Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies

• H.J.M. Beijer and C.J. de Blaey

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HJM Beijer (correspondence) and **CJ de Blaey:** Scientific Institute Dutch Pharmacists (WINAp), P.O.Box 30460 2500 GL The Hague, The Netherlands
(e-mail: h.j.m.beijer@winap.nl)

Keywords
ADR related hospital admission
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Abstract
Aim: to establish the percentage hospital admission related to adverse drug reactions (ADRs) from the data available in the literature.
Method: literature search in the Medline database, meta-analysis.
Results: from the literature it is revealed that a considerable part of all hospital admissions are related to adverse drug reactions. However, these data are not homogenous, i.e. larger studies display a lower percentage of ADR related hospital admission, while smaller studies display a higher percentage. Subgroup analysis showed that for elderly people the odds of being hospitalised by ADR related problems is 4 times higher than for younger ones (16.6% vs. 4.1%). A considerable part of these hospitalisations can be prevented. Subgroup analysis revealed that in the elderly up to 88% of the ADR related hospitalisations are preventable; for the non-elderly this is only 24%. Comparatively more elderly people are hospitalised than younger ones. Combining these findings, twice as much elderly people are hospitalised by ADR related problems than non-elderly, while preventability of ADR related hospitalisation might yield 7 times more people in the elderly than in the non-elderly. The estimation of the costs of ADR related hospitalisations in the Health Care system in The Netherlands is discussed.
Conclusion: many elderly people are hospitalised by ADR related problems; an important part of these hospitalisations can be avoided.

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Introduction

To the patient an unnecessary hospital admission caused by adverse drug reactions (ADRs) is an unnecessary loss of health as well as an unnecessary loss of quality of life; besides it is a waste of money. In other words, unnecessary hospital admission by ADRs is very inefficient. Prevention will avoid part of this waste of health as well as part of the waste of money. Thus, prevention of unnecessary hospitalisations by ADRs might be an important goal in health policy decision-making.

No meta-analysis on unnecessary hospital admissions by ADRs could be found in the literature; therefore we tried to apply meta-analysis techniques on this topic.

The goal of this study is to establish the percentage adverse drug reactions related hospital admission from the data available in the literature using meta-analysis techniques. Besides we will discuss its preventability.

Method

A literature search was performed in the Medline Database, first search in April 2000; last search in April 2001. Inclusion criteria were the keywords: hospitalisation, hospital admission, drug related-problems, adverse drug reactions. The number of papers found with these inclusion criteria was 306. For reasons of reducing heterogeneity, the following exclusion criteria were used: elicit drug use, drug abuse, alcohol abuse, and drug-related problems during hospitalisation. Number of papers left after this selection was 159. Among these we found 38 papers containing data on ADR related hospitalisations as well as data on the total number of patients hospitalised.

Complementary searches were performed in the Cochrane Library CD-ROM [1], yielding one paper [2]. In this review and in a second one [3] we found an additional 26 papers containing similar data. Overall we found 68 studies, published in 64 papers [4-67].

As for the definition of an adverse drug reaction (ADR), we used the definition by the World Health Organisation: an adverse drug reaction is a noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylactics, diagnosis or therapy. Thus, therapeutic failures, intentional and accidental poisoning (overdose) and drug abuse were excluded from the search [2].

In each of the selected studies the authors had calculated the percentage of ADR related hospitalisation. Per study we calculated the uncertainty of this estimator; it depends on the value of the proportion found, and on the study size. A proportion is binominally distributed with mean = proportion p, and SE = sqrt[p*(1-p)/N]. The 95% confidence interval = p-(z*SE) to p+(z*SE) with z = 1.960 (z: standardised normal distribution). These confidence intervals (CI) encompass the value of the parameter with a probability of 95%.

Microsoft Excel97 was used for data recording. Excel97 and SPSS version 10 were used for statistical analysis.

Results

The papers that were selected in this review [4 - 67] contain data describing the total number of patients hospitalised as well as the proportion caused by unintentional harm by inappropriate drug use. Also some accessory characteristics of the drug use, such as age, preventability, type of hospital, were described in these studies. No case-control study, cohort study or experimental study for identifying risk factors for ADR related hospitalisations could be identified. So this review deals with observational studies only.

In these 68 studies, the hospitalisation of 6,071 patients was judged to be ADR related, in a grand total of 123,794 hospital admissions, which is 4.9% ± 0.1% (mean ± confidence interval). Per study the number of patients hospitalised varied considerably from 41 to 24,000; the number of patients hospitalised by ADR varied from 6 to 686. The percentage of patients hospitalised due to ADR varied from 0.2% - 41.3% (Table 1).

First the proportional hospital admission was plotted against study size, as a funnel plot (Fig 1). The larger studies display low proportions of ADR related hospitalisation, while smaller studies show much higher proportions. This curvilinear relation is rather peculiar, as it seems reasonable to expect ADR related hospitalisation to be not dependent from study size.

An alternative way to assess the ADR related hospitalisation is to calculate the arithmetical average of the proportions of ADR related hospitalisation, as published in each study; in this way the proportion is not weighed for the study size. This average was calculated to be 12.5% ± 2.6% (mean ± confidence interval). This is 2.6 times higher than 4.9% as found by dividing the total number of ADR patients by the total number of hospitalised patients.

The distribution of the proportional hospital admission by ADRs over study size (see Fig 1) was tested for skewness; this distribution turned out to be skewed (student t=3.59, df=67, p<0.001), implicating that the arithmetical average is not the better way of representing the parameters of this distribution. Consequently, the data in these studies are to be regarded heterogeneous, i.e. there may be some unknown factors influencing the ADR related hospitalisation. These factors may be detected by attempting to subdivide the 68 studies in subgroups. Subgroups to be nominated are the factors age, medication group, year of publication, kind of hospital, and country.

Subgroup analysis: elderly versus non-elderly

Among these 68 studies we found 17 studies (see Table 1) on elderly patients. In most studies, 65-year of age and older was the criterion for belonging to the elderly; in two studies this criterion was higher: 70 and 75 years of age [45,56]. These 17 studies described 7,553 hospitalisations of elderly patients, of which 1,251 (16.6% ± 0.8%, mean ± confidence interval) were judged to be hospitalised due to ADR related problems (Fig 2). The arithmetical average of the proportions of ADR related hospitalisation in the elderly, as published in each study, is 19.6% ± 4.6% (mean ± confidence interval). These 17 studies on the elderly were small sized, varying from 100 to 1988 hospitalisations.

In the remaining 51 studies on non-elderly people, 4,820 patients were hospitalised due to ADR related problems, on a grand total of 116,241 hospitalisations (4.1% ± 0.1%, mean ± confidence interval, Fig 2). The arithmetical average of the proportions of ADR related hospitalisation in the non-elderly, as published in these studies, is 10.0% ± 2.4% (mean ± confidence interval). In these 51 studies on the non-elderly, there were small studies as well as larger ones; all larger studies displayed a low percentage of ADR related hospitalisation (Fig 1). The mean percentage hospital admission in the elderly versus non-elderly was found to be statistically significant (t= 4.12, df= 66, p< 0.0001). However, larger studies on the elderly (N>2000) were found to be absent in the literature (Fig 1). Therefore, one may argue that the hospital admission of the elderly and non-elderly erroneously had been found significantly different, because larger studies in the elderly (N>2000), with presumably lower values of the percentage hospital admission, are lacking.

To test this objection, we compared similar groups of small and medium sized studies (N<2000) in both elderly and non-elderly. In these selected studies then the mean percentages hospital admission were tested with the student-t test; these means were found to be different (t = 2.937, df = 52, p = 0.005).

The proportions of the ADR related hospitalisation, as published in these 68 studies, were sorted by study size, and plotted equidistantly, including the mean and confidence interval of each study (Fig 3). Numbers 1 - 51 refer to studies on the non-elderly; numbers 53 - 69 refer to studies on the elderly, number 52 is a delimiter space. There is no relation with the numbers in the reference list. The weighted proportions, 4.1% in the non-elderly and 16.6% in the elderly, were plotted as horizontal lines. As these lines do not hit all confidence intervals, it is concluded that a considerable amount of heterogeneity still remains, caused by some unknown factors other than age. Thus, pooling the results of these heterogeneous studies may seem improper, but pooling may be the next best way to represent these data.

Subgroup analysis: medication

Medication might be the main factor able to explain the remaining heterogeneity in the data on ADR related hospitalisations. However, most studies do not specify

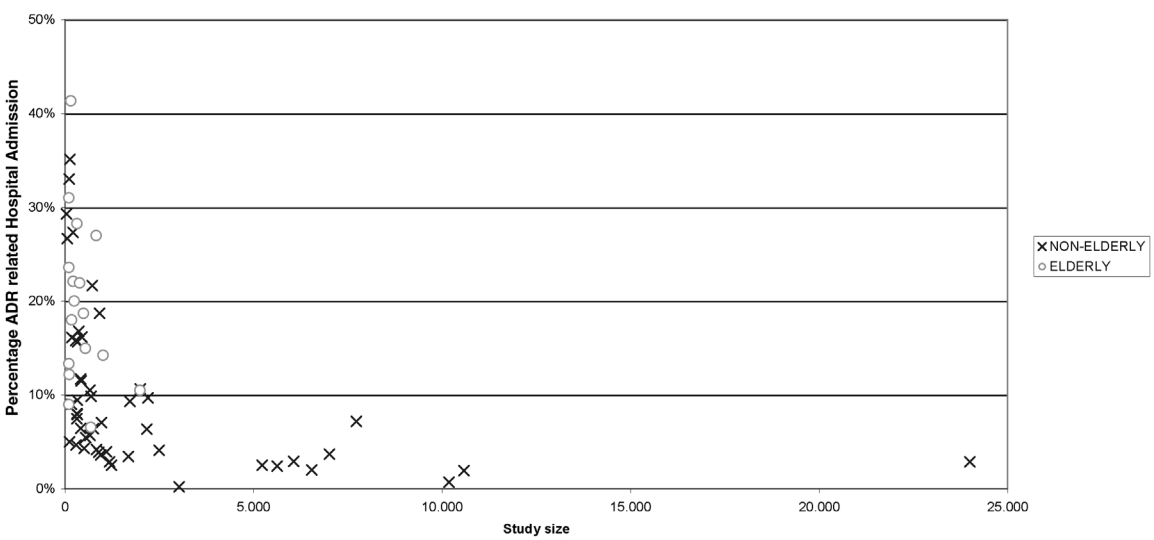

Figure 1 *Relation between the number of patients studied and the percentage unnecessary hospitalisation.*

Table 1

Non-elderly Reference	*Author*	*Year*	*Hosp.Admission*	*Size*	*Percentage*	*Country*
38	Larmour91	1991	136	5623	2.4%	Australia
20	Easton98	1998	58	1682	3.4%	Australia
18	Dartnel196	1996	68	965	7.0%	Australia
24	Gleeson88	1988	34	947	3.6%	Australia
22	Galbraith93	1993	48	751	6.4%	Australia
63	Stanton94	1994	68	691	9.8%	Australia
59	Sarkawi95	1995	49	419	11.7%	Australia
10	Blackbourn91	1991	29	180	16.1%	Australia
30	Hewitt95	1995	46	131	35.1%	Australia
39	Lee93	1993	37	112	33.0%	Australia
31	Huic94	1994	130	5227	2.5%	Croatia
26	Hallas91	1991	26	328	7.9%	Denmark
27	Hallas92	1992	212	1999	8.4%	Denmark
19	Davidsen88	1988	49	426	11.5%	Denmark
28	Halas92	1992	25	313	8.0%	Denmark
55	Perault99	1999	31	1235	2.5%	France
5	Allain83	1983	30	550	5.5%	France
51	Moore98	1998	31	329	9.4%	France
23	Gholami99	1999	62	370	16.8%	Iran
42	Levy79	1979	103	2499	4.1%	Israel
42	Levy82	1982	34	1184	2.9%	Israel
29	Hermesh85	1985	24	321	7.5%	Israel
41	Lepori99	1999	138	2168	6.4%	Italy
40	Leonegg	1999	6	120	5.0%	Italy
44	Major98	1998	213	2202	9.7%	Libanon
13	Cooke85	1985	14	300	4.7%	S.Africa
32	Ibanez91	1991	554	7728	7.2%	Spain
25	Guemes99	1999	43	1097	3.9%	Spain
46	Martinez-Mir96	1996	22	512	4.3%	Spain
7	Bergman81	1981	45	285	15.8%	Sweden
35	Klein76	1976	171	914	18.7%	Switzerland
67	Wu96	1996	38	666	5.7%	Saiwan
8	Bigby87	1987	686	24000	2.9%	USA
54	Pearson94	1994	203	10587	1.9%	USA
57	Prince92	1992	71	10184	0.7%	USA
49	Miller74	1974	260	7017	3.7%	USA
50	Mitchel188	1988	131	6546	2.0%	USA
11	Caranasos74	1974	177	6063	2.9%	USA
50	Mitchel188	1988	6	3026	0.2%	USA
6	Bates93	1993	27	420	6.4%	USA
14	Cooper87	1987	161	1728	9.3%	USA
60	Smith66	1966	35	900	3.9%	USA
37	Lakshmanan86	1986	35	834	4.2%	USA
50	Mitchel188	1988	157	725	21.7%	USA
48	McKenzie73	1973	69	658	10.5%	USA
52	Nelson96	1996	73	452	16.2%	USA
15	Cooper99	1999	52	332	15.7%	USA
47	McKenny76	1976	59	216	27.3%	USA
33	Ives87	1987	16	178	9.0%	USA
64	Stewart80	1980	16	60	26.7%	USA
58	Salem84	1984	12	41	29.3%	USA
	Total:		4.820	116.241	10.0%	= average
	Percent:		4.1%			

Elderly Reference	*Author*	*Year*	*Hosp.Admission*	*Size*	*Percentage*	*Country*
66	Wong93	1993	81	541	15.0%	Australia
66	Wong93	1993	49	245	20.0%	Australia
5	Atkin94	1994	48	217	22.1%	Australia
53	Ng96	1996	31	172	18.0%	Australia
56	Popplewel182	1988	31	100	31.0%	Australia
62	Soon85	1985	223	826	27.0%	Canada
16	Courtman95	1995	62	150	41.3%	Canada
45	Mannesse00	2000	25	106	23.6%	Netherlands
36	Kraaij94	1994	14	105	13.3%	Netherlands
65	Williamson80	1980	209	1988	10.5%	UK
17	Cunningham97	1997	144	1011	14.2%	UK
8	Bero91	1991	45	684	6.6%	USA
34	Kernan94	1994	91	486	18.7%	USA
21	Frisk77	1977	86	392	21.9%	USA
12	Col90	1990	89	315	28.3%	USA
33	Ives87	1987	14	115	12.2%	USA
61	Smucker90	1990	9	100	9.0%	USA
	Total		1251	7553	19.6%	=average
	Percent:		16.6%			

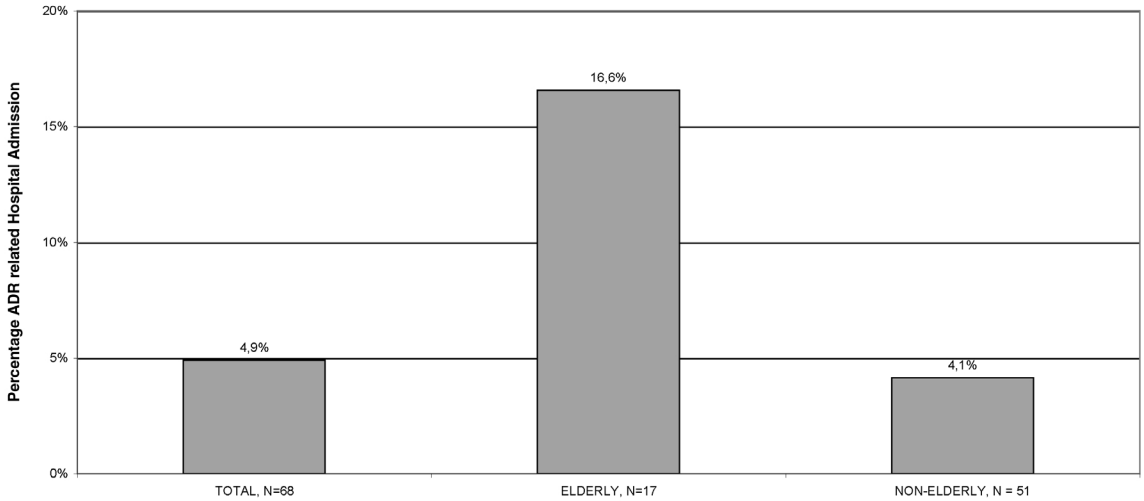

Figure 2 *Subgroup analysis of the elderly versus the non-elderly.*

a cross-tabulation of medications vs. number of patients, which is the information necessary for this subgroup analysis. These studies only give a list of medications on an aggregated level, i.e. only a collection of the medications held responsible for unnecessary hospitalisations. Only a few studies mention a list of specified medications and the accompanying number of patients hospitalised by ADRs by these drugs. Subgroup analysis of aggregated data would result in counting patients manifold, which will confuse rather than clarify. Therefore, a subgroup analysis on medication level could not be performed.

What could be done is to give the aggregated medication categories that, according to the author's opinions, were held responsible for the unnecessary hospital admission. Among these medications, nine categories could be detected: cardiovascular (38 studies), NSAIDs and analgetics (30 studies), psychotropics (23 studies), antibiotics (23 studies), antidiabetics (12 studies), antineoplastics (8 studies), diuretics (20 studies), anticoagulantia (19 studies), corticosteroids (6 studies).

The authors also named the diagnoses or indications that, according to their opinions, were held responsible for unnecessary hospital admissions. These indications may be regarded as factors capable to predict hospitalisations due to ADRs. Among these indications seven categories could be detected: non-compliance (12 studies), gastro-intestinal complications (6 studies), elderly (9 studies), polypharmacy (15 studies), physicianís decision (4 studies), underdosing (5 studies), overdosing (3 studies).

Subgroup analysis: year of publication

During this 35-year study period, information on ADR related hospital admission might have been liable to change. Therefore the correlations of the study size, respectively the percentage of ADR related hospitalisations against the year of publication were calculated. The year of publication did not correlate with study size ($r = -0.043$, $p = 0.76$), nor with the percentage of ADR related hospitalisations ($r = -0.075$, $p = 0.59$). So no regression of the number of patients or the percentage of ADR related hospitalisations over the study period could be established.

Subgroup analysis: type of hospital, community hospital or university hospital

In 37 studies, the kind of hospital mentioned was either community (N=20) or university hospital (N=17). As there might be a difference between the

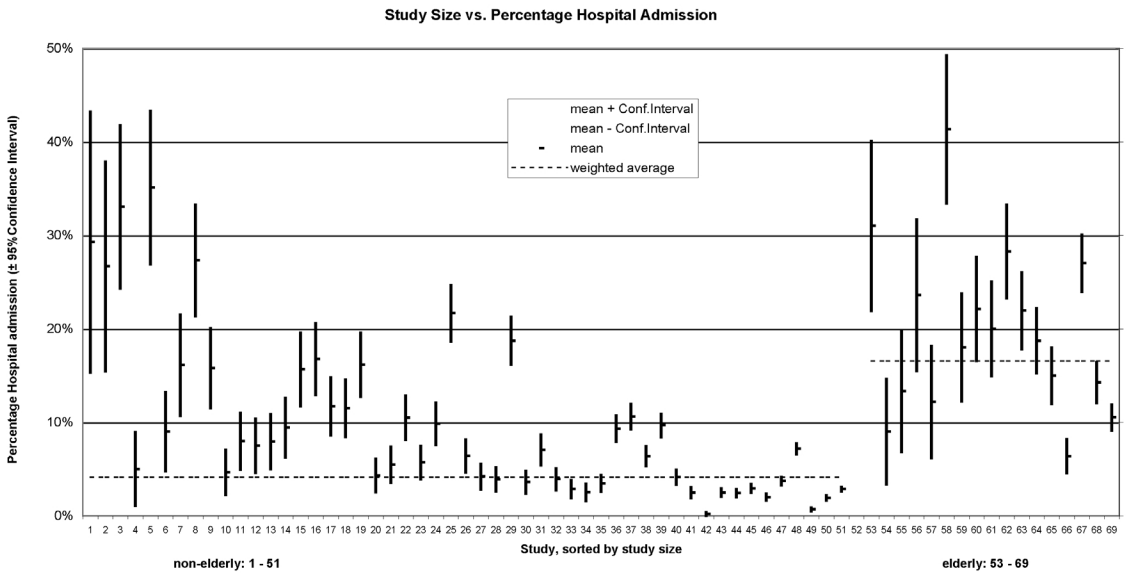

Figure 3 *Study size versus percentage ADR related hospital admission; studies 1-51: non-elderly; studies 53-69: the elderly. Vertical lines represent 95% confidence intervals.*

proportion hospitalisation of elderly patients among different types of hospitals, we have tested this hypothesis. No difference on this topic between community and university hospitals could be detected, using the data from these 37 studies (student t = 0.96; df = 35; p = 0.34).

Subgroup analysis: country

Data was collected from three major regions in the world; USA: 25 papers, Australia: 15 papers, Europe: 19 papers. In each of these regions a similar pattern can be seen: larger studies display lower proportions of ADR related hospitalisation, while small studies show much higher proportions (Fig 4abc). As only 2 papers including data from second world countries versus 61 papers from western world countries were found, a subgroup analysis for first vs. second world countries did not seem feasible.

Prevention

Only 12 studies [6,8,9,16,20,23,28,37,42,51,52,54] provided data on prevention of unnecessary hospital admissions. A preventable hospital admission was defined as a hospital admission that could have been prevented by an intervention by any caregiver. In these 12 studies, 1,410 patients had been hospitalised due to ADRs, of which 407 (28.9% ± 0.02%, mean ± confidence interval) were regarded as preventable. The remaining hospital admissions were regarded as not preventable; these hospitalisations were regarded as unavoidable; a hospitalisation caused by the ADRs of e.g. cytostatics was named as an example of an unpreventable hospital admission.

The data in these 12 studies were broken down into two subgroups: elderly and non-elderly. Two studies [8, 16] on elderly patients and 10 studies on middle aged and younger patients were compared. In the elderly a high percentage, 94/107 = 87.9% ± 0.06% (mean ± confidence interval) of the hospitalisations was found to be preventable. In middle aged and younger patients, a much lower percentage was seen, 313/1,303 = 24.0% ± 0.02% (mean ± confidence interval), (Fig 5).

Methods of prevention

Several activities were proposed as remedy against unnecessary hospital admissions: improve physicianís judgement and decision on the prescription (3 studies), improve the patientís compliance (3 studies), improve the communication with the patient (3 studies), automate the signalling of risk events to improve surveillance results (2 studies).

The finding that errors made by physicians were much more likely to result in ADRs than were errors by others suggest that interventions for preventing ADRs are likely to be most effective if they directly affect physicians decision making or provide checks on those decisions [6]. These findings are also consistent with the hypothesis that nursing and pharmacy personnel may have already come further regarding developing effective safeguards for the process of giving drugs than physicians have [6].

A few studies [47,52,68,69] refer to the pharmacist as the pivotal professional who is able to execute a program on the prevention of unnecessary hospitalisation. No other caregiver in patient care is mentioned specifically as being able to do so.

Discussion

All studies in this analysis were observational ones. The evidence consisted of assessing the number of hospital admissions over a certain period of time and then establishing an opinion whether the admission was being caused by an ADR or not. As Randomised Controlled Trials about this topic are lacking, these observational studies may be regarded as second best evidence for the problem of medications causing unnecessary hospital admission.

The data on ADR related hospital admissions were found to be heterogeneous, i.e. larger studies display a lower percentage of ADR related hospital admission while smaller studies show a higher percentage. Although a small part of this peculiar phenomenon may be explained by differences in quality of the methods used in these studies (e.g. differences in definition of adverse drug reactions of in the data collection methods), this phenomenon may be called publication bias. This means that smaller studies displaying a high percentage have had a higher chance of being published than larger studies showing lower percentages [70]. Although we used the reference list extensively, a small part of this bias may be explained by the use of Medline as the main source to identify the studies.

The proportion of ADR related hospitalisations, as calculated in each study, could not have been originated from one common population, so from the proportions, as calculated in each individual study, no common estimator should be calculated. The best resolution for this problem is to choose for the weighted average, in these studies 4.8%, which is the sum total of the ADR related hospital admissions divided by the sum total of all admissions, and not to choose for the arithmetical average of the proportions of ADR related hospitalisations, in these studies 12.5%. The latter method of calculation yields a proportion that is 2.6 times too high; this would overestimate the problem as well as any money savings that might be calculated.

What is the proportion of the hospitalisations that are caused by ADRs in the Netherlands? In our country 1,590,000 patients were hospitalised during the year 1998 [71]. Not surprisingly, relatively more elderly people (13% of the population) were admitted to a hospital than non-elderly elderly people accounted for 33.2% of the hospital admissions [72], i.e. 527,880 admissions. The sub-group analysis of international data revealed that 4.1% of the non-elderly hospital admissions was ADR related while for the elderly this percentage was four times higher, 16.6%. If these data from the international literature were applicable to our national situation, then on a yearly base 16.6% of 33.2% of 1,590,000 = 87,400 elderly patients are estimated to be hospitalised due to ADRs. This is twice as much as for non-elderly people: 4.1% of 66.8% of 1,590,000 = 44,000 non-elderly patients. In total 131,400 of 1,590,000 hospital admissions can be regarded as ADR related, which gives the proportion of ADR related hospitalisations in the Netherlands as 8.2% (Table 2, numbers are rounded off).

Part of these hospital admissions cannot be prevented, but a considerable part can. Data in the literature reveal that 24.0% of the ADR related hospital admissions of non-elderly people could have been prevented; in The Netherlands this would be 10.600 ADR

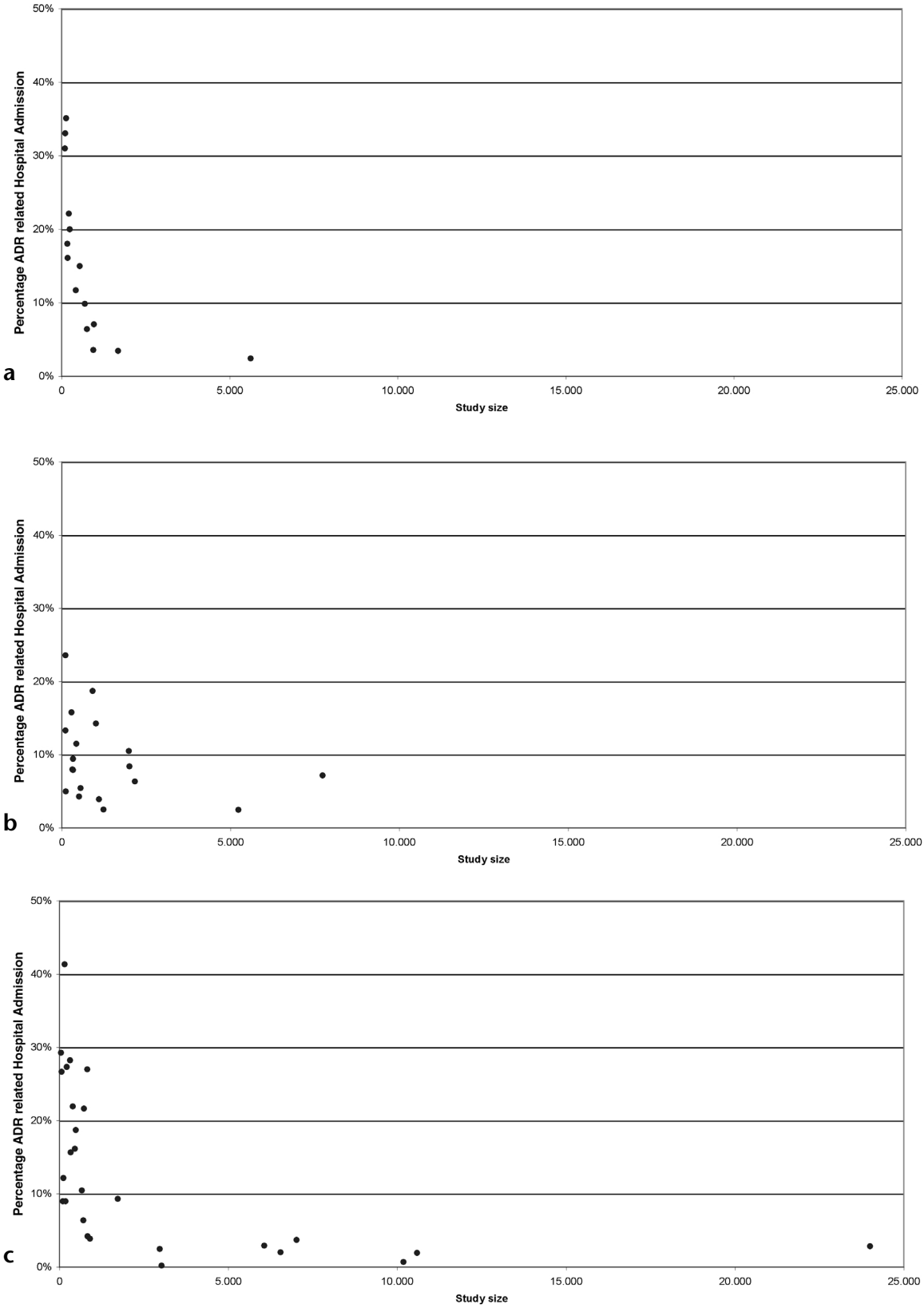

Figure 4 *Study size versus percentage ADR related hospital admission in Australia (a), the USA (b) and Europe (c).*

related hospital admissions. For elderly people 87.9% of these hospital admissions were found to be preventable. Extrapolation then reveals that, on a yearly base, the hospital admission of 76,800 elderly people in The Netherlands may be avoidable, which is 7 times as much as for non-elderly people. If a prevention program is as effective as described in the studies mentioned above, these patients will not experience the morbidity that otherwise would have had them hospitalised (Table 2).

How reliable is the very high percentage of 87.9% of avoidable hospital admissions in the elderly. This percentage is based on 2 studies, in which 107 hospitalisations of elderly people were observed of which 94 have been judged as avoidable, which is 87.9% with a confidence interval of 0.06%. This means that, with a probability of 95%, the true percentage may lie between 87.1% and 88.5%. So from these only two studies the high percentage of avoidable hospital admissions in the elderly may be regarded as fairly trustworthy.

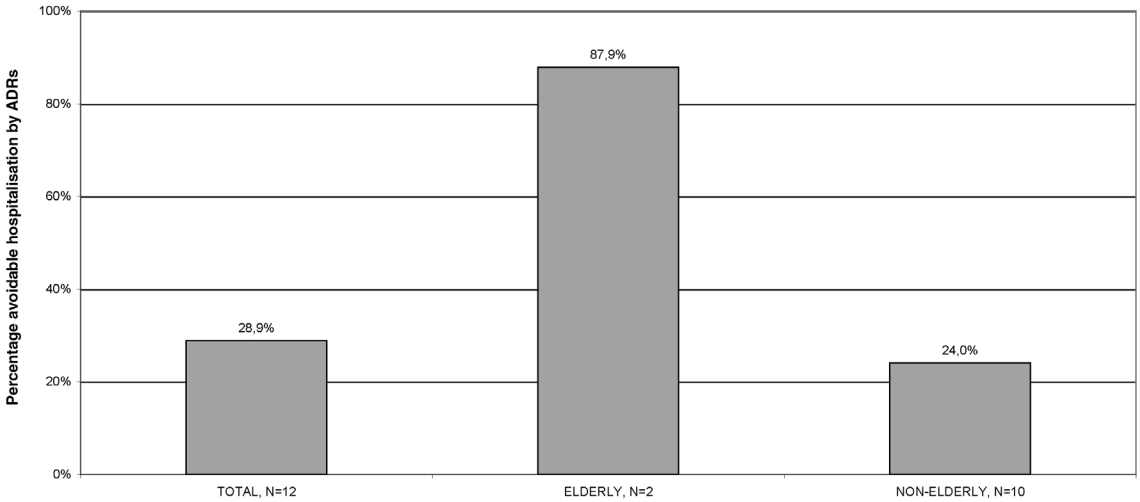

Figure 5 *Percentage avoidable ADR related hospital admissions in the population, in the elderly and in the non-elderly.*

The numbers above were calculated by extrapolation, assuming that the data from international studies are applicable to the health care system in The Netherlands. But, can this assumption be kept upright. There are two papers displaying data on ADR related hospitalisations of elderly people in The Netherlands [36,45]. In these papers the percentage ADR related hospital admissions is 18.5 ± 5.4% (mean ± confidence interval, 39 out of 211 admissions), which is quite similar to the overall average from the international studies of the elderly, i.e. 16.6%. Therefore it seems appropriate to estimate the costs of preventable ADR related hospital admissions in the Netherlands by applying the international data to our national situation.

Estimating these costs, several uncertainties are met with:

- The health care system in The Netherlands may be called very good, meaning that linear extrapolation from global data to our national system may overestimate the national problem.
- The average length of stay of an ADR related hospitalisation, 8.7 days according to Goettler [73] may be a bit shorter than the overall mean length of stay, 9.9 days [71].
- Because of declining reserve capacity of many of their organs, the hospital admission of elderly people may be more expensive than the admission of younger ones.
- The cost per day may be calculated including or excluding complex medical activities, such as operations and functional and diagnostic tests, which may be carried out in a lesser extent on ADR related hospitalised persons. If complex medical activities are included, a higher admission price can be calculated: all costs over all admissions = € 7.830 million/1.593.000 admissions = € 4.915 per admission. Excluding complex medical activities, a lower admission price can be calculated: combining admission to a university hospital [14% of admissions [74], costs € 325 per day [75]] with admission to a community hospital [86% of admissions [74], costs € 231 per day [75]], yields: 14%*€ 325 + 86%*€ 231 = € 245 per day, times 8.7 days per admission = € 2.128 per admission.

Thus, a lower estimation of the costs of preventable ADR related hospital admissions may be calculated as 87.400 patients per year* 8.7 days* € 245 per day = € 186 million per year, which is an equivalent of $158 million or £110 million. A higher estimation of these costs may be 87.400 patients per year* € 4.915 per admission = € 430 million per year, which is an equivalent of $365 million or £256 million.

Recomendations

Because larger studies on ADR related hospital admissions of elderly people have not been performed and because of scarce data on preventability of ADR related hospital admissions we recommend larger studies in the elderly to be performed on ADR related hospitalisation, with special interest in measuring avoidability. In the literature data on medications with ADRs leading to hospital admission have been published on an aggregated level. We recommend studies that

Table 2

	Hospital admissions, Percentages	*Hospital admissions, Abs.numbers*	*ADR related Admissions Percentages*	*ADR related Admissions Abs.numbers**	*Avoidable Admissions Percentage*	*Avoidable Admissions Abs.numbers**	*Costs € Lower Estimate**	*Costs € Higher Estimate**
Source	[71, 72]	calculated	this study	calculated	this study	calculated	this study	this study
Elderly	33.2%	527,880	16.6%	87,400	87.9%	76,800	163 million	378 million
Non-elderly	66.8%	1,062,120	4.1%	44,000	24.0%	10,600	23 million	52 million
Total	1.590.000	1.590.000		131,400		87,400	186 million	430 million

*: Numbers are rounded off

publish data on ADR related hospital admission, as related to specific drugs, or to specific ATC levels.

Conclusion

Data in the literature on ADR related hospitalisation are heterogeneous, i.e. larger studies display lower percentages while smaller studies show higher percentages. Subgroup analysis revealed that ADR related hospitalisation among the elderly is 4 times higher than for the non-elderly people. ADR related hospital admissions therefore are a significant and expensive public health problem, especially for the elderly. Preventing these hospitalisations will keep 7 times more elderly people out of the hospital than non-elderly ones. Therefore ADR related hospital admissions are a significant and expensive public health problem, in the first place because of the many elderly persons who are hospitalised unnecessary, but also because of the amount of money that seems to be wasted.

A few studies suggest that monitoring the medications of elderly people by pharmacists may prevent at least a big part of the complex problem of ADR related hospital admissions.

References

1 The Cochrane Library. 2000 issue 3. Update Software Ltd, Oxford, United Kingdom.
2 Lazarou J Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998,279:1200-5.
3 Roughead EE, Gilbert AL, Primrose JG, SansomLN. Drug-related hospital admissions: a review of Australian studies published 1988 - 1996. Med J Austr 1998,168:405 - 8.
4 Allain H, Chevrant-Breton J, Beneton C, Bousser AM, Bentue-Ferrer D, Mazeas D, Driessche J van den. Consequences dermatologiques indesirables des medicaments. Resultat díune enquete pharmacovigilance. Ann Med Interne (Paris). 1983;134:530-6.
5 Atkin PA, FinneganTP, Ogle SJ. Prevalence of drug related admissions to an Australian Hospital. Aust J Aging 1994;13:17-21.
6 Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med. 1993;8:289-94.
7 Bergman U, Wiholm BE. Drug-related problems causing admission to a medical clinic. Eur J Clin Pharmacol. 1981;20:193-200.
8 Bero LA, Lipton HL, Bird JA. Characterization of geriatric drug-related hospital readmissions. Med Care. 1991;29:989-1003.
9 Bigby J, Dunn J, Goldman L, Adams JB, Jen P, Landefeld CS, Komaroff AL. Assessing the preventability of emergency hospital admissions: a method for evaluating the quality of medical care in a primary care faculty. Am J Med 1987;83:1031-6.
10 Blackbourn J. Readmission to Fremantle Hospital. Part II. Drug related admissions. Fremantle Hosp Drug Bull 1991;15:13-6.
11 Caranasos GJ, Steart RB, Cluff LE. Drug-induced illness leading to hospitalization JAMA 1974;228:713-7.
12 Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch Intern Med. 1990;150:841-5.
13 Cooke DI, van der Merwe W, Pudifin DJ. Hospital admissions for adverse reactions to drugs and deliberate self-poisoning. S Afr Med J. 1985;67:770-2.
14 Cooper JW. Adverse drug reactions and interactions in a nursing home. Nurs Homes Sr Citiz Care. 1987;36:7-11.
15 Cooper JW. Adverse drug reaction-related hospitalizations of nursing facility patients: a 4-year study. South Med J. 1999;92:485-90.
16 Courtman BJ, Stallings SB. Characterization of drug-related problems in elderly patients on admission to a medical ward. Can J Hosp Pharm. 1995; 48:161-6.
17 Cunningham G, Dodd TR, Grant DJ, McMurdo ME, Richards RM. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. Age Ageing 1997;26:375-82.
18 Dartnell JGA, Anderson RP, ChohanV, GalbraithKJ, Lyon MEH, Nestor PJ, Mouldrs RFW. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996;1634:659-62.
19 Davidsen F, Haghfelt T, Gram LF, Brosen K. Adverse drug reactions and drug non-compliance as primary causes of admission to a cardiology department. Eur J Clin Pharmacol. 1988;34:83-6.
20 Easton KL, Parsons BJ, Starr M, Brien JE. The incidence of drug-related problems as a cause of hospital admissions in children. Med J Aust 1998;169:356-9.
21 Frisk PA, Cooper JW Jr, Campbell NA. Community-hospital pharmacist detection of drug-related problems upon patient admission to small hospitals. Am J Hosp Pharm. 1977;34:738-42.
22 Galbraith K. Is there a role for a clinical pharmacist in tje emergency department? [Graduate Diploma thesis] Melbourne: Victorian College of Pharmacyt, Monash University, 1993.
23 Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother. 1999;33:236-40.
24 Gleeson CA. Adverse drug reactions causing hospital admission. [Graduate Diploma thesis]. Sydney: University of Sidney, 1988.
25 Guemes Artiles M, Sanz Alvarez E, Garcia Sanchez-Colomer M. Reacciones adversas y problemas relacionados con medicamentos en un servicio de urgencia. Rev Esp Salud Publica 1999;73:511-8.
26 Hallas J, Jensen KB, Grodum E, Damsbo N, Gram LF. Drug-related admissions to a department of medical gastroenterology. The role of self-medicated and prescribed drugs. Scand J Gastroenterol. 1991;26:174-80.
27 Hallas J, Davidsen O, Grodum E, Damsbo N, Gram LF. Drug-related illness as a cause of admission to a department of respiratory medicine. Respiration. 1992;59:30-4.
28 Hallas J, Gram LE, Grodum E, Damsbo N, Brosen K, Haghfelt T, Harvald B, Beck-Nielsen J, Worm J, Jensen KB, Davidsen O, Frandsen N, Hagen C, Andersen M, Frolund M, Kromann-Andersen H, Schou J. Drug related admissions to medical wards: a population based survey. Br J Clin Pharmacol. 1992;33:61-8.
29 Hermesh H, Shalev A, Munitz H. Contribution of adverse drug reaction to admission rates in an acute psychiatric ward. Acta Psychiatr Scand. 1985;72:104-10.
30 Hewitt J. Drug-related unplanned readmissions to hospital. Aust J Hosp Pharm 1995;25:400-3
31 Huic M, Mucolic V, Vrhovac B, Francetic I, Bakran I, Giljanovic S. Adverse drug reactions resulting in hospital admission. Int J Clin Pharmacol Ther. 1994;32:675-82.
32 Ibanez L, Laporte JR, Carne X. Adverse drug reactions leading to hospital admission. Drug Saf. 1991;6:450-9.
33 Ives TJ, Bentz EJ, Gwyther RE. Drug-related admissions to a family medicine inpatient service. Arch Intern Med. 1987;147:1117-20.
34 Kernan WN, Castellsague J, Perlman GD, Ostfeld A. Incidence of hospitalization for digitalis toxicity among elderly Americans. Am J Med. 1994;96:426-31.
35 Klein U, Klein M, Sturm H, Rothenbuhler M, Huber R, Stucki P, Gikalov I, Keller M. The frequency of adverse drug reactions as dependent upon age, sex and duration of hospitalization. Int J Clin Pharmacol Biopharm. 1976;13:187-95.
36 Kraaij DWJ van, Haagsma CJ, Go IH, Gribnau FWJ. Diuretic use and withdrawal in patient populations. Neth J Med 1994;44:166-73.
37 Lakshmanan MC, Hershey CO, Breslau D. Hospital admissions caused by iatrogenic disease. Arch Intern Med. 1986;146:1931-4.
38 Larmour I, Dolphin RG, Baxter H, Morrison S, Hooke DH, McGrath BP. A prospective study of hospital admissions due to drug reactions. Aust J Hosp Pharm 1991; 21: 90-5.
39 Lee A, Oldenburg B. A survey of patients with cardiac disease: risk factors for admissions. Aust J Hosp Pharm 1993;23:104 - 8.
40 Leone R, Conforti A, Ghiotto E, Moretti U, Valvo E, Velo GP. Nimesulide and renal impairment. Eur J Clin Pharmacol. 1999;55:151-4.
41 Lepori V, Perren A, Marone C. Unerwunschte internmedizinische Arzneimittelwirkungen bei Spitaleintritt. Schweiz Med Wochenschr. 1999;129:915-22.
42 Levy M, Lipshitz M, Eliakim M. Hospital admissions due to adverse drug reactions. Am J Med Sci. 1979;277:49-56.
43 Levy M, Mermelstein L, Hemo D. Medical admissions due to noncompliance with drug therapy. Int J Clin Pharmacol Ther Toxicol. 1982; 20:600-4.
44 Major S, Badr S, Bahlawan L, Hassan G, Khogaoghlanian T, Khalil R, Melhem A, Richani R, Younes F, Yeretzian J, Khogali M, Sabra R. Drug-related hospitalization at a tertiary teaching center in Lebanon: incidence, associations, and relation to self-medicating behavior. Clin Pharmacol Ther. 1998;64:450-61.
45 Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ: Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 2000;29:35-9.
46 Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Estan L, Rubio E, Morales-Olivas FJ. A prospective study of adverse drug reactions as a cause of admission to a paeditric hospital. Br J Clin Pharmacol. 1996;42:319-24.

47 McKenney JM, Harrison Wl. Drug-related hospital admissions. Am J Hosp Pharm. 1976;33:792-5.
48 McKenzie MW, Stewart RB, Weiss CF, Cluff LE. A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. Am J Hosp Pharm. 1973;30:898-903.
49 Miller RR. Hospital admissions due to adverse drug reactions: a report from the Boston Collaborative Drug Surveillance Program. Arch Intern Med. 1974;134:219-23.
50 Mitchel AA, Lacouture PG, Sheehan JE, Kaufman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. Pediatrics. 1988;82:24-9.
51 Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol. 1998;45:301-8.
52 Nelson KM, Talbert RL. Drug-related hospital admissions. Pharmacotherapy. 1996;16:701-7.
53 Ng D. Adverse medication-related events and unplanned admissions to an acute care general teaching hospital [Master thesis] Adelaide: University of South Australia, 1996.
54 Pearson TF, Pittman DG, Longley JM, GrapesT, Vigliotti DJ, Mullis SR. Factors associated with preventable adverse drug reactions. Am J Hosp Pharm. 1994 15;51:2268-72.
55 Perault MC, Pinelli AL, Chauveau I, Scepi M, Remblier C, Vandel B. Enquete prospective sur les admissions pour iatrogenie medicamenteuse dans le service díaccueil des urgences du centre hospitalier universitaire de Poitiers. Therapie. 1999; 54:183-5.
56 Popplewell PY, Henschke PJ. Acute admissions to a geriatric assessment unit. Med J Aust. 1982;1:343-4.
57 Prince BS, Goetz CM, Rihn TL, Olsky M. Drug-related emergency department visits and hospital admissions. Am J Hosp Pharm. 1992;49:1696-700.
58 Salem RB, Keane TM, Williams JG. Drug-related admissions to a Veterans' Administration psychiatric unit. Drug Intell Clin Pharm. 1984;18:74-6.
59 Sarkawi H, Daud TM. A study of drug induced illness as a contributor to hospital admissions. Adelaide: Pharmacy Department, Royal Adelaide Hospital, 1995.
60 Smith JW, SeidlLG, Cluff LE. Studies on the epidemiology of adverse drug reactions, V: clinical factors influencing susceptibility. Ann Intern Med. 1966;65:629-640.
61 Smucker WD, Kontak JR. Adverse drug reactions causing hospital admission in an elderly population: experience with a decision algorithm. J Am Board Fam Pract. 1990;3:105-9.
62 Soon JA. Assessment of an adverse drug reaction monitoring program in nursing homes. Can J Hosp Pharm. 1985;38:120-5.
63 Stanton LA, Peterson GM, Rumble RH, Cooper GM, Polack AE. Drug-related admissions to an Australian hospital. J Clin Pharm Ther. 1994;19:341-7.
64 Stewart RB, Springer PK, Adams JE. Drug-related admissions to an inpatient psychiatric unit. Am J Psychiatry. 1980;137:1093-5.
65 Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: A multicentre investigation. Age Aging 1980;9:73-80.
66 Wong ME, Ioannides-Demos LL, Li SC, McClean AJ, Christophidis N. Drug related hospital admissions of geriatric patients. Aust J Hosp Pharm 1993;23:75.
67 Wu FL, Yang CC, Shen LJ, Chen CY. Adverse drug reactions in a medical ward. J Formos Med Assoc. 1996;95:241-6.
68 Nathan A, Goodyer L, Lovejoy A, Rashid A. ëBrown bagí medication reviews as a means of optimizing patientsí use of medication and of identifying potential clinical problems. Family Practice 1999;16:278-82.
69 Taras-Zazowski KM, Einarson TR. Review of Canadian pharmacist involvement in adverse drug reaction reporting. Can J Hosp Pharm 1989;42:105-8.
70 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.
71 Statistical Yearbook 1999. Statistics Netherlands. Voorburg/ Heerlen, The Netherlands. (Statistisch Jaarboek 1999. Centraal Bureau voor de Statistiek)
72 Landelijke Medische Registratie, LMR, Prismant, 2000.
73 Goettler M, Schneeweiss S, Hasford J. Adverse Drug Reaction Monitoring - Cost and Benefit Considerations Part II: Cost and Preventability of Adverse Drug Reactions Leading to Hospital Admission. Pharmacoepidemiology and Drug Safety 1997,6:79-90.
74 Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen; 2000, pag. 169.
75 Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen; 2000, pag. 78. [Manual for cost research, methods and guidelines for economic evaluations in health care. Amstelveen The Netherlands: Council of Health Care Insurances, 2000.]