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REVIEW

A systematic review of observational studies evaluating costs of adverse drug reactions

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Introduction: The growing evidence of the increased frequency and severity of adverse drug events (ADEs), besides the negative impact on patient's health status, indicates that costs due to ADEs may be steadily rising. Observational studies are an important tool in pharmacovigilance. Despite these studies being more susceptible to bias than experimental designs, they are more competent in assessing ADEs and their associated costs.

Objective: To identify and characterize the best available evidence on ADE-associated costs.

Methods: MEDLINE, Cochrane Library, and Embase were searched from 1995 to 2015. Observational studies were included. The methodological quality of selected studies was assessed by Cochrane Collaboration tool for experimental and observational studies. Studies were classified according to the setting analyzed in "ambulatory", "hospital", or both. Costs were classified as "direct" and "indirect". Data were analyzed using descriptive statistics. The total incremental cost per patient with ADE was estimated.

Results: Twenty-nine (94%) longitudinal observational studies and two (7%) cross-sectional studies were included. Twenty-three (74%) studies were assessed with the highest methodological quality score. The studies were mainly conducted in the US (61%). Twenty (65%) studies evaluated any therapeutic group. Twenty (65%) studies estimated costs of ADEs leading to or prolonging hospitalization. The "direct costs" were evaluated in all studies, whereas only two (7%) also estimated the "indirect costs". The "direct costs" in ambulatory ranged from €702.21 to €40,273.08, and the in hospital from €943.40 to €7,192.36.

Discussion: Methodological heterogeneities were identified among the included studies, such as design, type of ADEs, suspected drugs, and type and structure of costs. Despite such discrepancies, the financial burden associated with ADE costs was found to be high. In the light of the present findings, validated methods to measure ADE-associated costs need future research efforts.

Keywords: drug costs, health care costs, drug-related side effects and adverse reactions, review

Introduction

In 1999, Wolfe et al described nonsteroidal anti-inflammatory drug toxicity as a leading cause of mortality in the US, ahead of multiple myeloma, asthma, cervical cancer, and Hodgkin's disease, and similar to the acquired immunodeficiency syndrome.[1] A marked increase in reported deaths and serious injuries associated with drug therapy in the US highlighted the importance of this problem as a public health issue, providing strong evidence that postmarketing drug surveillance plays an increasingly important and essential role in the fields of clinical risk management and drug regulation, mainly in terms of assessing benefit/risk ratios, health economics, and public health.[2]

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The growing evidence of the increased frequency and severity of adverse drug events (ADEs), besides the negative impact on patient's health status, indicates that costs due to ADEs may be steadily rising. The epidemiology of drug iatrogenesis across Europe has been identified as an area needing more study, particularly in the ambulatory health care environment, due to the scarcity of available data.[3] Furthermore, in some European countries, underreporting of ADEs has been identified as a pharmacovigilance shortcoming, anticipating that the economic burden of adverse effects of drugs may be underestimated.[3]

The costs of ADEs are a key component of the cost structure in health economic analysis and pharmacoeconomic studies. However, both data sources for ADE costs identification and methods of costs measurement vary among the different available studies.[4] Moreover, previous reviews pointed out a large methodological heterogeneity in measuring drug-induced morbidity.

Experimental and observational studies data can be used to estimate costs of ADEs. However, experimental studies are mainly designed to evaluate the efficacy of an intervention and the conclusions of ADEs and their related costs are difficult to draw due to their methodological limitations, such as length of exposure and the homogeneity of included patients. Observational studies, despite being more susceptible to bias, are more competent in assessing ADEs in clinical practice and allocating their costs than experimental studies.[5,6]

In this light, a systematic review of observational studies was carried out aiming at identifying and characterizing the best available evidence on ADE-associated costs.

Methods

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7]

Literature search

A systematic search was conducted from 1995 to 2015 in MEDLINE, Cochrane Library, and Embase to identify studies describing the costs of ADEs. Search terms related with costs of ADEs were identified consulting the Medical Subject Headings[8] and Emtree terms.[9] Only literature published in English language in the last 20 years was considered for inclusion in this analysis. The search strategy is listed in Tables S1 and S2.

Study selection and quality assessment

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. In case of disagreement, the opinion of a third investigator was sought.

Longitudinal and cross-sectional observational studies were eligible for inclusion if they had been conducted in the US or European countries, and reported on average costs of treating ADEs or reported enough data to perform such estimations.

For the purposes of this study, an ADE was defined according to the World Health Organization definition as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product".[10]

The quality of the retrieved studies was assessed using the checklist proposed by the Cochrane Collaboration for assessment of nonrandomized studies.[11]

Data extraction

Data on study design, study duration, data source, country, and setting of cost analysis were extracted in order to characterize the study design of the included studies. Additionally, data on study size, eligible patients, type of ADE(s) evaluated, drug(s) considered, type of cost analysis, cost component(s) assessed, and the estimated cost(s) were retrieved.

Studies were classified in two categories according to the type of costs analyzed: "ambulatory" if the costs estimated were of ADE(s) leading to hospitalization occurring in non-hospitalized patients, and in "hospital" if the costs estimated were of ADE(s) occurring during hospitalization.

Data analysis and presentation

Data were analyzed using descriptive statistics. The unit of measure of costs considered was the average incremental cost per patient with an ADE compared to a patient without an ADE. Some assumptions and conversions had to be made when studies reported other outcomes. As an example, if a study reported the incremental cost of treating a patient with an ADE over a month, that cost was converted to the total cost of treating a patient with an ADE irrespective of the time frame by considering the total number of patients analyzed and the average time of follow-up. The incremental cost was calculated as ([consumer price index in 2014/ consumer price index in the year of analysis]* incremental cost in the year of the study). All costs were presented in euros (€). The website of The Organisation for Economic Co-operation and Development was screened to identify currency exchange rates and consumer price indices per country.[12] Currency exchange rates established by the end of the year 2014 were used to convert other currencies to euros (€). Consumer price indices were used to adjust for the effect of costs' inflation estimated in studies conducted

years ago to predicted costs by the year 2014. Data analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

The search yielded a total of 625 potentially relevant references. After excluding for duplicates, 458 abstracts were reviewed and screened for eligibility. Based on inclusion criteria, 90 references were selected for full-text further evaluation. A final sample of 31 studies was eligible for inclusion. The selection of references is shown in Figure 1.

Characteristics of the selected studies

The 31 studies selected for further analyses included 22 cohort studies (71.0%), seven case–control studies (22.6%), and two studies based on pharmacovigilance databases of spontaneously reported ADEs (6.4%). Table 1 describes the main characteristics of the studies. Seventeen cohort studies (77.3%) and six case–control studies (85.7%) were assessed as having a low risk of bias (Table S3).

The mean duration of the included studies was 19 months (53 days to 18 years). The studies were mainly conducted in the US (n=19; 61.3%).

Thirteen studies (41.9%) estimated the costs of ADEs occurring in the outpatient setting, ten studies (32.3%) estimated the costs both in "ambulatory" and "hospital" settings, and eight studies (25.8%) assessed the costs occurring during hospitalization.

Twenty studies (64.5%) did not evaluate any therapeutic group in particular. Among the studies which analyzed a specific therapeutic group, the costs of ADEs caused by medicines used for cancer treatment were the more commonly evaluated (n=6; 19.4%).

Most part of the studies assessed all ADEs resulting from the utilization of a drug. They not assessed a specific ADE (eg, skin toxicity related with erlotinib). Regarding studies assessing an ADE of a particular type, cutaneous events were the most evaluated (n=4; 12.9%).

Two studies (6.5%) evaluated the costs of ADEs in pediatric population and three studies (9.7%) studied specifically the geriatric population.[13–17]

Cost analysis

Table 2 describes the costs analysis and the main results of the included studies.

A total of 29 (93.5%) studies evaluated "direct health care costs", and two studies (6.5%) issued both "direct and

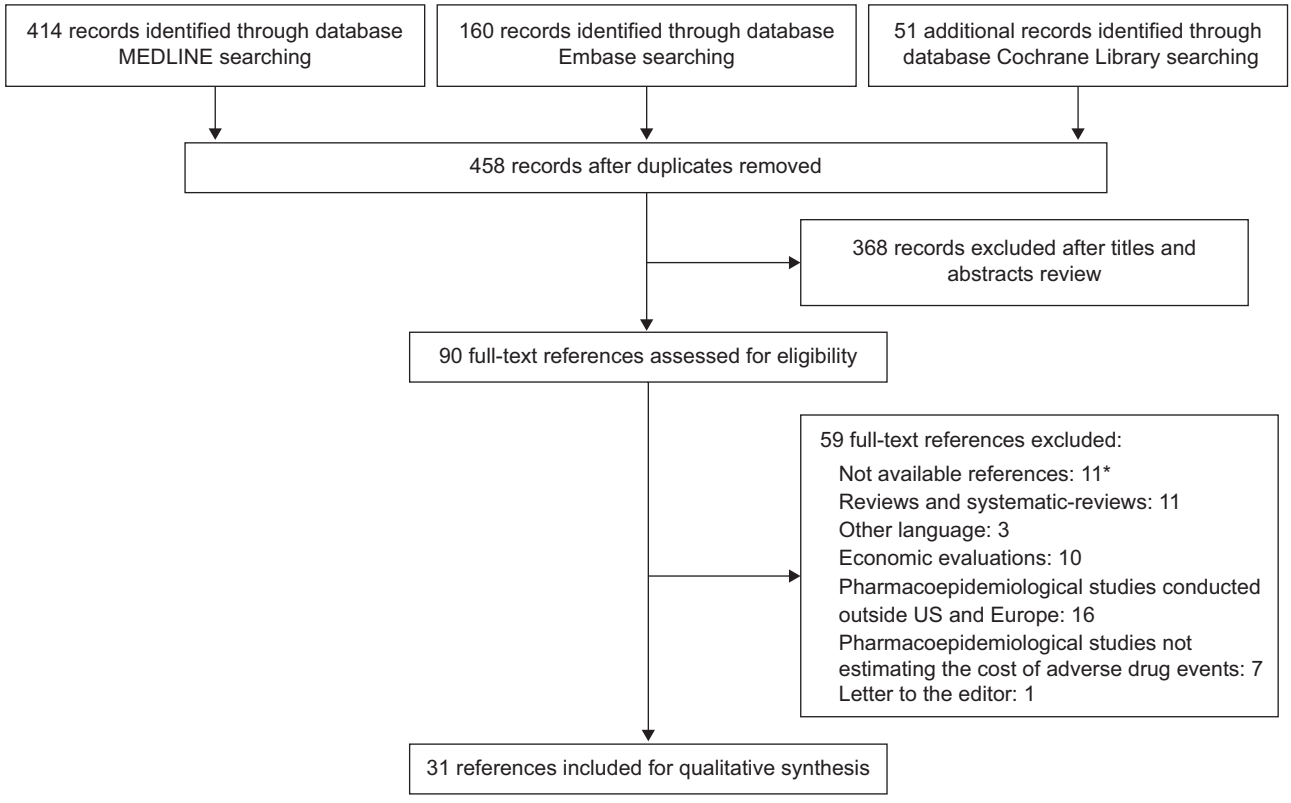

Figure 1 Flow diagram of literature search.
Notes: *The references are not available on the electronic databases searched. The publications' authors did not reply to our request to access the publication's full-text.

Table 1 Main characteristics of the included studies

Study	Design	Country	Study period	Setting	Characteristics of the patients	Suspected drug(s)	Type of ADE	Type and structure of costs	Risk of bias
Pirmohamed et al (2004)[18]	Prospective cohort study	England	6 months	Outpatient	Patients aged >16 years admitted to hospital	Any drug	Any ADE	Costs: total time spent in hospital, and invasive investigations performed	Moderate
Bordet et al (2001)[19]	Prospective cohort study	France	18 months	Outpatient	Patients admitted to a cardiological hospital	Any drug	Any ADE	Direct costs: A) additional investigations, B) laboratory tests, C) noninvasive procedures, D) invasive monitoring or procedures, E) additional treatment, and F) increased length of stay	Low
Carrasco-Garrido et al (2010)[20]	Retrospective cohort study	Spain	6 years	Outpatient	Patients admitted to hospital	Any drug	Any ADE	Direct medical costs	Low
Kim et al (2009)[21]	Retrospective cohort study	US	5 years	Outpatient	Patients treated for atrial fibrillation	Rhythm-control, rate-control, and combined rhythm/rate-control	Any ADE	Direct medical costs: inpatient (facility and professional) and outpatient (medical, laboratory, and pharmacy)	Low
Yee et al (2005)[22]	Retrospective cohort study	US	1 year	Outpatient	Patients aged >18 years who visited the ED	Any drug	Any ADE	Costs: drugs administered, laboratory tests, and follow-up outpatient clinic visits	Moderate
Lagnaoui et al (2000)[23]	Retrospective cohort study	France	4 months	Outpatient	Patients admitted to hospital	Any drug	Any ADE	Costs: length of stay and hospitalization costs	Moderate
Leendertse et al (2011)[13]	Prospective case–control study	The Netherlands	53 days	Outpatient	Patients aged >18 years admitted to hospital	Any drug	Preventable ADE-induced hospitalization	Medical costs during hospital admission; production loss costs: time off work and reduced productivity on the job	Moderate
Hafner et al (2002)[24]	Retrospective case–control study	US	3 months	Outpatient	Patients who visited the ED	Any drug	Any ADE	Costs: hospitalized days and hospitalized charges	Low
Bates et al (1997)[25]	Prospective case–control study	US	6 months	Outpatient	Patients admitted to hospital	Any drug	Any ADE	Costs: intensive care unit, intermediate and routine care, pharmacy, laboratory, and surgery	Low
Rottenkolber et al (2011)[26]	PV database*	Germany	2 years	Outpatient	Patients admitted to hospital	Any drug	Spontaneously reported ADE leading to hospitalization	Direct costs: A) hospitalizations; B) medical consultations; C) laboratory tests; and D) drug treatments	–

Senst et al (2001)[27]	Prospective case–control study	US	53 days	Inpatient and outpatient	Patients having ADE during hospitalization and patients admitted to hospital due to ADE	Any drug	Any ADE	Costs of resource use	Low
Tafreshi et al (1999)[28]	Prospective cohort study	US	2 months	Outpatient	Patients admitted to hospital	Any drug	Any ADE	Costs: total cost to the institution, not charges to the patient, or third-party payers, including overhead costs such as personnel and supplies	Low
Schneeweiss et al (2002)[29]	Prospective cohort study	Germany	2 years and 6 months	Outpatient	Patients admitted to hospital	Any drug	Any ADE, except skin ADE	Costs: reimbursement per hospital day	Low
Du et al (2013)[14]	Prospective cohort study	US	7 months	Outpatient	Children (median age 4 years) admitted to ICU	Any drug	Any ADE	Costs: facility-based cost data	Low
Rottenkolber et al (2012)[30]	Retrospective cohort study with a case–control analysis	Germany	1 year	Inpatient and outpatient	Patients admitted to hospital	Any drug	Any ADE	Direct medical costs: personnel costs (clinicians, nursing staff, and medical technicians) and nonpersonnel costs (pharmaceuticals, implants, grafts, and medical expenditure not otherwise specified); medical and nonmedical infrastructures (general ward, intensive care units, operating room, anesthesia, cardiac and endoscopic diagnoses and therapies, radiology, laboratory tests, etc)	Low
Hug et al (2012)[31]	Retrospective cohort study	US	20 months	Inpatient	Patients aged >18 years being treated in hospital	Any drug	Any ADE	Diagnosis-related group weighted hospitalization cost and cost of length of stay	Low

(*Continued*)

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Table 1 (*Continued*)

Study	Design	Country	Study period	Setting	Characteristics of the patients	Suspected drug(s)	Type of ADE	Type and structure of costs	Risk of bias
Schneider et al (1995)[32]	Retrospective cohort study	US	2 years	Inpatient	Patients having an MRP during hospitalization	Any drug	Any ADE	Direct costs: A) extra laboratory tests, B) noninvasive procedures, C) additional treatments, D) invasive monitoring or procedures, E) increased length of stay, and F) intensive care	Moderate
Suh et al (2000)[33]	Prospective case–control study	US	5 months	Inpatient	Patients having ADE during hospitalization	Any drug	Any ADE	Costs: length of stay and hospitalization costs	Low
Classen et al (1997)[34]	Retrospective case–control study	US	4 years	Inpatient	Patients admitted to hospital	Any drug	Any ADE	Cost of hospitalization	Low
Giuliani and Marzola (2013)[35]	Retrospective cohort study	Italy	5 years	Inpatient	Patients with NSCLC	Erlotinib	Skin toxicity	Direct medical costs: based on mean duration of skin rash and range of costs related to different drug prices	Low
Gyllensten et al (2014)[36]	Retrospective cohort study	Sweden	3 months	Inpatient and outpatient	Patients aged >18 years with health care encounters	Any drug	Any ADE	Costs: hospitalized days and hospitalized charges	Low
Lang et al (2009)[48]	Retrospective cohort study	US	6 years	Inpatient and outpatient	Patients aged >35 years with advanced squamous cell carcinoma of the head and neck	Radiotherapy, chemoradiotherapy	Any ADE	Costs: A) hospital inpatient, B) hospital outpatient, C) physician, and D) outpatient pharmacy	Low
Paessens et al (2011)[49]	Prospective cohort study	Germany	2 years and 6 months	Inpatient and outpatient	Patients undergoing multidrug chemotherapy with NSCLC and lymphoproliferative disorder	Multidrug chemotherapy	Any ADE	Costs: cost of hospitalization, cost of drugs, medical treatment, and diagnostic procedures	Moderate
Ray et al (2013)[50]	Retrospective cohort study	US	10 years and 7 months	Inpatient and outpatient	Patients with CRC, NSCLC, or HNC	EGFRI	Dermatologic ADE	Costs: pharmacy (EGFRI drug costs, other pharmacy costs), medical services (admissions, ED visits, outpatient visits, other medical services, ie, laboratory, radiology), and total costs (pharmacy and medical costs)	Low

Borovicka et al (2011)[37]	Retrospective cohort study	US	2 years and 8 months	Inpatient and outpatient	Patients diagnosed with cancer receiving one molecularly targeted agent	Molecularly targeted cancer agents	Dermatologic ADE	Costs for medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures	Low
Noize et al (2010)[38]	PV database*	France	18 years	Inpatient and outpatient	Any	Ketoprofen for topical use	Spontaneously reported cutaneous ADE	Direct costs: A) hospitalizations, B) medical consultations, C) laboratory tests, and D) drug treatments	–
Suh et al (2012)[39]	Retrospective cohort study	US	5 years	Inpatient and outpatient	Patients aged >18 years with PD	Levodopa	Dyskinesia	Medical costs: hospitalizations, outpatient services, and ED; Medication costs: dispensed by outpatient, community-based, or mail-service pharmacies	Low
Foley et al (2010)[44]	Retrospective cohort study	US	3 years	Inpatient and outpatient	Patients with CRC	Cetuximab	Infusion ADE	Costs: A) inpatient care, B) inpatient length of stay, C) ED, D) outpatient care, and E) prescription	Low
Parekh et al (2014)[15]	Retrospective cohort study	US	4 years	Inpatient and outpatient	Patients aged >65 years with diabetes and a concomitant infection	Antimicrobial drugs	Hypoglycemia	Costs: emergency department services, hospitalizations, and professional services	Low
Wan et al (2015)[16]	Retrospective cohort study	US	1 year	Inpatient and outpatient	Patients aged >18 years	Opioids	Constipation	Costs: costs for inpatient, pharmacy, outpatient, emergency department, long-term care facility, and other costs	Low
Tundia et al (2011)[17]	Retrospective case–control study	US	1 year	Inpatient and outpatient	Children and adolescents aged ≤20 years having ADE during hospitalization and patients admitted to hospital due to ADE	Any drug	Pediatric ADE	Hospital costs, length of stay	Low

Notes: *Methodological quality was not assessed for pharmacovigilance databases studies.
Abbreviations: ADE, adverse drug event; CRC, colorectal cancer; ED, emergency department; EGFRI, epidermal growth factor receptor inhibitor; HNC, head and neck cancer; ICU, Intensive care unit; MRP, medication-related problems; NSCLC, non-small-cell lung cancer; PD, Parkinson disease; PV, pharmacovigilance.

indirect health care costs". Costs related to facility expenses and treatment were the type of direct health care costs most assessed (n=18; 58%; n=17; 55%, respectively).

The costs of ADEs related to any drug occurring in nonhospitalized patients has been estimated from €702.21 to €40,273.08.[13,14,18–29] A study investigated the costs of ADEs related to rhythm-control, rate-control, and combined rhythm-/rate-control medication; the costs per patient with an ADE were estimated to be €2,737.46.[21] Leendertse et al assessed the costs of ADEs in geriatric population whereas Du et al estimated the costs of ADEs in pediatric population.[13,14] The incremental total cost per patient with an ADE was estimated as €6,527.37 and €40,273.08, respectively.[13,14]

The costs of ADEs that occurred during hospitalization varied from €943.40 to €5,972.74.[30–35] Hug et al compared the costs of any ADE, serious ADE, and life-threatening ADE; an increase in costs related to the seriousness of the ADEs was found (€3,030.79; €3,234.61; €7,192.36, respectively).[31] Another study estimated the costs of skin ADEs related to erlotinib as €1,105.54.[35]

Several studies assessed the costs of ADEs both in hospitalized and nonhospitalized patients (Table 2). The costs of skin ADEs related to antineoplastic agents were estimated from €1,592.89 to €15,037.97.[36,37] A study evaluated the costs of nonserious and serious skin ADEs according to spontaneous reports; the incremental total cost per patient was estimated as €373.33 and €3,383.56, respectively.[38] Suh et al estimated the costs of levodopa-induced dyskinesia as €4,617.65.[39] Parekh et al assessed the costs of hypoglycemia in patients aged >65 years as €25.41 per episode.[15] Another study investigated the costs of ADEs in pediatric population as €3,242.59.[17]

Few studies (n=2; 6.5%) assessed indirect health care costs of ADEs (Table 3). Leendertse et al estimated the indirect health care costs of any ADE leading to hospitalization as €1,982.41 for patients younger than 65 years and as €0.00 for patients aged 65 years or older, according to productivity costs including time off work and reduced productivity on the job.[13] Another study evaluated the indirect health care costs of any ADE both in hospitalized and nonhospitalized patients as €2,985.26.[36]

Discussion

A wide range of values representing both incremental and total costs was found in this study, which may be explained by the methodological differences between included studies.

Of a total of 31 studies (19 from North-America and 12 from Europe), observational longitudinal designs (cohort [n=22; 71%] and case–control [n=7; 23%]) constituted the most frequent methodology observed (94%).

As pointed out by the results of this study, the identification of ADE costs has been focused on hospital setting in two ways: as cause of hospitalization or hospitalization prolongation. Therefore, studies were grouped according to the settings from where data were collected: nonhospitalized patients with ADEs leading to hospitalization, hospitalized patients with ADEs during the hospitalization, and a third group of ADEs simultaneously from outpatients and inpatients. In this last group, a specific setting could not be well established. Several reviews also illustrated these results.[4,40,41] The hospital setting was the privileged set for identification of ADEs and their costs. These data are easier to assess in administrative databases from hospitals while a complete description of each case was hard to obtain in ambulatory setting.[41]

Within the different above-established groups, several methodological heterogeneities were found. Some studies focused on the associations between any drug and any ADE, others on the association of one specific ADE, and several drugs or on the association between any ADE and one specific drug. The study of the association between one specific drug and one specific ADE was also found. Moreover, some studies only included serious ADEs, while others included serious and nonserious ADEs. In addition, some studies assessed ADEs treated in different hospital units, such as emergency departments and intensive care units, resulting in disparate values of ADE costs. For instance, in the study of Du et al, the incremental total cost per patient with ADE was estimated as €40,273.08, not only due to the specific population analyzed (pediatric) but also due to the setting analyzed (intensive care unit).[14] Another source of heterogeneity was the diversity of the drugs evaluated in the studies, which may have contributed to the high costs variation. Most of the studies included in this systematic review did not focus in any particular therapeutic group of drugs. Among the studies evaluating specific therapeutic groups (n=11), six were designed to estimate the costs associated with antineoplastic drugs. Of note, oncology was one of the therapeutic areas receiving more positive opinions for new active substances in recent years, both in Europe and the US.[42,43] The study of the costs associated with treatments used in cancer is of upmost importance since these drugs are usually associated with a high burden of iatrogenics.[44]

Another source of heterogeneity was the metrics for cost evaluation in the different studies. Ninety percent of the studies solely identified direct costs, and different indexes were used for cost identification among studies. Information on indirect costs was difficult to access as it is associated with individual loss of productivity, and most studies evaluated different ADEs in a heterogeneous group of patients.[44]

Table 2 Incremental total direct health care cost per patient with ADE (€)

Type of ADE	Reference	Drug	Incremental total cost per patient with ADE (€)
Nonhospitalized patients with ADEs leading to hospitalization			
Any ADE	Pirmohamed et al (2004)[18]	Any drug	3,682.82
	Bordet et al (2001)[19]	Any drug	5,187.50
	Carrasco-Garrido et al (2010)[20]	Any drug	4,910.12
	Kim et al (2009)[21]	Rhythm-control, rate-control, and combined rhythm-/rate-control drug	2,737.46
	Yee et al (2005)[22]	Any drug	3,593.60
	Lagnaoui et al (2000)[23]	Any drug	3,500.80
	Leendertse et al (2011)*,‡,[13]	Any drug	5,891.65
	Hafner et al (2002)[24]	Any drug	702.21
	Bates et al (1997)[25]	Any drug	3,209.82
	Bates et al (1997)‡,[25]	Any drug	5,794.99
	Rottenkolber et al (2011)[26]	Any drug	2,427.45
	Rottenkolber et al (2012)[30]	Any drug	2,140.49
	Senst et al (2001)[27]	Any drug	7,318.14
	Tafreshi et al (1999)[28]	Any drug	1,303.40
Any ADE, except skin ADE	Schneeweiss et al (2002)[29]	Any drug	820.16
Any ADE in pediatric population	Du et al (2013)[14]	Any drug	40,273.08
Any ADE in geriatric population	Leendertse et al (2011)[13]	Any drug	6,527.37
Hospitalized patients with ADEs during the hospitalization			
Any ADE	Rottenkolber et al (2012)[30]	Any drug	1,049.69
	Senst et al (2001)[27]	Any drug	2,366.77
	Hug et al (2012)¥,[31]	Any drug	3,030.79
	Hug et al (2012)μ,[31]	Any drug	3,234.61
	Hug et al (2012)§,[31]	Any drug	7,192.36
	Schneider et al (1995)[32]	Any drug	943.40
	Suh et al (2000)[33]	Any drug	5,972.74
	Classen et al (1997)[34]	Any drug	2,797.92
Skin ADE	Giuliani and Marzola (2013)[35]	Erlotinib	1,105.54
Other (both hospitalized and nonhospitalized patients; spontaneous reports)			
Any ADE	Gyllensten et al (2014)[36]	Any drug	349.98
	Lang et al (2009)[48]	Radiotherapy, chemoradiotherapy	8,509.24
	Paessens et al (2011)[49]	Multidrug chemotherapy	4,213.97
Skin ADE	Ray et al (2013)[50]	Panitumumab or cetuximab	13,150.34
	Ray et al (2013)[50]	Erlotinib or gefitinib	14,860.76
	Ray et al (2013)[50]	Cetuximab	15,037.97
	Borovicka et al (2011)[37]	Molecularly targeted cancer agents	1,592.89
	Noize et al (2010)¥,[38]	Ketoprofen for topical use	373.33
	Noize et al (2010)μ,[38]	Ketoprofen for topical use	3,383.56
Dyskinesia	Suh et al (2012)[39]	Levodopa	4,617.65
Infusion ADEβ	Foley et al (2010)α,[44]	Cetuximab	5,603.70
Hypoglycemia	Parekh et al (2014)≥,[15]	Antimicrobial drugs	25.41
Constipation	Wan et al (2015)*,[16]	Opioids	8,711.33
Constipation	Wan et al (2015)£,[16]	Opioids	4,606.79
Constipation	Wan et al (2015)¤,[16]	Opioids	1,240.17
Any ADE in pediatric population	Tundia et al (2011)[17]	Any drug	3,242.59

Notes: *Population aged <65 years; £population aged 18< n <65 years; ≥population aged >65 years; ‡preventable; ¥any ADE; μonly serious ADE; §only life-threatening ADE; αmean of both hospitalized and nonhospitalized patients; βallergic and hypersensitivity ADE; ¤patients with long-term treatment with opioids.
Abbreviation: ADE, adverse drug event.

Table 3 Incremental total indirect health care cost per patient with ADE (€)

Type of ADE	Reference	Drug	Incremental total cost per patient with ADE (€)
Nonhospitalized patients with ADEs leading to hospitalization			
Any ADE	Leendertse et al (2011)*[13]	Any drug	1,982.41
Any ADE in geriatric population	Leendertse et al (2011)[13]	Any drug	0.00
Other (both hospitalized and nonhospitalized patients; spontaneous reports)			
Any ADE	Gyllensten et al (2014)[36]	Any drug	2,985.26

Note: *Population <65 years.
Abbreviation: ADE, adverse drug event.

The main strategy to identify ADEs and their related costs was the use of codes, such as International Classification of Diseases and Diagnosis-Related Group, and length of stay and their associated cost as an index measure.[4,40,41] Analysis of spontaneous reports, review of medical charts, and computer searches are some examples of the different methods used to detect ADEs.[45] Each of these methodologies had different sensitivities to identify ADEs, leading to a possible underestimation of the real number of ADEs, therefore, reflecting the heterogeneity of the observed results.[46]

The calculation of costs was also subject of heterogeneity. Whereas some studies estimated the costs per episode of ADE per patient, such as in Parekh et al which assessed the costs of one episode of hypoglycemia,[15] other studies estimated the costs of total ADEs per patient resulting from the total period of treatment, such as in oncology treatments.[16]

Data on the causality assessment between drug exposure and ADE were not available in any study. From a clinical and drug safety evaluation point of view, this is a relevant issue that should be included in future studies. However, when reflecting about ADE costs, investigators should carefully interpret studies as different causality methods can be applied,[47] as well as distinct definitions of ADE.[45] Such dissimilarities could lead to more heterogeneity. In addition, only for ADEs assessed as possible, probable and certain, the sensitivity analysis should be presented.[45]

The present findings are in line with the results from other studies. In fact, data on ADE costs not related with hospitalization are scarce, sometimes conflicting and mainly limited to direct costs. A more profound lack of knowledge on the subject is particularly seen in the ambulatory (outpatient) setting.[4,40,41]

This study has some limitations. The search was developed according to Medical Subject Headings and Emtree terms and only includes articles published in English, conducted in the US and Europe, and during the last 20 years. Methodological differences in the studies' designs can make the ADE cost impact assessment difficult. Such difficulties were encountered in this systematic review.

Despite the methodological discrepancies found between the studies included in this work, the burden of ADE costs is high, anticipating that the study of this issue deserves particular attention and further research efforts.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Search strategy – Medline and Cochrane Library (MeSH)

Search	Search strategy
1	("Costs and Cost Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Drug Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Health Care Costs"[Mesh] OR "Cost-Benefit Analysis"[Mesh])
2	"Drug-Related Side Effects and Adverse Reactions"[Mesh]
3	#1 AND #2
4	#3
	Filters: English; 20 years

Abbreviation: MeSH, medical subject headings.

Table S2 Search strategy–Embase (Emtree)

Search	Search strategy
1	"cost of illness"/exp OR "cost"/exp OR "health care costs"/exp OR "cost benefit analysis"/exp OR "hospital cost"/exp
2	"drug induced disease"/exp/mj
3	#1 AND #2
4	#3
	Filters: English; 20 years

Table S3 Methodological quality assessment results according to ACROBAT-NRS (2014) from Cochrane collaboration for cohort and case–control studies

References/topics	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Cohort studies								
Wan et al (2015)[1]	Low	Low	Low	NA	Low	Low	Low	Low
Gyllensten et al (2014)[2]	Low	Low	Low	NA	Low	Low	Low	Low
Parekh et al (2014)[3]	Low	Low	Low	NA	Low	Low	Low	Low
Du et al (2013)[4]	Low	Low	Low	NA	Low	Low	Low	Low
Giuliani and Marzola, (2013)[5]	Low	Low	Low	NA	Low	Low	Low	Low
Ray et al (2013)[6]	Low	Low	Low	NA	Low	Low	Low	Low
Rottenkolber et al (2012)[7]	Low	Low	Low	NA	Low	Low	Low	Low
Suh et al (2012)[8]	Low	Low	Low	NA	Low	Low	Low	Low
Hug et al (2012)[9]	Low	Low	Low	NA	Low	Low	Low	Low
Borovicka et al (2011)[10]	Low	Low	Low	NA	Low	Low	Low	Low
Paessens et al (2011)[11]	Moderate	Low	Low	NA	Low	Low	Low	Moderate
Carrasco-Garrido et al (2010)[12]	Low	Low	Low	NA	Low	Low	Low	Low
Foley et al (2010)[13]	Low	Low	Low	NA	Low	Low	Low	Low
Kim et al (2009)[14]	Low	Low	Low	NA	Low	Low	Low	Low
Lang et al (2009)[15]	Low	Low	Low	NA	Low	Low	Low	Low
Pirmohamed et al (2004)[16]	Low	Low	Moderate	NA	Low	Low	Low	Moderate
Yee et al (2005)[17]	Low	Low	Low	NA	Low	Low	Moderate	Moderate
Schneeweiss et al (2002)[18]	Low	Low	Low	NA	Low	Low	Low	Low
Bordet et al (2001)[19]	Low	Low	Low	NA	Low	Low	Low	Low
Lagnaoui et al (2000)[20]	Low	Low	Moderate	NA	Low	Low	Low	Moderate
Tafreshi et al (1999)[21]	Low	Low	Low	NA	Low	Low	Low	Low
Schneider et al (1995)[22]	Moderate	Low	Moderate	NA	Low	Low	Moderate	Moderate
Case–control studies								
Tundia et al (2011)[23]	Low	Low	Low	NA	Low	Low	Low	Low
Leendertse et al (2011)[24]	Low	Low	Low	NA	Low	Low	Serious	Moderate
Hafner et al (2002)[25]	Low	Low	Low	NA	Low	Low	Low	Low
Senst et al (2001)[26]	Low	Low	Low	NA	Low	Low	Low	Low
Suh et al (2000)[27]	Low	Low	Low	NA	Low	Low	Low	Low
Bates et al (1997)[28]	Low	Low	Low	NA	Low	Low	Low	Low
Classen et al (1997)[29]	Low	Low	Low	NA	Low	Low	Low	Low

Notes: Low, low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain); moderate, moderate risk of bias (the study is sound for a nonrandomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial); serious risk of bias (the study has some important problems in this domain); critical risk of bias (the study is too problematic in this domain to provide any useful evidence on the effects of intervention). Data from https://www.nlm.nih.gov/mesh/MBrowser.html.[30]

Abbreviations: ACROBAT-NRS, assessment tool for nonrandomized studies of interventions; NA, not applicable.

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