SYSTEMATIC REVIEW

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How are the Costs of Drug-Related Morbidity Measured?

A Systematic Literature Review

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Abstract

Background: Drug-related morbidity has been associated with increased healthcare costs and has been suggested as one of the leading causes of death. Previous reviews have identified heterogeneity in research methods in studies measuring the cost of drug-related morbidity. To date, no attempt has been made to analyse different methods and cost sources used when estimating the costs of drug-related morbidity.

Objective: The aim of this review was to evaluate and compare methods and data sources in cost estimates of drug-related morbidity.

Methods: A literature search was conducted in three electronic databases (CINAHL, EMBASE and MEDLINE) to identify peer-reviewed articles written in English and published between January 1990 and November 2011. Articles were included if estimating the direct or indirect costs of drug-related morbidity based on clinical data from general patient groups. The general patient groups were defined as patients visiting, being admitted to, treated at or discharged from a general hospital, excluding studies from nursing homes or specialized hospitals. Study information was collected using a standardized data collection sheet. Studies were categorized according to the type of costs included in the cost analysis. Thereafter, the cost analyses of included studies were reviewed regarding viewpoint, costing methods and adjustments for timing of costs.

Results: In total, 9569 articles were identified, of which 25 publications were included in this review, and four additional articles were identified from reference or citation lists of publications already included. Eighteen studies measured either the total or attributable costs of drug-related morbidity, while seven studies estimated the increased costs using matched controls or regression analyses. Six studies measured costs from a payer perspective, while the other 23 measured costs to the hospital. One study included costs

resulting after discharge, and discounted future costs, while the remaining 28 studies measured costs during the initial admission only and involved no adjustment for timing of costs.

Conclusions: The data sources and costs measured in the included studies varied considerably in terms of perspectives and use of data sources. Even though there is a trend towards more studies estimating costs from the payer perspective, the identified studies still focused on costs resulting from patients attending hospital, therefore underestimating the cost of drug-related morbidity. There is thus a need for more research on the costs of drug-related morbidity to providers other than hospitals, and costs occurring outside of hospitals and after the initial care episode. Such studies require clear descriptions of how the costs of drug-related morbidity are measured, and should adhere to published guidelines for observational studies and economic evaluation studies.

1. Background

Drug-related morbidity includes unwanted effects of drugs, such as adverse drug reactions (ADRs), drug dependence and intoxications by overdose, as well as insufficient effects of medicines. Drug-related morbidity has been suggested not only to affect the clinical outcome of drug treatment, but also as a cause of increased healthcare use resulting in major costs.[1] However, little is known about the actual costs to society and individual patients, and resources needed for prevention and monitoring of these outcomes.[2]

Previous reviews[1-3] have suggested there has been large methodological heterogeneity between studies measuring costs of drug-related morbidity, e.g. methods for detection of cases of drug-related morbidity, assessment of causal relationship between the drug and the resulting morbidity, and how drug-related morbidity has been defined. In 2003, Rodriguez-Monguio et al.[1] reviewed the cost of drug morbidity in hospitalized patients, ambulatory care and the population. The authors concluded that results need to be interpreted carefully because of differences in, for example, methodological approaches, inclusion of resources and the healthcare system. In addition, cost studies need to clearly describe, for example, the viewpoint and timeframe of the economic analyses[4,5] and which costs are included.[6,7] To our knowledge, no attempt has been made to evaluate the methods for cost analysis used in studies measuring the cost of drug-related morbidity. Economic analyses are largely dependent on the sources of cost data.[8] There is thus a need for reviewing the methods and sources of cost data used within studies on the costs of drug-related morbidity.

The aim of this review was to evaluate and compare methods and data sources in cost estimates of drug-related morbidity.

2. Methods

2.1 Identification of Studies on the Cost of Drug-Related Morbidity

A literature search was conducted on 24 November 2011 in three electronic databases: CINAHL, EMBASE and MEDLINE (via PubMed). Headings and keywords emerged from screening of search terms used in selected review studies on drug-related morbidity and associated healthcare utilization,[1,9-13] and from headings or MeSH terms identified from a selection of research papers within the field.[14-19] Search terms were then adapted to keywords or subject headings available in each database (table I).

Observational studies of drug-related morbidity, written in English and published electronically between January 1990 and November

Table I. Search methods, designed according to data source, used to identify articles in this review

Database	Search method
CINAHL	MH "Adverse Drug Event" Explode: Adverse Effects, Analysis, Economics, Epidemiology and Evaluation
EMBASE	('exp drug treatment failure/' OR 'exp medication error/' OR 'exp therapeutic error/' OR 'exp *adverse drug reaction/') AND ('health economics'/exp)
MEDLINE	((drug OR "Drug Therapy"[Mesh]) AND ("Medication Errors"[Mesh] OR "adverse effects"[Subheading]) AND ("Economics"[Mesh])) OR (("medication error" OR "adverse drug event" OR "drug related morbidity") AND (economic OR cost))

2011, were considered for inclusion. Articles were included if estimating the direct or indirect costs of drug-related morbidity based on observational studies of clinical data from general patient groups. Clinical outcomes of, for example, adverse drug events, ADRs and medication errors were included in drug-related morbidity. The general patient groups were defined as patients visiting, being admitted to, treated at or discharged from healthcare facilities, excluding studies from nursing homes for elderly patients only, and in specialized hospitals. Case reports were excluded, as were studies of drug-related morbidity associated with a specific patient group (e.g. cardiology or internal medicine patients), selected treatment or disease (e.g. selective serotonin reuptake inhibitors or anxiety disorders), a particular drug-related illness or symptom (e.g. nausea), potential drug-related problems, or change in outcome resulting from an intervention. Commentaries, notes, editorials, letters and short reports were deemed unsuitable for extracting information on methods and cost analysis and were excluded. One author (HG) performed the search and scrutinized identified titles as well as potentially relevant abstracts based on the inclusion and exclusion criteria, to identify eligible articles.

Further potentially relevant publications were located by manual search of references and lists of articles citing included papers, and a selection of reviews addressing the costs of drug-related morbidity.[1-3,13,20] Citation lists of 22 of the included studies were retrieved from Webb of Science (ISI Web of Knowledge^{SM}/Thomson Reuters) and, of those not available in Webb of Science citations, lists of six articles were identified from Scopus (Elsevier B.V.). Titles, abstracts and articles published between 1990 and 2011, and deemed potentially relevant from the reference or citation list search, were scrutinized as described previously, using the same inclusion and exclusion criteria.

2.2 Data Extraction and Analysis

Information from included studies was extracted using a standardized data collection sheet, including study design, methods and perspectives used for cost analyses, sources used for identifying costs, and how the resulting costs were presented. Studies including costs to the healthcare setting were judged to use a provider perspective, while those including costs paid by the government, insurance company, individual patients or sickness funds were judged to use a payer perspective. Studies were judged to measure the societal costs if they included direct and indirect costs to the hospital, to any third-party payer and to the patient. In the included studies, costs were divided into direct and indirect costs. Direct costs were expenditures for prevention, detection, treatment, rehabilitation, research, training and investment in medical facilities, while indirect costs were the loss of output to the economy due to illness.[21]

Studies were reviewed according to the methods used for measuring the cost of drug-related morbidity. The review was based on items used for assessing economic evaluation studies, including study viewpoint[4,5] (i.e. the perspective of the cost analysis: provider, payer, other), costing (i.e. methods used for estimations, and quantities and prices of resources reported separately;[4] data sources used for estimating costs: charges, unit costs, length of stay [LOS][1]), and adjustments for timing of costs[4,5] (i.e. the period of cost inclusion, and possible discounting). The guidelines also contain items concerning consequences (as opposed to costs), which were deemed irrelevant for the current review and were therefore excluded. Studies were

also categorized according to how costs were included, i.e. total healthcare costs of patients with drug-related morbidity, all costs resulting from drug-related morbidity, the incremental costs of drug-related morbidity using matched controls, or the incremental costs of drug-related morbidity using regression analyses.[6,7]

3. Results

The electronic search identified 9569 unique article titles between January 1990 and November 2011. After application of inclusion and exclusion criteria, 25 relevant articles were included, together with four articles identified from the bibliographic search of citations and references (figure 1). Included studies are presented in table II.[14,16,22-48]

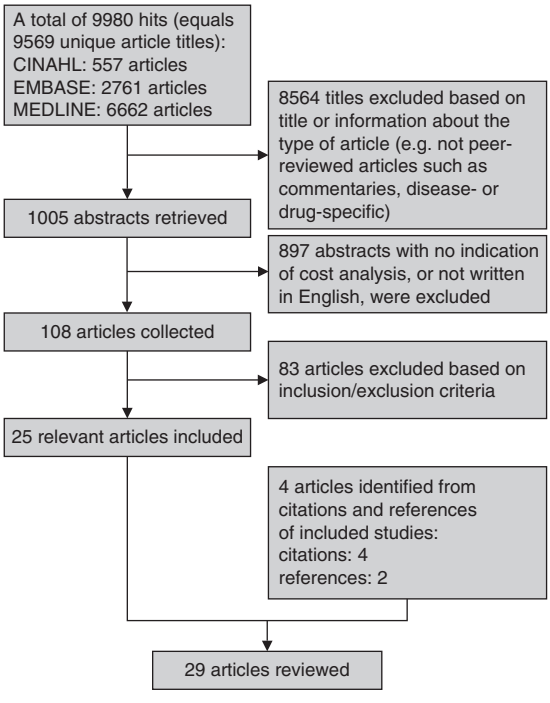

Fig. 1. Identification of relevant studies. Inclusion criteria: observational studies measuring the overall cost of drug-related morbidity, written in English and published between January 1990 and November 2011; exclusion criteria: case reports, intervention studies or other observational studies of selected patient groups, therapies, diseases or drug-related symptoms, or where only potential drug-related morbidity is studied. Studies published only in brief, as commentaries, notes, editorials, letters or short reports.

Six studies were judged to measure costs of drug-related morbidity from a payer perspective, including costs paid by the public healthcare sector,[33] patient,[32] sickness funds[27] or an insurance company.[36,40,41] The remaining 23 studies included costs from the provider perspective, limiting the analysis to in-hospital costs from the hospital perspective. Thomas et al.[36] also measured costs resulting after the initial healthcare episode. One study included indirect costs, e.g. lost income and household production.[36] Another study presented travel costs and costs resulting from the patients' care episode (i.e. accommodation and food) as indirect costs.[32] These were judged to be direct non-healthcare costs.

Of the 29 included studies, three studies[31,35,37] listed the quantities of resources used and the applied prices, and three studies[38,40,41] reported the method used for estimating both quantities and prices.

Of the 29 included articles, one study[36] identified costs after discharge from the healthcare setting. This study discounted future costs to 1996 dollars using a real interest rate of 2.75%, and provided a reference for the rate used.[36] The remaining 28 studies did not include future costs, and therefore did no discounting.

4. Discussion and Implications of Findings

Regarding the perspective dimension, a majority of the included studies focused on drug-related morbidity in patients attending hospital, and measured the direct costs from a hospital's perspective. The review has identified a large variation in sources (e.g. costs from charges, billed charges or claims payments, several methods for measuring unit costs, and length-of-stay-based cost estimates based on reimbursements or daily hospital costs), and the type of costs (e.g. total, attributable or incremental costs), included in studies measuring the cost of drug-related morbidity. In a majority of the included studies, costs were measured only during the initial care episode; therefore, adjustments of future costs were rarely made. Moreover, the cost analyses of included studies were often described in brief, thus making it difficult to interpret how the analyses were made.

Table II. Description of the 29 studies included in this review, categorized according to the methods used

Study (y)	Quantity: included cases [and controls] (country)	Cost analysis perspective	Prices: direct costs	Prices: indirect costs	Cost/case
Studies of the total cost of patients with drug-related morbidity (total cost)					
Prince et al. (1992)[22]	Review of medical records identified 71 admitted through ER (of 10 184 visits) because of drug-related illness (USA)	Provider	Billed charges		$US8888
Dartnell et al. (1996)[23]	Review of medical records identified 55 admissions (of 965) through ER because of adverse events related to drugs (Australia)	Provider	Costs from cost-accounting system, TSI		$AU5227
Dennehy et al. (1996)[24]	Review of medical records identified 49 ED visits (of 1260) with drug-related illness, of which 8 admitted (USA)	Provider	Costs from cost-accounting system, TSI		$US696 (ADE) $US2815 (ADR)
Tafreshi et al. (1999)[25]	Patient interviews identified 71 medication-related ED visits [of 253] (USA)	Provider	Costs from cost-accounting system		$US1563
Jha et al. (2001)[26]	Computerized alerts identified 76 admissions (of 3238 visits) because of ADE (USA)	Provider	Cost from charges		$US16 177
Schneeweiss et al. (2002)[27]	Review of medical records identified 993 patients (from the general population) admitted because of symptoms or diagnoses of known ADR (Germany)	Payer	LOS (reimbursement/day)		€3731
Wu and Pantaleo (2003)[28]	Review of medical records identified 191 admissions through ER because of serious ADR (USA)	Provider	Billed charges		$US9491
Pirmohamed et al. (2004)[29]	Review of medical records identified 1225 admissions (of 18 820) because of ADR (UK)	Provider	LOS (cost/day)		£1824 (= €2744 = $US3312)
Patel et al. (2007)[30]	Review of medical records identified 141 admissions (of 2046) because of ADR (India)	Provider	LOS (cost/day)		Re6197 (= $US150)
Chan et al. (2008)[31]	43 patients (of 142 295) admitted because of ADR, from voluntary reports (Taiwan)	Provider	Billed charges		$US3489
Pattanaik et al. (2009)[32]	Review and voluntary reports identified 92 ED visits (of 1833) because of drug-related events, of which 47 were hospitalized >48 hours (India)	Payer	Billed charges and unit costs[a]		Re18 884 (= €329)
Carrasco-Garrido et al. (2010)[33]	ICD-9 codes E930–E949 as primary or secondary diagnosis identified 350 835 admissions (1.69% of all admissions during 6 years) for ADR, from a national hospital administrative database (Spain)	Payer	DRG-based estimate (reimbursement)		€4382 (2006 value)[b]
Studies of costs resulting from drug-related morbidity (attributable cost)					
Clyne and German (1992)[34]	226 ER visits with ADR, and 315 admissions causing ADR, from voluntary reports (USA)	Provider	Billed charges		$US228
Schneider et al. (1995)[35]	109 admissions with known clinical consequences of ADR or ME, from voluntary reports (USA)	Provider	Cost from charges		$US2489
Thomas et al. (1999)[36]	Review of medical records identified discharges with drug-related adverse events (USA)	Payer	Unit costs	Unit costs	NA

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Table II. Contd

Study (y)	Quantity: included cases [and controls] (country)	Cost analysis perspective	Prices: direct costs	Prices: indirect costs	Cost/case
Ayani et al. (1999)[37]	135 EW visits (of 5209) with ADR, from voluntary reports (Spain)	Provider	Unit costs (administrative data)		€317 (= $US341)
Wasserfallen et al. (2001)[38]	Review of medical records identified 229 patients (of 3195) admitted mainly because of ADR [imputability >50%] (Switzerland)	Provider	LOS (cost/day)		CHF2393 (= $US4273)
Ramesh et al. (2003)[39]	164 hospitalized patients (of 3717) with ADR, from voluntary reports (India)	Provider	Unit cost		Re690 (= $US15)
Hoonhout et al. (2009)[40]	Review of medical records identified 66 discharged or deceased patients (of 7889) hospitalized because of medication-related adverse events (Netherlands)	Payer	Unit cost		€3105
Hoonhout et al. (2010)[41]	Review of medical records identified 140 discharged or deceased patients (of 7889) with medication-related adverse events during admission (Netherlands)	Payer	Unit cost		€2507
Palanisamy et al. (2011)[42]	36 patients attending hospital because of ADR, and 24 patients attending hospital causing ADR, from voluntary reports (India)	Provider	Cost (non-specific)		Re309
Studies of the added cost of drug-related morbidity, using matched controls (incremental cost)					
Evans et al. (1993)[43]	786 hospitalized patients with ADE, identified from voluntary reports and computerized alerts, and 10 542 controls (USA)	Provider	Charges from cost-accounting system, SCM		$US1939
Suh et al. (2000)[44]	131 hospitalized patients with ADR, from voluntary reports, and 1338 controls (USA)	Provider	Cost from charges		$US5456
Senst et al. (2001)[45]	42 admissions (of 3187) because of ADE, and 74 admissions causing ADE, from voluntary reports and review of medical records, and controls (USA)	Provider	Cost from charges		$US2162
Hafner et al. (2002)[46]	Review of medical records identified 217 patients visiting ED with ADE, and 217 controls (USA)	Provider	Cost from charges		$US631
Pinilla et al. (2006)[47]	63 hospitalized patients with ME, from voluntary reports, and 63 controls (Spain)	Provider	Unit cost (micro-costing)		€1641
Studies of the added cost of drug-related morbidity, using regression analysis (incremental cost)					
Bates et al. (1997)[14]	Review of medical records identified 190 hospitalized patients with ADE, and 190 controls (USA)	Provider	Cost from charges		$US2595
Classen et al. (1997)[16]	Review of medical records identified 1580 hospitalized patients with ADE, and 20 197 controls (USA)	Provider	Costs from cost-accounting system, SCM		$US2013
Hohl et al. (2011)[48]	Medical record review and patient interviews identified 122 patients (of 1000) visiting ED with ADE (Canada)	Payer	Unit cost (micro-costing), SPHCM and MSP		$US233/month, over a period of 6 months

a Billed charges for direct healthcare costs, and unit costs for direct non-healthcare costs.

b Average cost for drug-related morbidity is presented for each year during the study period (2001–6).

ADE = adverse drug event; **ADR** = adverse drug reaction; **$AU** = Australian dollars; **CHF** = Swiss Francs; **DRG** = Diagnosis-Related Group; **ED** = emergency department; **ER** = emergency room; **EW** = emergency ward; **ICD-9** = International Classification of Diseases, 9th edition; **LOS** = length of stay; **ME** = medication error; **MSP** = Medical Services Plan; **NA** = not available; **Re** = Indian Rupees; **SCM** = Standard Cost Manager; **SPHCM** = St Paul's Hospital cost model; **TSI** = Transition System Inc.; **$US** = US dollars.

4.1 Study Viewpoint

4.1.1 Provider Perspective

All included papers measuring costs to the provider were judged to identify costs from a hospital perspective, and included only costs that occurred during the visit or admission to hospital. If the major costs of drug-related morbidity occur during hospital episodes, the focus on costs during hospitalization does not present a problem. However, previous research has indicated there are considerable costs outside of the hospital setting. Thomas et al.[36] suggests lost wages and household production equals 47% of the total costs, with, for example, an estimated average of 460 days of lost household production for each adverse event at $US20 assigned per day. According to an expert panel appraisal by Johnson and Bootman,[19] of drug-related morbidity in the ambulatory setting, the associated direct costs to American healthcare were $US76.6 billion during 1995, from which drug-related morbidity resulting in admission to long-term care facilities represented the second largest cost component. Also, a mail-survey conducted by Isacson et al.[49] estimated that 10% of all prescription drug users and 6% of the Swedish population experienced side effects during a 2-week period, compared with the 5% frequency in hospitalized patients suggested in previous studies.[10,11] Therefore, focusing on hospitalization costs and including costs to providers only will underestimate the costs of drug-related morbidity to society.

4.1.2 Payer Perspective

Six studies were judged to measure costs from the payer perspective, although it may be argued that studies using charges (the price claimed by the provider, from the payer) as a proxy for costs are measuring costs from a payer perspective rather than the hospital. Because of differences in the healthcare systems of each country, the payer varied between studies. Hence, the differing health-care systems make it unfeasible to compare the studies. Also, focusing on a specific payers perspective does not give the entire cost since, for example, mixed payer systems are common in health-care. One example would be the study by Pattanaik et al.,[32] whereby costs during the first 48 hours were not all included in the costs paid by the patients since the initial 48 hours were partially subsidized by the hospital.

4.1.3 Alternative Perspectives

The current review identified several studies estimating costs from the payer perspective, and mainly published after 2002; therefore, only one of these studies was identified in the review by Rodriguez-Monguio et al.[1] However, none of the included studies measured the societal costs of drug-related morbidity. Therefore, the costs of drug-related morbidity resulting in primary care, indirect costs from lost productivity and out-of-pocket costs paid by the patients are still to be measured. Knowledge about the costs to society is needed for directing financial incentives and policy decisions in society. Therefore, there is a need for studies of costs of drug-related morbidity in the general population, including patients not attending hospital due to the event. Since the outcome of costs analyses of drug-related morbidity depend not only on the methods, definitions and costing data used, but also on the healthcare system under study, it is important that results on costs are reported in sufficient detail. Providing only a cost per case gives little information on the actual implications to the hospital, and even less information on the burden to society. Therefore, future research measuring the cost of drug-related morbidity should clearly state the economic perspective.

4.2 Costing

The cost analyses of identified studies used data from administrative cost-accounting data,[14,16,22-26,28,31-35,42-46] unit costing data[36,37,39-41,47,48] or reported hospital costs based on length of stay multiplied by a reference daily price.[27,29,30,38]

4.2.1 Administrative Cost-Accounting Data on Charges

Administrative data on charges were the most common source of costs in the included studies. As has been established in a previous review,[3] research on costs associated with drug-related morbidity has so far been based on pragmatism

and easily available data. The main aim of the included studies was not always to conduct a cost analysis, but the cost analysis was conducted e.g. since the data were available.[43] Administrative data can be billed charges, e.g. the price for services conducted, claim payments that differ depending on insurance company agreements and the healthcare system under study, and costs estimated from charges using cost-to-charge ratio, either departmental- or hospital-specific.[50] Therefore, at least in US studies, billed charges would be the amount of money the hospital demands for its services, while claims payments are the payments of the insurance company, and costs should be an estimate of the actual expenses resulting from the treatment. However, none of the studies using costs based on charges, reported how costs were developed from charges. Moreover, of the five studies using billed charges as a proxy for costs, three studies[28,31,34] described charges as costs. Of the included studies, only Bates et al.[14] reported both charges and costs, and four studies[16,23,24,43] included the cost-accounting programme used. Two[31,35] of the studies using charges reported more detailed information on the quantities and prices of resources used, but costs were otherwise reported as total cost of drug-related morbidity or an average cost per patient with drug-related morbidity. With insufficient information on the administrative system under study, charges or costs derived from charges are difficult to interpret or extrapolate to other settings. As was identified by Rodriguez-Monguio et al.,[1] costs provide a more accurate measurement to the hospital, i.e. the provider, than charges. Also, billed charges are an overestimation compared with the costs to the payer, while claims payments can underestimate the costs to the provider depending on the reimbursement or insurance system. Therefore, the perspective of the cost analysis becomes important when deciding on the methods for estimating costs.

Nine of the studies[22-26,28,31-33] using administrative cost data and three studies[27,29,30] using LOS-based estimates included the total cost of patients suffering from drug-related morbidity. Since the studies did not specify costs resulting from drug-related morbidity, the analyses were likely to overestimate the average cost per patient. In ten of the included studies,[22,23,25-32] this was solved by only including patients hospitalized because of drug-related morbidity, and one study[33] included patients with International Classification of Diseases (ICD) codes related to ADRs as the primary or secondary diagnosis. However, since previous research[51] has suggested there is an underreporting of drug-related morbidity when only including ICD codes or voluntary reports, compared with medical record review, including the resulting costs will underestimate the total magnitude of costs resulting from drug-related morbidity.

4.2.2 Unit Costing Data

Compared with the review by Rodriguez-Monguio et al.,[1] which identified only one study using unit costs, according to the studies included in this review this is now the second most common method for estimating costs. To include both quantities and prices of resources used, studies using unit costs need to report both detailed information on what is included and how the prices and resource use were measured. In the included studies using unit costs, only one study[37] reported the quantities of resources used, but all six studies[36,37,39-41,47] reported how the resource use was measured. In addition, Ayani et al.[37] reported the prices of resources used, while five of the studies[36,37,40,41,47] reported how and when prices were set. In the majority of included studies identifying costs resulting from drug-related morbidity, costs were applied using unit costs for each service, which is a common method for conducting a bottom-up cost-of-illness study.[7] However, alternative methods were also used, either multiplying the total cost by an imputability score based on a WHO algorithm for imputability,[38] including all patients with drug-related morbidity but only charges of patients where the visit or admission was caused mainly by the drug-related morbidity,[34] or identifying charges of services used for treating drug-related morbidity were possible to transform to costs using service-specific cost-to-charge ratios.[35]

Micro-costing is a detailed analysis of changes in resource use due to a particular interven-

tion.[52] Estimating costs based on the collection of patient-specific cost data (time and motion studies, e.g. how much time does this patient require, and what laboratory tests are done), using applicable unit costs, can be argued to be the most valid approach to cost analysis.[8] If collecting cost-accounting data at a high level of detail, the information available will be similar to the results of time and motion studies, and therefore equally valid. One example is the study by Pinilla et al.,[47] where costs are estimated by multiplying the resource consumption from the cost-accounting system by its unit cost. Collection of detailed resource consumption from, for example, medical record review, is costly but gives informative cost data.

In this review, studies were interpreted as using unit costs if costs were not based on charges or costs estimated from charges, and were measured at a more detailed level than the average daily cost. However, the terminology is open for discussion. Charges may be based on unit costs depending on the accounting system used, and unit costs may entail only using an average cost *per diem* multiplied by LOS.[8] Studies may also use a combination of methods, e.g. applying unit costs to services used while LOS is used for days in hospital.[40,41] Pattanaik et al.[32] used charges for hospitalization costs, while non-healthcare costs were estimated using unit costs for each service used. Studies reporting quantities of resources from clinical data should make extrapolations to other settings relatively easy since prices are exchangeable, but data collection will be costly compared with studies using LOS-based measures or administrative data on costs.

4.2.3 Length of Stay

When using LOS-based measures, the quantity will be the days spent in hospital, while the price is the cost *per diem*. LOS-based estimates of costs give useful information on how much time is spent in hospital because of drug-related morbidity, and it is possible to model the costs within another setting with similar patients' characteristics (e.g. the analysis by Goettler et al.[20]). Of the four studies using LOS for measuring the cost of drug-related morbidity, three[27,29,38] report the cost applied to each day, but only one study gave information of how and when the daily cost was estimated.[38] However, estimates based on LOS also have the disadvantage of using an average cost per day, assuming that there are no variations in costs during a hospital admission. Evidence suggests the incremental costs decline during the hospitalization, which causes the LOS method to overestimate the cost of longer hospital admissions,[53] and the costs of short hospital admissions could be underestimated due to comparably high treatment intensity during the brief stay. The possibility of measuring increased LOS has also been questioned. In one study of internal medicine admissions the researchers chose to measure the cost of drug-related hospitalizations only, since it was judged too difficult to discriminate prolongation of stay or procedures related to drug-related morbidity.[54] None of the studies measuring costs resulting from drug-related morbidity used LOS-based measures, which would require a decision to be made on the actual increased LOS that was due to drug-related morbidity. However, studies using unit costs will suffer the same disadvantage in terms of putting a unit cost on the increased LOS. A solution has been suggested, i.e. conducting a sensitivity analysis using several methods for measuring the increased LOS,[55] but this was not done in the included studies. Both matched controls and regression analyses may solve the issues with measuring increased LOS; however, using LOS-based measures for estimating costs assumes costs are evenly distributed between days in hospital. As with all studies using matched controls, bias will be introduced if cases and controls are not well matched. Cost-estimates based on LOS may add useful knowledge about the cost of drug-related morbidity if they include clear information on patient's characteristics or if they use regression analyses for estimating the cost increase.

4.2.4 Methods and Sources for Costing

Irrespective of the methods used for cost analysis, the sources used and costs included should mirror the resource consumption resulting from the illness under study, e.g. drug-related morbidity. Including the total cost of all patients where

the main diagnosis was drug-related excludes the costs resulting from drug-related morbidity if there is another main diagnosis. If also including drug-related morbidity as a secondary or third diagnosis, the total cost will be an overestimate since the costs resulting from the main diagnosis are included. Using unit costs can result in double-counting of costs, but is still the most valid approach to cost analyses. The quality of results in studies estimating incremental costs of drug-related morbidity, using either matched controls or regression analyses, also depends on how costs are included since the analysis will not give better results than the initial data collection allows.

According to Chevat et al.[56] costs are country-specific, and the main difference is generally the cost applied to each healthcare intervention (e.g. cost per day in hospital or specific laboratory tests). Therefore, presentation of both quantities and prices are essential for comparison of results between studies and countries, together with information on the method used for estimating both costs and quantities.

4.3 Adjustments for Timing of Costs

All the included studies identify drug-related morbidity in patients admitted or visiting hospitals, and costs were only included during the care episode in all but one study.[36] None of studies report the date of costs in greater detail than when the study was conducted, or gave conclusive information on how costs were included at the start or end of the study period. If studies are incidence-based, all present and future costs should be collected or calculated based on previous research.[57] Since there are ADRs resulting in repeat admissions,[58] costs to the hospital need to also include costs resulting from readmissions, which may need to be discounted. Failing to include readmissions in incidence-based hospitalization costs will result in underestimation. Prevalence-based studies should identify all costs during the study period, exclude all future direct costs, but include future indirect costs resulting from permanent disability or death.[57] Therefore, drug-related morbidity initiated before the study period, but still resulting in costs, needs to be identified. Also, there should be a cut-off at the end of the study period. Not doing this is likely to result in a disproportion between included cases and estimated costs, and an underestimation of both the prevalence measure and the average cost of drug-related morbidity.

Only the study by Thomas et al.[36] reported any discounting, but since other studies only include costs during the care episode this should not be a problem. However, with those studies continuing over several years, it is unclear if costs should be discounted, depending on the maximum length of the included care episodes.

4.4 Implications for Future Research

According to the results of our review, the perspectives of costs analyses in the included studies are often limited to estimating costs to the hospital. Compared with a review conducted in 2003,[1] there is however a trend towards cost analyses using unit costs and estimating costs from the payers perspective. Still, there is a gap in the knowledge regarding the costs of drug-related morbidity to providers other than hospitals, costs occurring outside of hospitals and costs after the initial care episode. Because of the identified variation in methods and sources used for cost analysis, and few studies reporting both quantities and prices, there is a need to further elaborate the methods sections regarding cost analyses. Also, often the terminology used to describe the cost analyses deviates from what is usually recommended in economic evaluation studies. To avoid underestimating the economic impact of drug-related morbidity in society, future studies are needed to estimate the costs occurring outside of the hospital setting, during readmission, and using unit costs and detailed resource consumption identified from medical record review.

Previous reviews[1-3,20,59] have suggested there has been large methodological heterogeneity between studies measuring costs of drug-related morbidity, e.g. methods for detection of cases of drug-related morbidity, assessment of causal relationship between drug and the resulting morbidity, and how to define drug-related morbidity. According to the results of this review, there is also

a large heterogeneity between the methods and cost sources used for cost analysis within these studies. Methods for estimating costs should be viewed as an equally important part of the methods section. It has been argued that there is a need for closer relationships between researchers and research within the fields of pharmacoeconomics and pharmacoepidemiology.[60] A start would be to develop an evaluation tool based on published checklists aimed at measuring the quality or guiding research within the field of observational descriptive studies,[61-63] and economic evaluation,[4,5] respectively. Depending on the research question, adapting to international guidelines and terminology within economic cost analyses is recommended.[64,65] The recently published guidelines for critical evaluation of cost-of-illness studies[66] should add valuable items regarding the use of top-down/bottom-up methods, and of incidence/prevalence measures. Also, the term 'indirect costs' should be used primarily for reporting productivity loss due to illness, rather than hospital overhead costs, in accordance with the terminology suggested by Rice.[21] Such a tool can be adjusted to fit the needs of researchers measuring the costs of drug-related morbidity.

4.5 Limitations

The search was developed based on keywords and phrases identified from screening previous reviews and were designed to identify a wide range of articles, since the differences in terminology made it difficult to identify adequate keywords. To minimize the number of studies missed, the search of relevant articles was conducted in three databases. To verify that no articles had been missed, an initial search was also performed in the Cochrane Database for Systematic Reviews and the International Pharmaceutical Abstracts database, but without identifying any unique hits. Moreover, citation lists and reference lists of included articles as well as previous reviews were scrutinized to identify eligible articles.

More than 99% of articles found in the initial database search were excluded in the review process. The main reasons for exclusion were studies of a specific treatment or disease, articles not written in English or the text not presenting a peer-reviewed original study article. Also, articles excluded during the full-text analysis were mainly studies of costs within a specific setting (i.e. internal medicine, or only cardiology or oncology patients) or using a proxy measurement for identifying drug-related morbidity (e.g. prescription errors identified within the pharmacy or potentially inappropriate medicines use). The exclusion of studies estimating costs in specific settings or diseases does result in the review giving only partial knowledge of how costs of drug-related morbidity are measured, but was made to simplify comparisons between included studies. Since the aim was to study methods used rather than costs, excluding studies in specific settings or patient groups and eligible articles not identified through the search (as long as articles were left out randomly), should not affect the conclusions much. However, exclusion of non-English articles could result in a lack of knowledge regarding methods used in countries less likely to publish reports in English.

This review used selected items for assessing economic evaluation studies.[4,5] Development of a common standard for cost analysis in studies measuring the overall costs of drug-related morbidity may include using other categorizations and may find additional issues for discussion.

5. Conclusions

The data sources and costs measured in the included studies varied considerably in terms of perspectives and use of data sources. Even though there is a trend towards more studies estimating costs from the payer perspective, the identified studies still focused on costs resulting from patients attending hospital, therefore underestimating the cost of drug-related morbidity. There is thus a need for more research on the costs of drug-related morbidity to providers other than hospitals, costs occurring outside of hospitals and after the initial care episode. Such studies require clear descriptions of how the costs of drug-related morbidity are measured, and should adhere to published guidelines for observational studies and economic evaluation studies.

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