Montané Eva (Orcid ID: 0000-0002-1691-7652)

Epidemiology of drug-related deaths in European hospitals: a systematic review and meta-analysis of observational studies

Authors: Montané Eva, Castells Xavier.

Eva Montané, MD, PhD. Department of Clinical Pharmacology, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain. Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain. ORCID number: 0000-0002-1691-7652.

Xavier Castells, MD, PhD. Department of Medical Sciences, University of Girona, Girona, Spain. ORCID number: 0000-0002-2619-7273.

Corresponding author: Dr. Eva Montané. Carretera de Canyet s/n, 08916 Badalona, Barcelona, Spain. Telephone: (+34) 934978865. Fax: (+34) 934978864. E-mail address: emontane.germanstrias@gencat.cat

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Dr. Montané: conceived the idea, contributed to the study design, conducted the literature search, reviewed the selected cases, undertook data acquisition of included cases, performed analysis and interpretation of the data, and wrote the first draft of manuscript.

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ABSTRACT

Objectives: To perform a systematic review of observational studies on the epidemiology of drug-related death (DRD) in patients requiring hospitalisation or while hospitalised (hospital-acquired DRD).

Methods: We conducted a systematic review of observational studies investigating the occurrence rate of DRD episodes among deceased inpatients. Two independent researchers assessed eligibility criteria, extracted data, and evaluated the risk of bias. Both quality assessment and meta-analysis were performed.

Results: From 1,351 identified potential studies, six retrospective studies were included. DRD occurrences rates were 7.3% (CI 95% 4.1 – 12.5) among deceased inpatients and 0.13% (CI 95% 0.04 – 0.40) among hospitalised patients. During hospitalisation, acquired-DRD represented 2.7% (CI 95% 1.0 – 6.9) of inpatient deaths and occurred in 0.05% (CI 95% 0.01 – 0.23) of hospitalised patients. However, these estimates have to be viewed with caution because there was significant heterogeneity (I^2 >97%). None of the studies were considered to be at 'high risk of bias' according to the criteria of the NIH Quality Assessment Tool. The most common ADRs related to death were haemorrhages due to antithrombotic drugs (39%, CI 95% 26.5 – 53.2) and infections in drug-immunosuppressed patients (27.5%, CI 95% 16.7 – 41.7).

Conclusions: We found that the DRD occurrence rate of deceased hospital inpatients has been infrequently studied in Europe. Our findings suggest that drugs are an important cause of death in hospitals. The limited number of studies in European countries stresses the need for more research in this area.

1. INTRODUCTION

Adverse drug reactions (ADRs) are a known problem in terms of morbidity, costs and mortality [1,2]. In Europe, an estimated 5% of all hospital admissions are due to ADRs, and ADRs are the fifth most common cause of hospital death [3]. Extrapolated data from a meta-analysis revealed that in Europe about 197,000 deaths occur annually due to ADRs [4].

Several studies and some meta-analyses have been published in different settings or populations, mainly focusing on assessing the incidence of ADRs leading to hospitalisation [5-10]. Regarding the epidemiology of fatal ADRs among hospitalised patients, a meta-analysis conducted by Lazarou et al. reported an incidence of 0.32% in the USA [4] and a review conducted by Bouvy et al. reported an incidence of 0.5% in Europe [11]. Recently, Patel et al. published a meta-analysis including 48 international studies showing an incidence of fatal ADRs of 0.2% [12]. Differences in the prevalence of diseases that impact drug consumption could result in large differences in drug-related death (DRD) incidences between low- and high- income countries (0.3% vs 3%) [4,13].

The occurrence rate of DRD in hospitalised patients is an important epidemiological indicator of mortality caused by drugs. Recently Montané et al. [14] found that DRDs among deceased inpatients was 7%. This is, less than half of Pardo Cabello's finding [15], despite both studies being from Spain. Meta-analysis in the context of a systematic review is the most reliable method for understanding the findings from studies with different and sometimes conflicting results. We performed a systematic review and meta-analysis aiming to assess the incidences and occurrence rates of DRD in hospital settings from studies performed in European countries and studying the sources of between-study variability of results. We limited these to this specific geographic area in order to obtain more homogenous data taking into account the fact that European countries have quite similar health systems, with comparable disease prevalence and patterns of drug consumption [16,17].

To our knowledge, no meta-analysis has studied the incidence of DRD among deceased inpatients so far. The approach of this meta-analysis differs from others which included studies evaluating ADRs

that led to hospital admission or occurred during hospitalisation, regardless of whether the outcome was fatal or not.

2. MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [Prisma statement] [18]. The study was registered in PROSPERO International prospective register of systematic reviews in December 2018. Registration number: CRD42019105618 [19].

2.1 Data sources and search strategy

Three databases: PubMed, Web of Science, and SCOPUS were searched from inception to July 2019. Search strings were constructed using Boolean operators (AND, OR) and combining keywords. The following syntax was used in each database: (((adverse drug effect) OR "adverse drug reaction") AND "Hospital Mortality" AND (incidence OR prevalence)), without language restriction (Electronic Supplementary Material [ESM] 1). Furthermore, the citations and references of the included studies and review articles were screened for relevant articles.

2.2 Study selection criteria

The inclusion criteria were observational studies that assessed the DRD occurrence rate among all deceased inpatients as a main study objective, providing epidemiological data (such as the number of admitted patients and the number of deceased patients in the hospital) or data allowing their calculation, and performed in European countries.

The exclusion criteria were clinical trials, review articles, systematic reviews, meta-analyses, commentaries, and editorials, as well as studies with other designs (e.g. spontaneous reporting or case-reports). No studies assessing mortality rate among patients treated in specific hospital services or with specific drugs or drug-classes were included. Studies performed in Asian, American, Oceanian or African countries were also excluded from the study.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened by the primary author to identify studies that potentially met the inclusion criteria. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by the same researcher. Doubts about any particular study were settled after a thorough discussion with the second author.

2.3 Data extraction

Both authors retrieved the study data independently. A standardised, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included: year of publication, country where the study was conducted, study setting, study period, study design, study methodology, ADR definition, causality assessment tool, study population with demographics of participants and baseline characteristics, incidences of DRD and hospital-acquired DRD among inpatients and overall deceased patients, characteristics of suspected drugs (using the Anatomical Therapeutic Chemical [ATC] classification [20]), drug-drug interactions, characteristics of ADR, median hospital stay, risk factors and preventability of ADR. Discrepancies were resolved through discussion between the researchers. Missing relevant and necessary data were requested from authors of the study.

2.4 Methodological quality

To assess the risk of bias in individual studies, two raters (EM and XC) independently assessed the methodological quality using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [21]. This quality tool comprises 14 items or criteria and guidance for rating. Six of the 14 criteria (43%) were not applicable due to the design of the studies (retrospective cohorts), these were: items 4, 5, 7, 10, 12 and 13 (table 1). The quality score was calculated by dividing the number of criteria that were present ("yes") by the total number of applicable criteria. A quality of 100% was obtained if all eight applicable criteria were present in the study and studies were considered to be at high risk of bias if they achieved a score lower than 50%.

2.5 Data analysis

The occurrence rate of DRD among deceased inpatients was calculated using the number of DRDs as the numerator and the total number of deceased inpatients during the study period as the denominator; for the incidence of DRD among hospitalised patients, the number of DRDs was used as the numerator and the total number of hospital admissions during the study period as the denominator. The rate of hospital-acquired DRD was calculated using the number of hospital-acquired DRDs as the numerator and the total number of DRDs as the denominator. For the incidence of hospital-acquired DRD among hospitalised patients, the number of hospital-acquired DRDs was used as the numerator and the total number of hospital admissions during the study period as the denominator.

As the most common DRDs have been found to be haemorrhages and infections in drug-immunosuppressed patients [14,22,23], we assessed the occurrence rate of these specific type of DRD which were calculated by dividing the number of patients dying from each specific types of DRD by the total number of patients dying from DRDs. Both internal and external haemorrhages were

considered. Infections were considered both when disseminated and also when affecting a single organ.

2.6 Statistical analysis

Individual results were pooled using a random effects model. Statistical heterogeneity was determined by calculating the I^2 statistic, which measures the percentage of variance across studies due to heterogeneity rather than chance [24].

We initially planned to study the sources of statistical heterogeneity by means of meta-regression using patient characteristics and the type of causality scale administered as covariates. However, the final number of studies identified was too low for this to be undertaken.

Publication bias was analysed by means of funnel plot, and Begg and Mazumdar rank correlation test and Egger's test of the intercept [25,26]. Statistical analysis was achieved with comprehensive meta-analysis v3 [27].

3. RESULTS

3.1 Study selection

The database searches identified 1,351 potentially relevant citations. After duplicate removal, a total of 1,029 studies were reviewed, 1,016 (98.7%) were excluded after screening of the titles and abstracts. After full text review of the remaining 13 studies, five publications met the inclusion criteria. One article identified was an abstract published at the society's journal [28]; for which detailed data were available in a doctoral thesis published online [29].Thus, a total of six studies were included in the review (Figure 1: PRISMA Diagram) [14,15,29-32].

3.2 Study Characteristics and measures

All the included studies were observational retrospective cohorts performed in the last 20 years (from 2000 to 2015) in University Hospitals of three European countries: France (one study), Finland (two studies) and Spain (three studies). The study period was 12 months in all studies except for one which lasted 22 months [15]. All the studies reported the number of DRDs and the number of deceased inpatients. All studies reported the number of hospital admissions except for one which reported an approximate value [31]. The number of hospital-acquired DRDs was reported in all studies but two (in one of which it could be calculated) [15,30]. **Table 2** summarises the characteristics of the included studies.

3.3 Assessment of methodological quality

On the basis of the NIH Quality Assessment tool for observational studies, no study scored under 50%, which was our pre-specified criterion for low quality. The quality score ranged from 75 to 100%. Three studies did not report details of exposures (item 8), such as doses, routes of administration and time of starting treatment. Descriptions of potential confounding variables measured and adjusted statistically (item 14) were also lacking in three studies (table 1).

3.4 ADR definition

All studies but one used the "WHO" definition for an ADR as "a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease" [33]. The remaining study used the definition proposed in the latest European pharmacovigilance legislation (Directive of the European Parliament and of the Council 2010/84/EU) as "a response to a medicinal product which is noxious and unintended" [34]. The European definition widened the WHO definition of ADR (including medication errors, abuse, misuse as well as doses and indications not authorized for the regulatory agencies or "off label" uses).

3.5 Pooled DRD incidences and occurrence rates

A total of 676,548 patients were hospitalised over 2000-2015. Of the 7,578 patients who died, 657 died as a result of an ADR. The number of DRD per year ranged from 17 to 256 [15,32], the number of in-hospital deceased per year ranged from 820 to 1,708 [29,32], and the number of hospital admitted patients per year ranged from 21,483 to 400,000 [14,31]. The overall incidence of DRD among hospitalised patients was 0.13% (CI 95% 0.04 – 0.40), ranging from 0.01% to 0.74% (ESM 2). The occurrence rate of DRD among deceased inpatients was 7.3% (CI 95% 4.1 – 12.5), ranging from 3% to 18% (ESM 3). The incidence of hospital-acquired DRD among hospitalised patients was 0.05% (CI 95% 0.01 – 0.23, I^2=98.9%) ranging from 0.03% to 0.4% (ESM 4). The occurrence rate of hospital-acquired DRD among deceased inpatients was 2.7%, (CI 95% 1.0 – 6.9, I^2=97.6%) ranging from 0.6% to 11.5% (ESM 5) (table 3).

As the final number of studies included in the statistical analysis was low, we did not determine the sources of between-study variability by means of meta-regression.

3.6 Causality assessment

All the studies reported the tool used for causality assessment; three studies used two different causality tools [14,29,32]. The WHO-UMC criteria and the Naranjo algorithm were the most frequently used tools [35,36]. The French algorithm and the Wulff criteria were the other tools used for causality assessment in one study each [37,38] (table 2). In two studies using the WHO-UMC criteria, cases were included only if DRD attribution causality was 'certain' or 'probable', excluding all 'possible' DRD cases [30,31]. In the other two studies using the Naranjo algorithm, DRD were 'probable' or 'possible' related to drugs in 100% and 98,7% of patients respectively [14,29]. Finally, the study using the Wulff criteria, DRDs were classified as 'suspected of causing death' or 'suspected of contributing to deaths'.

3.7 Characteristics of patients with DRD

Patients with DRDs were predominantly men (mean proportion of 61.2%, ranging from 50% to 73%), with a mean age of 74.2 years (ranging from 65 to 77 years). For studies that provided data (all except two), the mean hospitalisation stays ranged from 8 to 16 days (table 2).

3.8 Adverse drug reactions

Haemorrhages were the most common ADR with proportion of 39.0% (CI 95% 26.5 – 53.2), ranging from 19 to 71% of DRDs (ESM 6). Infections in drug-immunosuppressed patients were the second leading cause of DRD, with a proportion of 27.5% (CI 95% 16.7 – 41.7), ranging from 16% to 44% (ESM 7). Another commonly reported cause of DRD in one study was cardiac arrhythmia (14%) (table 2).

3.9 Suspected drugs

Cytostatic agents, classified as group L (Antineoplastic and immunomodulating agents), and antithrombotic agents, classified as group B (Blood and blood forming organs), were the most commonly involved drug type. Drug-drug interactions were reported in four studies. The proportion of drug-drug interactions was 37.4% of DRDs (CI 28.3 – 47.6); ranging from 30% to 64% (ESM 8) (table 1). All except one of the DRDs due to drug-drug interactions, were due to pharmacodynamic and synergistic interactions.

3.10 Avoidability assessment

Only two studies assessed potential avoidability of DRDs, using two different tools: Olivier score [39] and Schumock Thornton criteria [40]. One study [29] found that the main reasons for causing preventable DRDs were that drugs were not appropriate for the patient's condition and that the

duration of treatment was too long. The other study [14] found that the drug-drug interactions involved in the DRDs were the main cause of avoidability. Proportions of DRD avoidability were 34% and 47%, respectively (table 2).

3.11 Risk factors assessment

Three (50%) studies reported the assessment of risk factors for DRDs. The number of administered drugs and the effect of comorbidity were the most consistent findings of these studies, with positive associations between these risk factors and the rate of DRD. The number of administered drugs was assessed using mean, median and ≥10 drugs, depending on the study. The comorbidity was assessed using the Charlson score in two studies and having ≥4 diseases in one study. Mixed results were found for gender and age, with two studies finding no association with DRD and another finding that men and younger patients have a higher risk of DRD.

3.12 Publication bias

All funnel plots were reasonably symmetrical (ESM 9 to 12) and neither Egger nor Begg tests were statistically significant for any outcome.

4. DISCUSSION

In this meta-analysis, we investigated the epidemiology of DRDs in the hospital setting. We found that the DRD occurrence rate of deceased hospital inpatients has been infrequently studied. All the included studies were performed in the last two decades. Overall, DRD occurrence rate of deceased hospital inpatients was 7.3%, and more than a third were hospital-acquired. Both rates are high and denote that is a relevant healthcare problem in European countries. Another important finding of this meta-analysis is the DRD incidence among hospitalised patients, which was 0.1%. Other studies with different methodology, such as a European review and a meta-analysis including worldwide

studies reported higher incidences, which were 0.5 and 0.2% respectively [11,12]. The incidence of hospital-acquired DRD among hospitalised patients in our study was almost 0.1%. This result is similar to that of the recently published meta-analysis by Patel et al., despite differences in the study design, which included cross-sectional studies [41].

Although all the included studies had a similar study design and length, there was high heterogeneity in the incidence results due to variability in the methodological characteristics, as follows: Selection and assessment of deceased patients were not well reported in all studies. When they were, in one study a preselection was carried out (from predefined diagnoses of death suggesting ADR) leading to an underestimation of DRD incidence [14]. Even though most studies used WHO's definition for ADR, there was significant variability in causality assessment of DRD cases, using at least four different causality methods, which could lead to differences in ADR attribution. Moreover, in two studies [30,31], the DRD cases were included only if attribution causality was certain or probable, excluding possible DRD cases, thus possibly leading to an underestimation of the number of DRD cases. A clear example of this is a cerebral haemorrhage in an anticoagulated patient with a preceding trauma, which could be classified as a possible DRD or as a probable DRD with a contributing role, depending on the study. There was also great variability in the sample size of studies, with the number of patients admitted and the number of patients assessed, varying from 300 to almost 2,000.

Demographic characteristics of patients with DRD showed a predominance of elderly men, which surprisingly diverged from other studies where the proportion of women is higher [23]; although elderly people are also the group with higher DRD incidences [41,42]. This could be due to elderly patients often being polymedicated, as well as having other comorbidities and pharmacokinetic changes that facilitate the appearance of ADRs and fatal outcomes [43-45].

Regarding the characteristics of ADR, there was also a high variability in the reporting of the types of ADRs identified, making a summarized report problematic. The two most common ADRs related to death were haemorrhages and infections in drug-immunosuppressed patients, which was similar to other meta-analyses or population-based studies [12,23]. Both these ADRs are type A, that is, dose dependent, augmented pharmacological effect, predictable and potentially avoidable reactions [46]. For cerebral haemorrhages in patients with head trauma or high blood pressure, antithrombotic drugs could be a contributing factor. Accordingly, two pharmacologic groups were responsible for most ADR, chemotherapy (group L) and antithrombotic agents (group B), which was similar to the findings of other meta-analyses [12,41,42]. Chemotherapy-induced neutropenia and subsequent infections were an important cause of mortality, where medulla aplasia is a pharmacologic effect often necessary for chemotherapy effectiveness, but which can lead to patient death. Antithrombotic agents were associated with a significant risk of haemorrhage. Contrary to other studies, non-steroidal anti-inflammatory agents (NSAIDs) and cardio-vascular drugs (such as digoxin, diuretics or renin-angiotensin system inhibitors) were not frequently involved in DRD in this study [12,41]. Moreover, nervous system agents and antiinfectives were frequently involved in DRDs in studies assessing data from voluntary reporting registers of ADR but not in our study.[47,48]. This difference could be explained by a bias in voluntary registers, where type A and well-known ADRs are underreported, making voluntary registers not useful for calculating ADR prevalences.

Drug-drug interactions were present in more than one third of deceased patients, mainly due to pharmacodynamic interactions. In chemotherapy, combining drugs that have similar pharmacologic effect but different mechanisms of action is common and necessary to achieve the desired immunosuppressant effect. A common synergic drug-drug interaction is a cytotoxic agent with a corticosteroid [49]. Regarding antithrombotic agents, they are sometimes prescribed by different medical specialists for different diseases. A typical example of synergic drug-drug interaction is when

patients receive AAS for ischemic cardiopathy, cilostazol for peripheral arteriopathy and anticoagulation for atrial fibrillation.

Avoidability of DRD was not widely assessed in the included studies, but when it was, rates were higher than in other studies which also assessed fatal drug poisoning [50]. This could be explained as the tools used differed, as well as the population studied.

The risk factors related to DRD were not systematically assessed. The number of drugs and comorbidities were the most commonly reported risk factors related to DRD in this and other meta-analyses [51]. Conversely, older age and female gender, despite having been associated with an increased risk for ADR-related hospitalisation [52], were not associated with DRD in two studies included in this meta-analysis and were associated with a reduced risk of DRD in another. Differences in how the effect of confounding covariates were analysed may explain the discrepancies between these findings.

We limited our meta-analysis to studies conducted in European countries in order to have greater homogeneity of data. Surprisingly, all the included studies were single-centre and were performed in only three European countries and four university hospitals leading to low representativeness of the obtained results. In Spain and Finland, researchers compared the studies' results at two different periods of time. This review clearly shows that few studies have been conducted using this epidemiological methodology which assess DRD cases among deceased inpatients. Therefore, multicenter studies conducted in several European countries assessing the epidemiology of DRD are needed to gain better knowledge of DRD incidences among deceased inpatients in this geographic area. In the same way, in low or middle-income countries, epidemiological DRD data are also scarce. The results of a study conducted in South Africa with a methodology similar to the studies included in this review, showed that epidemiological incidence data for DRD of inpatients were extremely

high; and antiinfectives for the management of HIV and tuberculosis were the drugs most commonly implicated in DRD [13].

Strengths and Limitations

The main limitation of this meta-analysis is that it was limited to studies assessing incidence of DRD among deceased inpatients. Therefore, studies which assessed fatal ADR as part of a broader study investigating all ADRs in hospitalised patients were excluded. Other study limitations are related to the quality of the studies included, which, in general, were deemed to have low risk of bias. Large statistical heterogeneity was found, which reduces confidence in the incidences and rates calculated. Reporting bias can threaten the validity of any meta-analysis. However, no evidence of small study effects was suggested by the funnel plots, nor by the Egger and Begg tests, indicating that publication bias is unlikely. Nevertheless, it must be stressed that the validity of these plots and tests is low when the number of studies included in the meta-analysis is, like in our review, also low [53]. The restriction of including studies conducted in Europe limits generalisability.

A strength of this study is that we performed a systematic review using the most important data bases, searching for a long period of time and with no language restriction, which allowed us to include as many studies as possible. Another relevant strength of the present study was the fact that we contacted the authors of the studies and hence were able to include one more study and calculate the maximum of the DRD and hospital-acquired DRD occurrence rates, as well as DRD and hospital-acquired DRD incidences to meta-analyse. No studies were excluded for not providing enough data to calculate incidence or occurrence rates.

CONCLUSION

Our findings suggest that in European hospitals drugs are an important cause of death, occurring in 1 out of 1,000 patients admitted to hospital, and in at least 1 in 14 deceased patients, denoting that is

a relevant healthcare issue. Despite the similarity of the design of the studies included, high heterogeneity was found. The number of drugs and comorbidities were the most common risk factors related to DRD. The limited number of studies in European countries highlights the need for more research in this area.

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Compliance with Ethical Standards

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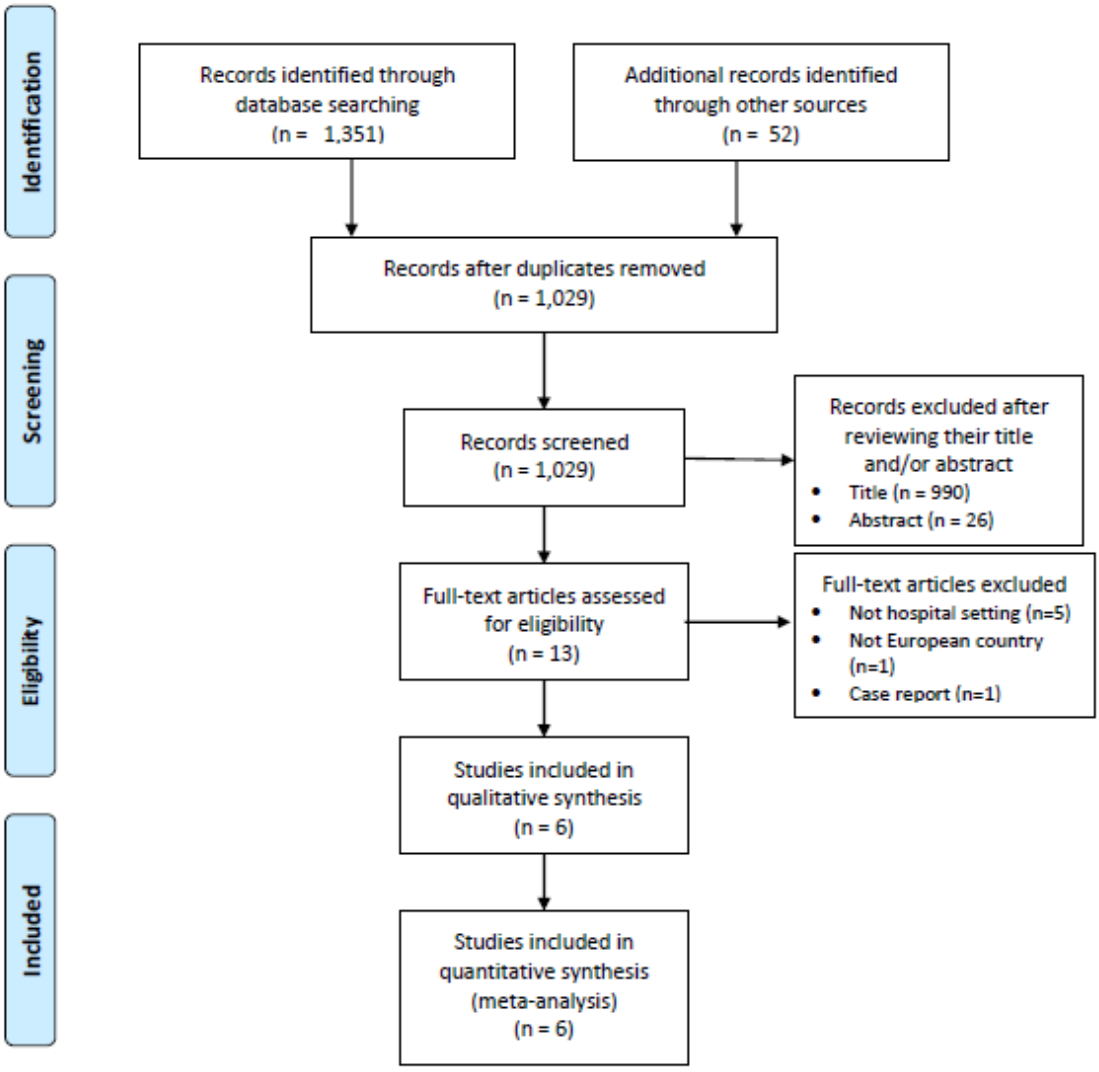

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Figure 1. Study Flow Diagram

Table 1: Quality rating of included studies

Criteria / Studies	Juntti-Patinen [30]	Pardo Cabello [32]	Lapatto-Reiniluoto [31]	Pardo Cabello [15]	Grévy [29]	Montané [14]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	No	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	NA	NA	NA	NA	NA	NA
5. Was a sample size justification, power description, or variance and effect estimates provided?	NA	NA	NA	NA	NA	NA
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	No	No	No	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA	NA	NA
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Yes	No	Yes	No	Yes
Quality score (n, %)	**7/8 87.5%**	**6/8 75%**	**6/8 75%**	**7/8 87.5%**	**7/8 87.5%**	**8/8 100%**

NA: not applicable

Table 2: Characteristics of included studies

Study Author	Study design	ADR definition	Causality assessment	Main suspected drug class (ATC)	Drug-drug interactions (%)	Main adverse drug reactions	DRD patients age (mean, range)	DRD patients gender (% women)	DRD hospitalization stay Mean, range (days)	DRD potentially preventable % (tool)	Risk factors
Juntti-Patinen [30]	Retrospective	WHO	- WHO - UMC	L and B	NR	- Haemorrhages (35%, 26/75) - Infections in immunosuppressed patients (29%, 22/75)	65 (3-93)	45.3 (34/75)	8.2 (1-81)	NR	NR
Pardo Cabello [32]	Retrospective	WHO	- WHO - UMC - Naranjo algorithm modified	M and B	65% (11/17)	- Haemorrhages (71%, 12/17)	73 (39-91)	29.4 (5/17)	7.9 (2-39)	NR	- Number of drugs - Charlson comorbidity index - Length stay
Lapatto-Reiniluoto [31]	Retrospective	WHO	- WHO - UMC	L and B	NR	- Haemorrhages (33%, 17/52) - Infections in immunosuppressed patients (25%, 13/52)	74 (25-99)	36.5 (19/52)	NR	NR	NR
Pardo Cabello [15]	Retrospective	WHO	- Wulff	B and N	30% (77*/256)	- Haemorrhages (19%, 48/256) - Cardiac arrhythmia (14%, 35/256)	77 (69-86)	50.4 (129/256)	NR	NR	- Number of drugs - Comorbidity
Grévy [29]	Retrospective	WHO	- French method - Naranjo algorithm	L and B	30.4% (56/184))	- Haemorrhages (46%, 85/184) - Infections in immunosuppressed patients (16%, 30/184)	76 (31-100)	43.5 (80/184)	15.5 (1-158)	34% (63/184) (Olivier)	NR
Montané [14]	Retrospective	European Directive	- WHO - UMC - Naranjo algorithm	L and B	44% (32/73)	- Haemorrhages (47%, 34/73) - Infections in immunosuppressed patients (44%, 32/73)	70 (19-94)	27.4 (20/73)	8.8 (0-57)	47% (34/73) (Schumok-Thornton)	- Age - Gender - Number of drugs - Charlson comorbidity index

ATC: Anatomical Therapeutic Chemical classification where B is Blood and blood forming organs, L is Antineoplastic and immunomodulating agents, M is Musculoskeletal System, and N is Nervous system; DRD: drug related death; NR: not reported; WHO: World Health Organization; WHO - UMC: World Health Organization - Uppsala Monitoring Centre; *: calculated

Table 3: Study characteristics and incidences of drug-related death (DRD) and hospital-acquired DRD

Study author	Country	Study period year	Number of admitted patients (A)	Number of deceased inpatients (B)	Number of deceased inpatients assessed (C)	Number of DRD (D)	Number of hospital-acquired DRD (E)	DRD incidence of hospitalized patients (D/A)	DRD occurrence rate of deceased inpatients (D/C)	Hospital-acquired DRD incidence of inpatients (E/A)	Hospital-acquired DRD occurrence rate of deceased inpatients (E/C)	Hospital-acquired DRD Incidence of DRD (E/D)
Juntti-Patinen [30]	Finland	2000	141,484	1,547	1,511	**75**	NR	0.053% (75/141,484)	4.96% (75/1,511)	Not calculable	Not calculable	Not calculable
Pardo Cabello [32]	Spain	2004	21,541	820	289	**17**	17	0.08% (17/21,541)	5.88% (17/289)	0.08% (17/21,541)	5.88% (17/289)	100% (17/17)
Lapatto-Reiniluoto [31]	Finland	2012	near 400,000	1,708	1,708	**52**	10	0.013% (52/400,000)	3.04% (52/1,708)	0.0025% (10/400,000)	0.58% (10/1,708)	19.2% (10/52)
Pardo Cabello [15]	Spain	2009 01-10/2010*	34,590	1,400	1,388	**256**	161**	0.74% (256/34,590)	18.44% (256/1,388)	0.5% (161/34,590)	11.6% (161/1,388)	63% (161/256)
Grévy [29]	France	2014	57,450	1,646	1,646	**184**	69	0.32% (184/57,450)	11.18% (184/1,646)	0.12% (69/57,450)	4.19% (69/1,646)	37.5% (69/184)
Montané [14]	Spain	2015	21,483	1,135	1,036	**73**	6	0.34% (73/21,483)	7.05% (73/1,036)	0.028% (6/21,483)	0.58% (6/1,036)	8.2% (6/73)
Meta-analysis % (CI 95%)	**Europe**	**2000-2015**	**676,548**	**8,256**	**7,578**	**657**	**263**	**0.1% (0.0 – 0.4)**	**7.3% (4.1-12.5)**	**0.1% (0.0 – 0.2)**	**2.7% (1.0 – 6.9)**	**37.4% (17.7-62.4)**

*: 22 months; **: calculated DRD: drug-related death; CI: confidence interval