inpatients affected by adverse drug events during hospital stay

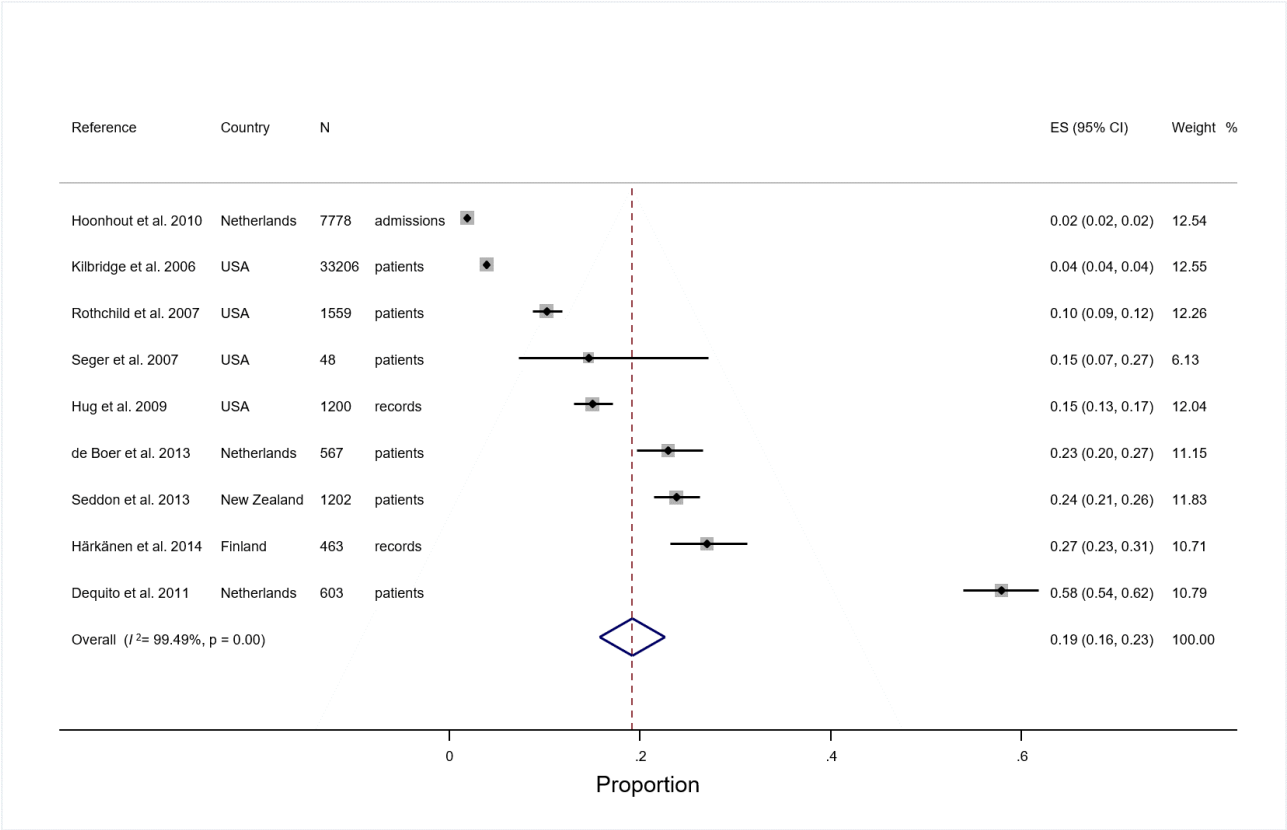


Table 1 Characteristics on included studies focusing on inpatient adverse drug events (ADEs) or adverse drug reactions (ADRs)

References (country)	Setting, study design (sample size; data collection year)	Studied event (definition)	Detection method	Patient characteristics	ADR/ADE prevalence % (/100 admissions)	Severity	Regrouped severity assessment	% Preventable	Quality score
Davies et al. (UK)	single-center, prospective observational (3322 pts; 2005)	ADR (Edwards & Aronson)	Medical record review	medical and surgical patients, mean age unknown, 48% male	15.8% (19.8 ADR /100 admissions)	Hartwig severity scale: 1: 0.1% 2: 20.6% 3: 56.3% 4: 20.7% 5: 0.1% 6: 0% 7a: 1.9% 7b: 0.1%	Minor: 0.1% Moderate: 76.9% Severe: 20.8% Life-threatening/fatal: 2%	53.3%	6/6
de Boer et al. (Neatherlands)	Multicenter, prospective observational cohort (567 pts; 2009)	ADE ("Preventable ADEs are defined as medication related harm caused by medication error")	GTT	surgical patients, mean age 62 [SD 14,5], 49% male	22.9% (27.5 ADE /100 admissions)	expert panel classification: life-threatening 2.2%, severe 8.3%, moderate 16.7%, mild 71.1%, Death 0%, unknown 1.7%	Minor: 71.1% Moderate: 16.7% Severe: 8.3% Life-threatening/fatal: 2.2%	15.4%	5/6

Dequito et al. (Neatherlands)	multicenter, prospective chart review (603 pts; 2006-2008)	ADE ("Preventable ADE was defined as an adverse event related to both drug and a medication error")	Medical record review	geriatric, general internal medicine, gastroenterology and rheumatology patients, mean age unkown, % male unknown	57.9 % (N/A)	WHO: 14.4% critical	N/A	12%	5/6
Hoonhout et al. (Neatherlands)	multicenter, retrospective chart review (7778 adm; 2004)	MRAE ("An MRAE was defined as an AE related to the use of medication in the treatment of a patient"	Medical record review	All patients, mean age unknown, 47% male	N/A (1.9 MRAE / 100 admissions)	N/A	N/A	41%	4/6
Härkänen et al. (Finland)	Single-center, retrospective chart review (463 rec; 2011)	ADE ("Situations that caused temporary or permanent harm to patient were included to ADEs, NCCMERP categories E-I")	GTT	adult inpatients, mean age 60,2 (SD 18,2 range 18-96), 51% male	27% (N/A)	NCCMERP-classification** E: 73.3% F: 21.1% H: 5.6%	Moderate: 73.3% Severe: 26.7%	41.1%	6/6

Hug et al. (USA)	multicenter, retrospective cohort (1200 rec; 2005-2006)	ADE (”ADE was defined as an injury resulting from medical intervention related to a drug”)	GTT	Adult inpatients, mean age 63,2 (range 18-107), 42% male	N/A (51 ADE / 100 admissions)	expert panel classification: significant: 38.3% serious: 49.4% life-threatening: 11.7% fatal: 0.6%	Moderate: 38.3% Severe: 49.4% Life-threatening/fatal: 12.3%	75%	4/6
Kilbridge et al. (USA)	multicenter, prospective cohort (33206 pts; 2005)	ADE (N/A[1])	Automated alert system (GTT)	All inpatients, mean age unknown, % male unknown	3.9% (4.9 ADE / 100 admissions)	Duke 7 point severity scoring system: 3: 86.1% 4: 13.5% 5: 0.1% 6: 0.3%	Moderate: 86.1% Severe: 13.6% Life-threatening/fatal: 0.3%	N/A	4/6
Rothchild et al. (USA)	Single-center, prospective observational (1559 pts; 2004-2005)	ADE (“ADEs were injuries due to medication”)	medical record review	psychiatric inpatients, mean age 43.4 (SD 18,5), 38% male	N/A (19.7 ADEs / 100 admission)	expert panel classification: significant: 66% serious: 31% life-threatening: 2% fatal: 0%	Moderate: 66% Severe: 31% Life-threatening/fatal: 2%	13%	5/6
Sánches Munos-Torrero et al. (Spain)	multicenter, prospective observational (405 pts; 2009)	ADR (Rawlins & Thompson)	daily intensive pharmacovigilance by 3 physicians	general internal medicine patients, mean age unknown, % male unknown	31.1% (N/A)	expert panel classification: minor: 8.6% moderate: 73% major: 17% fatal 1.6%	Minor:8.6% Moderate: 73% Severe: 17% Life-threatening/fatal: 1.6%	N/A	6/6
Seddon et al. (New Zealand)	N/A, retrospective record review (1202 pts; 2010-2011)	ADE (“Any injury resulting from the use of a drug” (including ADR and ME)”)	GTT	Adult inpatients, mean age unknown, % male unknown	31.2% (28.9 ADEs / 100 admissions)	NCCMERP: E: 61% F: 33.5% G: 1.1% H: 2.5% I: 1.5%	Moderate: 61% Severe: 37.1% Life-threatening/fatal: 1.5%	N/A	3/6

Seger et al. (USA)	Single-center, retrospective record review (48 pts; 2002)	ADE (N/A[1])	GTT	All inpatients, mean age unknown, 44% male	14.6 % (12.5 ADE /100 admissions)	N/A	N/A	28.6%	3/6

[1]Definition of ADE or ADR otherwise indicated to coincide with generally used definitions

NCCMERP-classification (National Coordination Council for Medication Error reporting and Prevention), pts = patients, adm = admissions, rec = patient records, ADE = adverse drug event, ADR = adverse drug reaction, MRAE = medication related adverse event, GTT = global trigger tool, WHO = World Health Organization, retrospective design = data gathered from patients treated in the past, prospective design = real time data collection

Table 2 Characteristics on included studies focusing on adverse drug reactions resulting in patient death

References (country)	Data collection year	Setting, Study design (sample size)	Studied event (definition)	Detection method	Causality assessment	Patient characteristics	Prevalence of FADRs %	Quality score
Pardo Cabello et al. [1] (Spain)	2009-2010	tertiary care hospital, retrospective observational (1388 pts)	ADR resulting in inpatient death (WHO)	medical record review	causality described by Henrik Wulff, criteria applied by Ebbsen et al.	Adult inpatients, mean age 78 (range 68-84), 56% male	18.4%	6/6
Pardo Cabello et al. [2] (Spain)	2004	university hospital, retrospective record review (289 pts)	ADR resulting in inpatient death (Rawlins & Thompson)	medical record review	WHO, adapted version of Naranjo scale	Adult inpatients, mean age 73 (range 21-93), 49% male	3.0%	5/6
Lapatto-Reiniluoto et al. (Finland)	2012	tertiary care teaching hospital, retrospective record review (1708 pts)	ADR resulting in inpatient death (WHO)	medical record review	case-by-case review	All inpatients, mean age 73 (men) 76 (women), 59% male	5.9%	6/6

pts = patients, FADR = fatal adverse drug reaction, ADR = adverse drug reaction, WHO = World Health Organization, retrospective design = data extracted from patients treated in the past