ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (3): 233-244
0114-5916/10/0003-0233/$49.95/0

The Relationship Between Study Characteristics and the Prevalence of Medication-Related Hospitalizations

A Literature Review and Novel Analysis

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Abstract

Background: Studies on medication-related hospitalizations differ in study setting, studied population, outcome, and method of data collection. Thus, extrapolations based on a meta-analysis of unselected studies may be biased.
Objective: To explore the influence of study characteristics on the prevalence of medication-related hospitalizations.
Methods: After a structured literature search, the retrieved studies were categorized based on the following aspects: (i) study setting (e.g. all hospital admissions vs only acute hospital admissions); (ii) study population (e.g. an entire hospital, study ward(s), selected population and/or age group); (iii) outcome of medication-related problem (e.g. adverse drug reaction [ADR] vs adverse drug event [ADE]); (iv) method of data collection (e.g. medical chart review, spontaneous reporting or database research); and (v) continent in which the study took place (only for studies looking at all acute admissions). We then examined the relationship between these factors and reported prevalence of medication-related hospital admissions.
Results: Ninety-five studies were analysed, with a range of reported prevalence of medication-related hospitalizations from 0.1% to 54%. Higher prevalences were found in the studies examining all hospital admissions than in the studies examining only acute hospital admissions. In addition, higher prevalences were found in the elderly population than in children. As would be expected, higher prevalences were also found in studies examining ADEs than in studies examining only ADRs. With respect to the method of data collection, medical chart screening resulted in higher prevalences of medication-related hospitalizations than database methods or spontaneous reporting.

Combined studies in Europe show lower prevalences of medication-related hospital admissions than in other continents included in the study.
Discussion: The reported prevalence of medication-related hospital admissions varies as a function of the setting (all admissions or only acute admissions), studied population (entire hospital, specific wards, selected population and age group), outcome (ADR/ADE), the method of data collection and the continent in which the study is performed.
Conclusion: Extrapolation using national hospital admission data and the prevalence identified by pooling international studies should be carried out with great caution.

Background

Medication safety, which is part of the broader context of patient safety, is considered an essential element of high-quality healthcare systems. This notion has gained recognition in recent years, especially since the publication of the report 'To err is human' by the Institute of Medicine in the USA.[1] This report fuelled social awareness and pressure to improve patient safety worldwide.

Data on patient and medication safety mainly originate from English speaking countries, which are often extrapolated to other countries and settings to estimate the burden of medication-related harm. An example of such an extrapolation is the meta-analysis of Beijer and de Blaey[2] regarding the prevalence of medication-related hospitalizations. Based upon the findings of previously published studies, they estimated that 4.8% of all hospital admissions were medication related, of which 29% were preventable. These findings were extrapolated to the Netherlands, taking age into account, and resulted in an estimated number of 130 000 medication-related hospitalizations annually, of which almost 80 000 admissions in the elderly were considered to be preventable. These figures have often been cited in the Dutch lay press and have resulted in political attention. However, after publication of the review by Beijer and de Blaey,[2] three Dutch studies were published that specifically investigated the prevalence of medication-related hospital admissions in the Netherlands.[3-5] The reported prevalences (1.8%, 3.5% and 2.4% in the three studies, respectively) of all medication-related hospital admissions were lower than the point estimate reported in the meta-analysis of Beijer and de Blaey.[2]

One explanation for the differences seen may be due to actual differences in healthcare systems in the USA, the UK and the Netherlands. Another reason may be that the published studies on this topic differ in certain key aspects that were examined, such as setting (e.g. entire hospital vs specific wards), type of admissions (e.g. all hospitalizations or only acute admissions), study population (e.g. specific wards), outcome (e.g. focus on adverse drug reaction [ADR] vs adverse drug event [ADE]), data collection method (e.g. clinical coding database, medical record screening or spontaneous reporting) and continent in which the study was performed. Therefore, the objective of this study is to explore the relationship between certain study factors and the prevalence estimate of medication-related hospital admissions.

Methods

Data Sources and Study Selection

Data for this review came from two sources. First, all studies included in the meta-analysis of Beijer and de Blaey[2] were included (these comprised studies performed up to 2001 and were counted as studies identified by screening reference lists). For retrieving studies performed since 2001, a PubMed search was performed

using the search terms 'hospitalization' or 'hospital admission' or 'admission to hospital' and 'medication', with the exclusion of search terms 'drug abuse' and 'alcohol abuse'. Other limits in this search were English language and publication date from April 2001 until March 2009. Additionally, the reference lists of all retrieved publications (both from the meta-analysis and from the PubMed search) were screened for additional eligible studies.

Studies were further selected from the above sources if they provided data that estimated the prevalence of medication-related hospitalizations of outpatients and if they were written in the English language. Studies were excluded if they addressed only specific types of ADEs (e.g. blood dyscrasias or cardiovascular events), ADEs in patients with a particular disease (e.g. heart failure patients or depressive patients), emergency visits without hospitalization, hospitalization after the use of one specific drug (e.g. digoxin or chemotherapy), ADEs without an evaluation of the relationship to admission or ADEs during admission.

Data Extraction and Definitions

For each included study the following data were extracted: bibliographic characteristics (year of publication, first author), characteristics of the study setting and population (country, hospital, study period, included admissions and patient age group), the outcome focus (ADE or ADR), methods of data collection (medical chart review, database method or spontaneous reporting method) and continent in which the study was performed. Every paper was studied for these characteristics and classified according to the definitions as stated below.

The study setting was defined as the location where the study participants were included – either admission to the entire hospital or specific categories of the hospitalized population. The first category of admission to the entire hospital was further subdivided into all admissions or only acute admissions. An acute admission was defined as any unscheduled admission to a hospital. All admissions were defined as a combination of planned admissions and acute admissions.

The second specific category of the hospitalized population was subdivided into admission to one or more specific wards (internal medicine, cardiology, gastroenterology, respiratory medicine, medical wards, paediatrics, paediatric oncology, neonatology, psychiatry, care of the elderly), a specific patient population (selection of hospital admissions of patients with polypharmacy or medication-related problems) or age group of patients (all ages, adults, children, elderly [defined by the authors or a cut-off of 65 years or older]).

An ADE was defined as medication-related harm, caused by either an ADR or a medication error. ADEs caused by medication errors are potentially preventable.[6] An ADR is defined by the WHO as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological functions".[7] These definitions were used to identify the exact outcome of the study. When any mention was made on preventability in the study then the outcome was defined as ADE (even when the authors themselves defined the outcome as ADR). Intentional and unintentional overdoses were classified as medication errors and thus the harm they caused was classified as an ADE.

A database method was defined as a method of data collection in which the medication-related admissions are identified from a database of hospital discharge diagnoses. A spontaneous reporting method was defined as a method of data collection in which the medication-related hospitalizations are identified from doctor and/or nurse reports of adverse events. Medical chart review was defined as the third method of data collection in which the medication-related hospitalizations were identified from the patients' medical record or case notes of the admission. This method could be retrospective or prospective.

Finally, the following six geographical areas ('continents') were defined: Australasia (Australia and New Zealand), North America (Canada and

the US), Europe, Middle and South America, Asia and Africa. To better compare studies from these continents we only included the studies that examined the outcome (ADRs or ADEs) for all acute admissions and that used medical chart review as the method.

Data Analysis

From the extracted data, the prevalence of medication-related hospital admissions was calculated by dividing the number of patients admitted to the hospital because of a medication-related event (the numerator) by the number of patients admitted to the hospital within the study period and within the study setting (the denominator). The included studies were stratified with respect to setting (included admissions), study population (subdivided into study ward, selected population and age group), outcome focus and method of data collection. For all strata, the weighted mean prevalences were calculated using the inverse variance method[8] in which the studies are weighted by their standard error (SE), which is related to the population size.

The SE is calculated using the formula $\sqrt{((p \times (1-p))/n)}$, where p is the proportion of medication-related admissions of the studied hospital admissions and n is the total number of studied hospital admissions. The confidence interval is calculated using the formula 'prevalence $\pm (1.96 \times SE)$'.

Results

Literature Search Results

The electronic search resulted in 17 articles; the study of the references of these articles and of several literature studies and the meta-analysis of Beijer and de Blaey[2] resulted in the identification of an additional 72 articles, resulting in 89 relevant articles (figure 1).[3,4,5,9-94] Of these 89 articles, four[10,33,74,88] concerned a combination of two studies and one[31] concerned a combination of three studies. Thus, 95 studies were analysed (see table, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A24). Table I shows the number of studies subdivided by study setting, study population (further subdivided into study ward, selected population and age group), outcome focus, data collection method and continent.

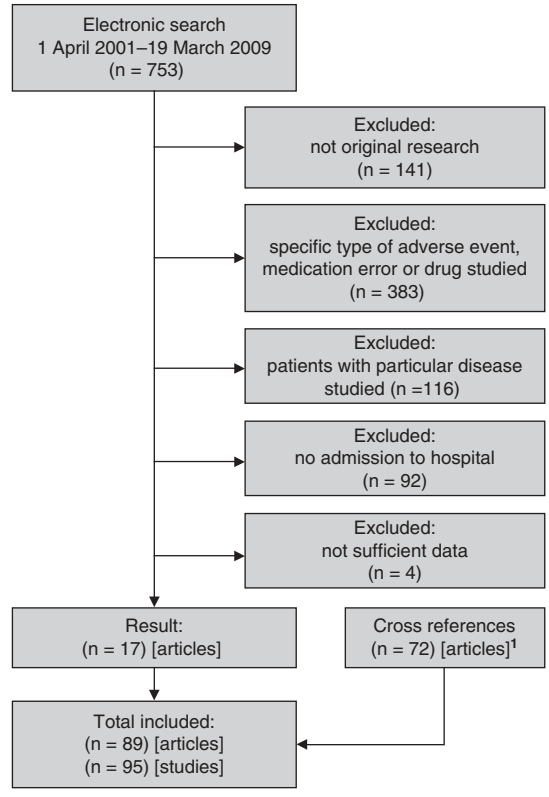

Fig. 1. Study design and numbers of included and excluded studies. **1** Cross references from other studies retrieved from the electronic search and from the meta-analysis of Beijer and de Blaey.[2]

The prevalence estimate for medication-related hospital admissions varied in the identified studies from 0.1% to 54%. Also, a large variation was found in the number of included admissions in the denominator, from 41 admissions studied by medical chart review[86] to a clinical coding database study of almost 89 million admissions.[44]

Prevalence Estimates

All studies combined (irrespective of study setting, study population, outcome focus and data collection method) resulted in a very low weighted mean prevalence of medication-related hospitalizations of 0.46% (95% CI 0.458, 0.460).

Study Setting

The weighted mean prevalence of medication-related hospitalizations was calculated for studies looking at all hospital admissions and only acute hospital admissions as a denominator. Higher prevalences were found in the studies examining all hospital admissions (3.03% [95% CI 2.87, 3.20] for admissions related to ADRs,[9-12] and 5.35% [95% CI 5.08, 5.62] for admissions related to ADEs[4,40-42]) than in studies only examining acute hospital admissions (1.14% [95% CI 1.04, 1.23] for admissions related to ADRs,[15] and 3.68% [95% CI 3.49, 3.87] for admissions related to ADEs[5,47-63]) [table II].

Study Population

Prevalences were also calculated for the different study populations found on different study wards. Studies examining ADEs on wards for care of the elderly (10.18% [95% CI 9.06, 11.29][87-91]) and psychiatric wards (23.05% [95% CI 14.84, 31.27][85,86] including intentional overdoses) showed high prevalences, whereas relatively low prevalences were found in studies in paediatric wards (3.94% [95% CI 3.11, 4.76] including all admissions related to ADEs,[74,83] and 4.33% [95% CI 3.59, 5.07] including only acute admissions related to ADEs[84]) [see table II]. This pattern of results was also seen when specific age groups were analysed: 3.60% [95% CI 3.39, 3.81] related to ADRs in the elderly[12,24,36-39] versus 0.19% [95% CI 0.16, 0.23] in children with ADR as the studied event,[30-34] and 12.30% [95% CI 11.30, 13.29] related to ADEs in the elderly[48,49,54,87-91] versus 4.16% [95% CI 3.61, 4.71] in children with ADEs as the studied event[74,83,84] (table II).

High prevalences were found in patients who had been admitted previously because of a medication-related problem (19.46% [95% CI 15.77, 23.15][93] and 17.71% [95% CI 17.27, 18.15][39]) or in patients with polypharmacy (five or more drugs; 6.63% [95% CI 4.01, 9.25][94]).

Outcome (Adverse Drug Event vs Adverse Drug Reaction)

Of the 95 studies, 59 examined ADEs and 36 examined ADRs. As would be expected, the weighted mean prevalence of studies that use ADE as an outcome was higher (see Study Setting section and table II).

Method of Data Collection

All medical chart review studies combined (irrespective of study setting, study population and outcome) resulted in a low weighted mean prevalence of medication-related hospitalizations of

Table I. No. of studies presented by setting, population, method of data collection and definition of outcome (adverse drug reaction [ADR]/adverse drug event [ADE])

Studies	ADR (n = 36)	ADE (n = 59)	Total (n = 95)
Setting			
Included admissions			
all hospital admissions	6	8	14
all acute hospital admissions	2	18	20
Population			
Studied ward or other population			
internal medicine	14	16	30
cardiology	1	0	1
gastroenterology	0	1	1
respiratory medicine	0	1	1
medical wards	0	1	1
paediatrics – all hospital admissions	5	2	7
paediatrics – acute hospital admissions	1	1	2
paediatric oncology	1	0	1
neonatology	1	0	1
psychiatry	1	2	3
care of the elderly	3	6	9
intensive care unit	0	1	1
others (polypharmacy, previous medication-related admission)	1	2	3
Studied age group			
all ages or adults	22	47	69
children	8	3	11
elderly	6	9	15
Continent of study			
Australasia	3	8	11
North America	10	17	27
Middle and South America	0	0	0
Europe	18	26	44
Asia	4	8	12
Africa	1	0	1
Method of data collection			
Medical chart review	32	55	87
Database/computer screening	3	2	5
Spontaneous reporting	1	2	3

Table II. Prevalence of drug-related hospital admissions with adverse drug reaction (ADR)/adverse drug event (ADE) as definition of outcome and various settings and studied populations (all chart review methods)[a]

Studies	ADR		ADE	
	weighted mean prevalence [% (95% CI)]	no. of studies	weighted mean prevalence [% (95% CI)]	no. of studies
Setting				
Included admissions				
all admissions	3.03 (2.87, 3.20)	4[b]	5.35 (5.08, 5.62)	4[b]
all acute admissions	1.14 (1.04, 1.23)	1[b]	3.68 (3.49, 3.87)	18
Population				
Studied ward or other population				
internal medicine	2.67 (2.54, 2.79)	14	4.32 (4.01, 4.62)	16
cardiology	11.50 (8.47, 14.53)	1		0
gastroenterology		0	11.89 (8.39, 15.39)	1
respiratory medicine		0	7.99 (4.98, 10.99)	1
medical wards[c]		0	10.61 (9.26, 11.96)	1
paediatrics – all admissions	0.19 (0.15, 0.23)	5	3.94 (3.11, 4.76)	2
paediatrics – acute admissions	0.93 (CI not available)	1	4.33 (3.59, 5.07)	1
paediatric oncology	21.7 (18.66, 24.65)	1		0
neonatology	0.20 (0.04, 0.6)	1		0
psychiatry	7.48 (4.60, 10.35)	1	23.05 (14.84, 31.27)	2
care of the elderly	10.80 (9.50, 12.10)	3	10.18 (9.06, 11.29)	6
intensive care unit		0	7.47 (4.42, 1058)	1
polypharmacy (>4)		0	6.63 (4.01, 9.25)	1
previous admission for drug-related problem		0[b]	19.46 (15.77, 23.15)	1
Studied age group				
all ages or adults	1.79 (1.72, 1.86)	19[b]	4.31 (4.17, 4.44)	43[b]
children	0.19 (0.16, 0.23)	8	4.16 (3.61, 4.71)	3
elderly	3.60 (3.39, 3.81)	5[b]	12.30 (11.30, 13.29)	9
Continent of study setting: all acute admissions				
Australasia		0[d]	8.09 (6.68, 9.51)	3[d]
North America		0[d]	14.73 (13.08, 16.37)	3[d]
Europe	1.10 (1.04, 1.23)	1[d]	3.30 (3.11, 3.50)	11[d]
Asia		0[d]	6.90 (5.80, 8.00)	1[d]
Africa		0[d]		0

a Only studies with similar study method, same denominator and same numerator compared.

b Studies with different study methods, such as spontaneous reporting or database method, were excluded.

c Admissions to geriatric, internal medicine, cardiology, respiratory and gastroenterology wards.

d Studies with different study methods, such as spontaneous reporting or database method, and studies with different settings, other than all acute admissions, were excluded.

0.85% (95% CI 0.82, 0.88).[4,5,9-12,15-38,40-42,47-94] A number of studies use methods other than medical chart review to find cases of medication-related hospitalization. These kinds of studies also show low prevalences of 0.14–1.83%,[3,13,14,39,43-46] with the exception of a study that included only patients who had been previously admitted because of an ADR (17.71% [95% CI 17.27, 18.15])[39] [table III].

Continent Where the Study Took Place

Studies conducted in the US, Europe or Australasia report similar prevalences of admission to hospital that are related to medication. The

Table III. Prevalence of drug-related hospital admissions with adverse drug reaction (ADR)/adverse drug event (ADE) as definition of outcome, and database methods of data collection and spontaneous reporting method of data collection[a]

Data collection method and denominator	ADR		ADE	
	weighted mean prevalence [% (95% CI)]	no. of studies	weighted mean prevalence [% (95% CI)]	no. of studies
Database				
Denominator: all admissions	0.14 (0.10, 0.18)	1	0.46 (0.46, 0.46)	2
Denominator: acute admissions	1.83 (1.59, 5.42)	1		
Denominator: previous admission for ADR	17.71 (17.27, 18.15)	1		
Spontaneous reporting				
Denominator: all admissions	0.70 (0.43, 0.97)	1	0.52 (0.44, 0.60)	2

a Only studies with a similar study method, the same denominator and the same numerator compared.

calculated weighted mean prevalence of studies in North America on ADEs and all acute admissions was 14.73% (95% CI 13.08, 16.37),[40,47,48] combined studies in Australasia was 8.09% (95% CI 6.68, 9.51)[49,50,54] and for combined studies in Europe was 3.30% (95% CI 3.11, 3.50).[5,51-62] Studies conducted in Europe therefore seem to have lower prevalences than studies in both Australasia and North America (see also table II). For Asia and Africa, too few studies were available.

Discussion

This literature review shows that in studies of medication-related hospitalizations a wide range of prevalences is reported. This variation can be explained by the differences in study setting, study population (and thus choice of denominator for prevalence calculation), outcome (ADRs or ADEs as the numerator for prevalence calculation) and data collection method. Furthermore, the variation may arise from differences in healthcare systems between countries. Therefore, it is not possible to combine all these different studies and present a representative prevalence of medication-related hospital admissions.

Outcome, Settings, Study Populations, Methods of Data Collection and Continent

In studies looking at ADEs, higher prevalences are found than in studies on ADRs. This higher percentage is to be expected because ADEs include not only ADR events but also harm caused by medication errors (i.e. the potentially preventable harm). Therefore, when studying medication-related hospitalizations, the broader focus of ADE as an outcome is to be recommended as the focus of the study.

An unexpected finding was the difference found in the prevalence of medication-related hospital admission when examined for all admissions versus only acute admissions. It is to be expected that ADEs and ADRs are acute problems and hospitalization due to these problems cannot be a scheduled admission. Therefore, all admissions should result in lower percentages of medication-related hospital admissions. Nevertheless, a higher percentage was found in this analysis. This can be partly explained by an outlier study on all admissions in a hospital in Iran by Zargarzadeh et al.[42] They found a large percentage of medication-related hospital admissions in the population (76%) due to literacy problems. This reason for medication-related problems is not widely recognized in other studies and therefore the study of Zargarzadeh et al.[42] in Iran might not be representative for developed countries. Also, Pirmohamed et al.[41] found a higher percentage than expected for all admissions. This could be explained by the fact that most patients in this study were admitted through either the accident and emergency department or the acute medical and surgical assessment units; in fact the admissions included were largely unplanned, which might have resulted in a higher proportion of medication-related hospital

admissions.[41] This unexpected difference in mean prevalence disappears when the study of Zargarzadeh et al.[42] is excluded and the study of Pirmohamed et al.[41] is reclassified as acute admissions due to ADEs. The prevalence of all admissions due to ADEs decreases from 5.35% to 3.34% and the mean prevalence of only acute admissions due to ADEs increases from 3.68% to 4.31%. Thus, in this re-analysis, the mean prevalence of only acute admissions is higher than the mean prevalence of all admissions, which is in accordance with expectations.

A higher prevalence was also found for the selection of specific study wards and for selection in the study population. Although the number of studies included was small, the identified prevalences can be regarded as a reflection of the different types of patients in the selected wards and their risk of an ADR or ADE. For example, elderly patients are regarded as high-risk patients because of their multiple drug use, which results in high prevalences in studies performed in an elderly population.[95,96] The high prevalences found on psychiatric wards[85,86] can be explained by the multiple drug use in psychiatric patients, together with their many drug-related problems,[97,98] and the inclusion of admissions due to drug abuse and intentional overdose in the included studies. Children, on the other hand, use few or no drugs, which results in low prevalences in studies performed in paediatric admissions or in children.[99,100] Yet, as stated before, these results need to be assessed with caution because of the relatively low number of studies per subcategory of patients.

With respect to the method of data collection, (retrospective or prospective) medical chart screening results in higher prevalences than database methods or spontaneous reporting. It can be concluded that ADEs and ADRs are underreported when using spontaneous reporting or database methods of data collection.

Finally, when looking at the effect of the continent in which the study was performed, European studies seemed to show smaller prevalences than North American and Australasian studies. This may be the result of different healthcare systems in the different countries, but conclusions on this outcome need to be drawn with care because of the relative limited number of studies on ADEs using a medical chart review method investigating all acute admissions performed in Australasia and North America.

Comparing Results

The meta-analysis of Beijer and de Blaey[2] does make a correction for sample size of the study and also divides the studies into elderly versus younger study populations, but the choices of numerator (ADRs or ADEs) and denominator (all admissions, only acute admissions, specific wards) were not taken into account. Disregarding the influence of the denominator will lead to an overestimation of the prevalence of medication-related hospitalizations. Combining studies, regardless of whether they look at ADRs or ADEs as a numerator, could result in an underestimation of the prevalence.

The results of the published, prospective, multicentre, HARM (Hospital Admissions Related to Medication) study[5] into medication-related hospitalizations in the Netherlands confirms that the meta-analysis of Beijer and de Blaey[2] overestimates the number of medication-related hospitalizations. Extrapolation of the results to the Dutch situation results in 16 000 potentially preventable hospital admissions each year according to the HARM study, while Beijer and de Blaey[2] estimated this number to be as high as 90 000 admissions.

Lazarou et al.[101] studied only ADRs and state that the heterogeneity in their results is due to variation in the examined population. However, they did not study ADRs exclusively, since a few included articles also studied medication errors. Furthermore, despite their statement on heterogeneity, the estimated number of hospital admissions was not adjusted for ward type when extrapolated. By over-representing medical wards in the analysis and including admissions due to medication errors, the incidence and number of admissions related to ADRs are likely to be overestimated.

Wiffen et al.[102] also studied ADRs and showed heterogeneity in the results. They identified a

prevalence of 2.6% from predominantly North American studies, which was shown to be about one-half the prevalence in Europe and the UK. Therefore, extrapolation on the basis of North American studies can result in an underestimation of the number of medication-related hospital admissions in Europe and the UK.

Finally, Kongkaew et al.[103] analysed studies on hospital admissions associated with ADRs only. This systematic review suggests that approximately 5.3% of hospital admissions are associated with ADRs. An overall prevalence was calculated, while heterogeneity between the studies, especially higher rates for elderly patients, were observed. Therefore, applying this prevalence of 5.3% to total numbers of admissions (including non-elderly patients) can result in an overestimation of the number of medication-related hospital admissions.

Lazarou et al.,[101] Wiffen et al.[102] and Kongkaew et al.[103] studied only ADRs as a numerator, while in our analysis, studies with ADEs as a numerator were also included. Because of the broader focus of ADEs than ADRs, more medication-related admissions in the numerator are expected. Therefore, the extrapolation based on ADRs only can give an underestimation of the number of medication-related hospital admissions.

Over- or underestimation may still be the case when applying the prevalences identified in our review. Even though we tried to group similar studies and separate those that are different, the definitions we used may still be too broad or the settings may not be comparable. Another limitation is the inclusion of studies limited to the English language. Notwithstanding our rigorous search method, we still may have missed some studies.

However, to our knowledge this review is the first that systematically analyses the influence of choice of outcome, settings, study populations and methods of data collection on the results reported in studies on medication-related hospitalizations. This reveals important information for the interpretation as well as the design of future studies on this subject. Future studies should use clear definitions, should preferably study ADEs instead of ADRs, should include entire hospital populations instead of subpopulations, and should use the more reliable method of chart review. Furthermore, studies into the differences between various countries and healthcare systems are needed.

Conclusion

In conclusion, this study shows that the prevalences of medication-related hospitalizations reported in studies looking at ADEs and/or specific wards such as those for care of the elderly and psychiatric patients are higher than in studies investigating ADRs as the numerator and/or all admissions as the denominator. Furthermore, the prevalences of medication-related hospitalizations are lower in studies using other methods than medical chart review for the prevalence calculation. As prevalences of hospital admissions related to medication depend on setting and focus of the outcome, extrapolation of these prevalences using local hospitalization data should be carried out with great caution.

Acknowledgement

The authors would like to thank Pamela M. Kato, PhD EdM, University Medical Centre Utrecht, for her comments on the manuscript.

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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