Incidence of Adverse Drug Reactions in Hospitalized Patients

A Meta-analysis of Prospective Studies

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Objective.—To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients.

Data Sources.—Four electronic databases were searched from 1966 to 1996.

Study Selection.—Of 153, we selected 39 prospective studies from US hospitals.

Data Extraction.—Data extracted independently by 2 investigators were analyzed by a random-effects model. To obtain the overall incidence of ADRs in hospitalized patients, we combined the incidence of ADRs occurring while in the hospital plus the incidence of ADRs causing admission to hospital. We excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs. Serious ADRs were defined as those that required hospitalization, were permanently disabling, or resulted in death.

Data Synthesis.—The overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalized patients. We estimated that in 1994 overall 2 216 000 (1 721 000-2 711 000) hospitalized patients had serious ADRs and 106 000 (76 000-137 000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death.

Conclusions.—The incidence of serious and fatal ADRs in US hospitals was found to be extremely high. While our results must be viewed with circumspection because of heterogeneity among studies and small biases in the samples, these data nevertheless suggest that ADRs represent an important clinical issue.

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PUBLIC ATTENTION is currently focused on adverse drug reactions (ADR) as evidenced by a recent bill passed by the US Senate requiring pharmaceutical companies to provide ADR information to consumers.[1] Heightened interest in ADRs was stimulated by the thalidomide tragedy in the 1960s.[2] To obtain an accurate estimate of ADR incidence in hospital patients, prospective studies were done, beginning in the 1960s, in which a defined population could be kept under close observation by monitors who recorded all ADR occurrences.[3-5] These prospective studies have been done on 2 separate populations of patients; those admitted to the hospital due to an ADR (ADRAd),[6] and those experiencing an ADR while in the hospital (ADRIn).[7] We report here a meta-analysis of 39 of these prospective studies done in the United States over a period of 32 years from which we obtained ADR incidences for ADRIn and for ADRAd and an overall ADR incidence that combines these 2 groups. We focused mainly on serious and fatal ADRs since they represent the greatest impact of drug therapy. While recognizing the benefits of drug therapy, we chose not to compare benefits of drugs to the side effects of drugs.

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METHODS

Definitions

One step we took to reduce heterogeneity was to exclude any data that did not use the following specific definitions:

Adverse Drug Reaction (ADR).—According to the World Health Organization definition,[8] this is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (ie, overdose), and drug abuse.[8] Also, this does not include adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount).[8] Using this conservative definition avoids overestimating the ADR incidence.

For editorial comment see p 1216.

Recently, some authors prefer the term *adverse drug event* (ADE), which is an injury resulting from administration of a drug. In contrast to the World Health Organization definition of ADR, the definition of ADE includes errors in administration.[9] However, we have chosen the World Health Organization definition for ADR because of its frequent use in the studies that we analyzed, and because of our goal to estimate injuries incurred by drugs that were properly prescribed and administered. In those articles that did not use the World Health Organization definition (eg, ADE was used), we examined the raw data and removed adverse events due to errors in administration. However, this was not always feasible since a few articles may have included errors in administration but did not report them separately. Therefore, unfortunately, these latter articles added to the heterogeneity of our data.

Possible ADR.—This is an ADR that follows a reasonable temporal sequence and for which the ADR is a known response to the drug, although the response may also be explained by the patient's clinical state.[10] Possible ADRs were excluded from our study.

Serious ADR.—This is an ADR that requires hospitalization, prolongs hospitalization, is permanently disabling, or results in death. Serious ADRs include fatal ADRs, which were also analyzed separately.

Prospective Studies.—Patients were present during the study, and monitors were able to interview physicians, nurses, or patients at least once per week. All ADRs were confirmed prior to patient's discharge from the hospital.

Retrospective Studies.—Chart reviews were performed after the patient had left the hospital. These studies were excluded from our analysis.

Literature Search

Electronic databases were searched using the following key word strategy: *adverse drug* or *adverse reaction* or *drug-related* or *drug-induced* and *hospital*. Three MeSH (Medical Subject Headings) terms were also used where appropriate (ie, *hospitalization, drugs, drug therapy/adverse effects*) in combination with key words. Databases that we used were MEDLINE (1966-1996), Excerpta Medica (1980-1996), International Pharmaceutical Abstracts (1970-1996), and Science Citation Index (1989-1996). The reference sections of all retrieved articles were manually searched for additional studies. In addition, we sent letters to researchers in the field to request unpublished data in order to reduce publication bias.

Selection Criteria

The following criteria were used:

1. The patients studied were not selected for particular conditions or specific drug exposures.

2. Sufficient information was reported in the published study to calculate the incidence of ADRs.

3. English translations of the papers were available.

4. Prospective monitoring was used to identify ADRs.

5. Definitions used in the studies coincided with ours (see "Definitions" subsection for our definitions).

Quality of the Data

Rather than merely assessing the quality of each study,[11] we chose instead to improve the quality of our database. First, we used prospective monitoring as an inclusion criterion to exclude the lowest-quality studies (ie, the retrospective studies). Second, ADRs classified as "possible" were excluded. Attributing causality is always a problem with ADR detection[12] and, by excluding possible ADRs, we reduced the number of false positives in the data.

Heterogeneity

We dealt with heterogeneity among the studies in numerous ways: (1) we placed considerable emphasis on the 95% confidence intervals (CIs) to draw attention to the heterogeneity,[13] (2) we used a random-effects model to do the analysis because it takes into account the heterogeneity of the various studies,[13,14] (3) to reduce heterogeneity, we excluded ADRs caused by errors in administration, noncompliance, overdose, drug abuse, or therapeutic failures, (4) for additional ways to reduce heterogeneity, we excluded ADRs not fitting our strict definitions, possible ADRs, and retrospective data.

Data Extraction

We determined the incidence of ADRs in the hospital by extracting the total number of hospital patients in each study experiencing at least 1 ADR and dividing this value by the total number of hospital patients in each study. The ADR incidence was expressed as the percent of patients with an ADR. A data collection form was developed prior to the study for this purpose. Information on nonserious, serious, and fatal reactions was extracted. Other data extracted included the year of the study, ward and hospital type in which the study was performed, mean age, average length of hospital stay, average number of drug exposures for the patients included in the study, and the number of men and women in each study. To test for reliability of our extraction procedures a randomly selected subset of the data was extracted independently by 2 of us (J.L. and B.H.P.) and was found to be very consistent for the published ADR incidence for serious, fatal, and all severities (intraclass correlation coefficient ranging from 0.89 to 0.92).

Analysis of ADR Incidence

We separately analyzed the incidence of ADRIn and the incidence of ADRAd and then combined the 2 groups to obtain an overall ADR incidence. We analyzed ADRs of all severities (which included nonserious and serious), ADRs that were serious (which included fatal), and ADRs that were fatal; however, we focused mainly on the serious and fatal ADRs. For each category, we analyzed the ADR incidences obtained from the different studies to determine the mean incidence and the 95% CIs. For this purpose we used a random-effects model for meta-analysis[15] similar to the method used in the only previous meta-analysis of ADRAds.[16] This is the method of choice because it takes into account the heterogeneity of the various studies.[14]

When combining the incidence of ADRIn and ADRAd to obtain the overall incidence of ADRs, we avoided double counting patients who were admitted for an ADR and who then also experienced an ADR while in the hospital by assuming the 2 types of events to be independent and deriving an adjusted estimate using the following formula:

$$\begin{aligned}\text{Adjusted Overall Incidence} &= (\text{Incidence of ADRIn} \\ &\quad + \text{Incidence of ADRAd}) \\ &\quad - (\text{Incidence of ADRIn} \\ &\quad \times \text{Incidence of ADRAd}).\end{aligned}$$

This provided a slightly smaller estimate of the ADR incidence. For example, the mean estimate for the overall number of serious ADRs per year (see "Results" section) would change by 33 000 patients, dropping from 2 249 000 (no adjustment) to 2 216 000 (our estimate using the adjustment).

When comparing groups, we used both parametric and nonparametric methods. The results were always the same for the 2 methods. Hence, for group comparisons, whenever possible, we reported the results of the more robust nonparametric Wilcoxon rank sum test.[17] All statistical analyses were performed using the SAS statistical software package, version 6.11 (Statistical Analysis System, Cary, NC).

Number of Patients With ADRs

We estimated the number of hospital patients with ADRs in the United States by using the incidence of ADRs in US hospitals derived from our data and multiplying this value by the number of hospital admissions in 1994 in the United States, obtained from published statistics.[18] In 1994, there were 33 125 492 hospital admissions in the United States. We calculated the 1994 fatal ADRIns as follows:

Number of Fatal ADRIns in US Hospitals in 1994 (63 000) = Incidence of Fatal ADRIns in Hospitals in the United States (0.0019) × Number of Hospital Admissions in the United States (33 125 492).

This estimate is based on the assumption that our sample is representative of the hospital population, and, hence, we examined representativeness at some length (see "Results" section).

RESULTS

Using our 5 selection criteria, 39 of the 153 studies found in the literature were included in our meta-analysis. Features

Table 1.—Studies on ADRs in Patients While in the Hospital (ADRIn)*

Source, y	Wards Studied†	Study Size	Incidence of ADRs, %‡		
			All Severities	Serious	Fatal
Bates et al, 1995[19]	1, 7	379	5.3	0.8	0
Bates et al, 1995[20]	1, 2	4031	4.4	1.5	0.08
Bowman et al, 1994[21]	1	1024	10.3	1.1	. . .
Bates et al, 1993[9]	1, 2, 6, 8	420	3.6	1.9	0
Steel et al, 1981[22]	1	815	14.8	2.8	. . .
Mitchell et al, 1979[23]	4	1669	16.8	. . .	. . .
Bennett and Lipman, 1977[24]	1, 2	152	7.2	1.4	. . .
May et al, 1977[25]	1	334	10.2	. . .	. . .
Miller, 1973[26]§	1	11 526	22.5	2.4	0.29
McKenzie et al, 1973[27]	4	658	12.2	2.3	0.15
Wang and Terry, 1971[28]	1, 2	8291	1.2	. . .	0.01
Gardner and Watson, 1970[29]	1	939	10.5	2.1	0.85
Borda et al, 1968[5]	1	830	24.1	6.0	. . .
Sidel et al, 1967[30]	1	267	10.9	. . .	. . .
Seidl et al, 1966[4]	1	714	13.6	0.8	0.42
Smith et al, 1966[7]	1	900	10.8	. . .	0.22
Reichel, 1965[31]	1	500	8.2	. . .	. . .
Schimmel, 1964[32]	1	1014	10.2	0.8	0.39

*ADR indicates adverse drug reaction; ADRIn, an ADR occurring in patients while in the hospital; and ellipses, data not available.
†Wards studied: 1, medical; 2, surgical; 3, geriatric; 4, pediatric; 5, psychiatric; 6, internal medicine; 7, intensive care; and 8, obstetric.
‡Incidence of ADRs = (number of patients with ADR/total patients studied) × 100.
§This study performed by the Boston Collaborative Drug Surveillance Program was categorized as United States in our analysis since only 1787 of the 11 526 patients were from hospitals outside the United States.

Table 2.—Studies on Patients Admitted to the Hospital Due to an ADR*†

Source, y	Wards Studied‡	Study Size	Incidence of ADRs, %§	
			Serious	Fatal
Nelson and Talbert, 1996[33]	6, 7	450	5.3	. . .
Col et al, 1990[34]	1	315	16.8	. . .
Mitchell et al, 1988[35]	4, 6, 7	6546	1.0	0.03
Bigby et al, 1987[36]	1	686	6.9	. . .
Lakshmanan et al, 1986[37]	1	834	4.2	. . .
Salem et al, 1984[38]	5	41	12.2	. . .
Stewart et al, 1980[39]	5	60	5.0	. . .
Frisk et al, 1977[40]	1, 2, 3, 4, 8	442	6.8	. . .
McKenney and Harrison, 1976[41]	1	216	5.6	0
McKenzie et al, 1976[42]	4	3556	1.9	0.11
Caranasos et al, 1974[43]	1	6063	2.9	0.18
Miller, 1974[6]	1	492	3.3	. . .
	1	555	1.8	. . .
	1	1025	3.0	. . .
	1	1193	5.6	. . .
	1	2065	2.9	. . .
McKenzie et al, 1973[27]	4	658	2.9	0.15
Gardner and Watson, 1970[29]	1	939	5.1	. . .
Sidel et al, 1967[30]	1	267	4.5	. . .
Seidl et al, 1966[4]	1	714	3.9	0.70
Smith et al, 1966[7]	1	900	1.7	. . .

*ADR indicates adverse drug reaction; ADRAd, an ADR causing admission to the hospital; and ellipses, data not available.
†Unlike Table 1, the column "All Severities" is missing from Table 2 because all ADRAds are classified as serious by definition.
‡Wards studied: 1, medical; 2, surgical; 3, geriatric; 4, pediatric; 5, psychiatric; 6, internal medicine; 7, intensive care; and 8, obstetric.
§Incidence of ADRs = (number of patients with ADR/total patients studied) × 100.

of these 39 studies are given in Tables 1 and 2.[4-7,9,19-43] Fifty-seven studies were excluded from our meta-analysis by the 2 blinded investigators because they did not meet our criteria. In addition 57 of the remaining 96 studies were performed in countries other than the United States and were excluded from our meta-analysis because one of our major goals was to determine representativeness of our sample in order to establish the accuracy of our summary statistics. Since we only had a sufficient number of studies from the United States to allow us to perform these tasks, we decided to exclude the remaining countries from our meta-analysis since a proper analysis for representativeness for any other country would be impossible to perform.

Incidence of ADRs

As shown in Table 3, the incidence of serious ADRIn was 2.1% (95% CI, 1.9%-2.3%) of hospital patients, while the incidence of serious ADRAd was 4.7% (95% CI, 3.1%-6.2%). The incidence of fatal ADRIn was 0.19% (95% CI, 0.13%-0.26%) of hospital patients and the incidence of fatal ADRAds was 0.13% (95% CI, 0.04%-0.21%). Combining ADRIn and ADRAd, the overall incidence of serious ADR was 6.7% (95% CI, 5.2%-8.2%) of hospital patients and the overall incidence of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%). The incidence of ADRIn of all severities (including nonserious and serious) was 10.9% (95% CI, 7.9%-13.9%) of hospital patients. The overall incidence of ADRIn plus ADRAd for ADRs of all severities was 15.1% (95% CI, 12.0%-18.1%) of hospital patients.

Eight ADRIn articles included the proportion of type A[44] (dose-dependent ADRs) and type B[44] (idiosyncratic and/or allergic ADRs). Of the "all severities" ADRIn, 76.2% (95% CI, 71.0%-81.4%) were type A reactions and 23.8% (95% CI, 18.6%-29.0%) were type B reactions. Unfortunately, none of these studies reported the proportion of type A and type B reactions for serious and fatal ADRs.

Number of Hospital Patients With ADRs

As shown in Table 4, we estimated that 702 000 (95% CI, 635 000-770 000) hospital patients in the United States experienced a serious ADRIn in 1994. We calculated that 1 547 000 (95% CI, 1 033 000-2 060 000) hospital patients experienced a serious ADRAd. Combining these values, overall 2 216 000 (95% CI, 1 721 000-2 711 000) hospital patients experienced a serious ADR in the United States in 1994. We calculated that there were 63 000 (95% CI, 41 000-85 000) fatalities due to ADRIn and another 43 000 (95% CI, 15 000-71 000) deaths occurred in association with ADRAd in the United States. Overall in 1994, we estimated that 106 000 (95% CI, 76 000-137 000) deaths were caused by ADRs in the United States, which could account for 4.6% (95% CI, 3.3%-6.0%) of the 2 286 000 recorded deaths from all causes during 1994 in the United States.[18] Using the mean ADR incidence (106 000) or the more conservative lower 95% CI (76 000), we found that fatal ADRs ranked between the fourth and sixth leading cause of death in the United States in 1994.

Table 3.—ADR Incidence According to ADR Severity*

ADR Group	No. of Studies	Total Patients Studied	Incidence of ADRs, %	95% CI
ADRs in Patients While in the Hospital (ADRIn)				
All severities	18	34 463	10.9	7.9-13.9
Serious	12	22 502	2.1	1.9-2.3
Fatal	10	28 872	0.19	0.13-0.26
Patients Admitted to the Hospital Due to an ADR (ADRAd)				
Serious†	21	28 017	4.7	3.1-6.2
Fatal	6	17 753	0.13	0.04-0.21
Overall ADR Incidence (ADRIn + ADRAd)‡				
All severities	39	62 480	15.1	12.0-18.1
Serious	33	50 519	6.7	5.2-8.2
Fatal	16	46 625	0.32	0.23-0.41

*ADR indicates adverse drug reaction; ADRIn, an ADR occurring in patients while in the hospital; CI, confidence interval; and ADRAd, an ADR causing admission to the hospital.
†By definition, all ADRAds are serious, hence there is no "All Severities" category for ADRAd.
‡Overall incidence is adjusted to avoid double counting (see "Methods" section).

Table 4.—Estimated Number of Hospital Patients in 1994 With ADRs, in Thousands (95% CI)*†

	ADRIn	ADRAd	Overall
All severities	3607 (2618-4596)	1547 (1033-2060)‡	4986 (3976-5995)
Serious	702 (635-770)	1547 (1033-2060)	2216 (1721-2711)
Fatal	63 (41-85)	43 (15-71)	106 (76-137)§

*ADR indicates adverse drug reaction; CI, confidence interval; ADRIn, an ADR occurring in patients while in the hospital; and ADRAd, an ADR causing admission to the hospital.
†Based on 33 125 492 US admissions[18] in 1994: estimates use values from Table 3 (eg, for all severities ADRIn: 33 125 492 × 0.1089 = 3 607 000 patients with an ADR).
‡By definition all ADRAds are serious, hence there are no data for nonserious ADRs in this category.
§From these numbers, we estimated that ADRs were the fourth to sixth leading cause of death in the United States.

Representativeness of Our Sample

Among the many factors possibly influencing ADR incidence, considerable research has identified average length of stay,[45,46] age,[45,47] gender,[48,49] and drug exposure.[45,46] Therefore, as shown in Table 5, we checked to see whether the population that we sampled was representative of the US hospital population[50] vis-à-vis these 4 factors. We determined that the differences were significant for length of stay and gender but not for age. Unfortunately, we were unable to find values for the average number of drug exposures from national statistics. Possible biases in our ADR incidence that may have been caused by the differences in length of stay or gender are estimated in the "Comment" section.

Another possible source of sampling bias might be the year of study, as our meta-analysis spans 4 decades. Hence, we studied the relationship between ADR incidence and year of study using a random-effects linear regression model and found no significant correlation for ADRIn (r=0.27, P=.14, n=18) or for ADRAd (r=0.23, P=.34, n=21). The Figure shows these results graphically and indicates that no change in ADR incidence occurred over the span of our study. This result seems surprising since great changes have occurred over the last 4 decades in US hospitals that should have affected the incidence of ADRs. Perhaps, while length of hospital stay is decreasing,[51] the number of drugs per day may be rising to compensate. Therefore, while the actual incidence of ADRs has not changed over the last 32 years, the pattern of their occurrence has, undoubtedly, changed.

It should be noted that additional factors have been proposed to have an effect on ADR rate: renal function, hepatic function, alcoholism, drug abuse, and severity of illness.[44,52] Unfortunately, these factors were rarely reported in our sample of studies and, thus, could not be used to determine representativeness.

Medical wards are overrepresented in our database, and some articles in the literature suggest that ward type might have an effect on ADR incidence.[9,40,53,54] Unfortunately, there is insufficient power in the 39 studies to calculate the incidence of ADRs for each ward type individually. Without these data, we cannot determine the possible effect that ward-type distribution might have on our ADR incidence. Nevertheless, in the "Comment" section, we estimate the possible bias due to ward type.

Similar to ward type, hospital type may also introduce bias into our results. It is thought that teaching hospitals contain more seriously ill patients than nonteaching hospitals, which may lead to a higher incidence of ADRs in teaching hospitals, but this has never been proven.[35,55] Teaching hospitals are overrepresented in our sample. However, when we compared ADR incidences for teaching and nonteaching hospitals in our study, we found no significant differences. Thus, despite an overrepresentation of teaching hospitals in our sample, there may not be a major bias.

Finally, our letters to researchers in the field produced no evidence of publication bias.

Table 5.—Is Our Sample Representative of US Hospitals?

Factor	US Hospitals*	Our Sample†	No. of Studies‡
Average age, y§	50.4	54.1	11
Average length of stay, d‖	7.6	10.6	14
Average drug exposure¶	. . .	8.0	7
Proportion female‖	0.60	0.50	16

*Statistics in this column were derived from data by the National Hospital Discharge Survey.[50]
†Values in this column were derived from combining our ADRIn (adverse drug reaction [ADR] occurring in patients while in the hospital) and ADRAd (ADR causing admission to the hospital) studies to increase the sample size, except for average drug exposure, for which data were unavailable for the ADRAd group.
‡The number of studies among the 39 US articles that provided data on this factor.
§P = .53 (Student t test).
‖P<.001 (Student t test).
¶No statistic could be obtained for the average drug exposure in US hospital patients; ellipses indicate data not available.

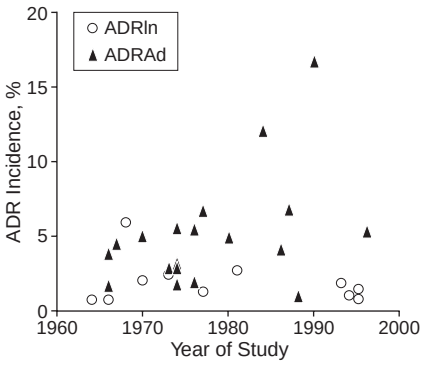
COMMENT

We have found that serious ADRs are frequent and more so than generally recognized. Fatal ADRs appear to be between the fourth and sixth leading cause of death. Their incidence has remained stable over the last 30 years.

There has been only one previous meta-analysis of ADR hospital studies,[16] and it focused only on ADRAd. Our article differs from this report in many respects: (1) we studied incidence of ADRIn as well as ADRAd, (2) we combined ADRAd and ADRIn to obtain the overall incidence of ADRs, (3) we gave special emphasis to serious and fatal ADRs, (4) we improved the quality of the data by excluding retrospective studies and by excluding ADRs that were classified as "possible," (5) we examined the representativeness of our sample, and (6) we estimated the total number of patients in US hospitals experiencing ADRs.

Recent studies have focused on ADEs, which include errors in administration.[9,19,20] One of the goals of ADE research is to alert physicians about the preventability of many ADEs.[20] In contrast, our study on ADRs, which excludes medication errors, had a different objective: to show that there are a large number of serious ADRs even when the drugs are properly prescribed and administered.

We found that a high proportion of ADRs (76.2%) were type A reactions. This may suggest that many ADRs are due to the use of drugs with unavoidably



Incidence of adverse drug reactions (ADRs) in 39 studies distributed over 32 years. All 39 points are not visible as several are superimposed on each other. Linear regression, using a random-effects model, showed no significant correlation for either those experiencing an ADR while in the hospital (ADRIn) (r=0.27, P=.14) or those admitted to the hospital due to an ADR (ADRAd) (r=0.23, P=.34).

high toxicity. For example, warfarin often results in bleeding. It has been shown that careful drug monitoring in hospitals leads to a reduction of many of these ADRs, suggesting that some type A and type B ADRs may be due to inadequate monitoring of therapies and doses.[56]

Recent studies have shown that the costs associated with ADRs may be very high. Research to determine the hospital costs directly attributable to an ADR estimated that ADRs may lead to an additional $1.56 to $4 billion in direct hospital costs per year in the United States.[57,58]

Heterogeneity

As outlined in the "Methods" section, we dealt with heterogeneity in numerous ways. After taking these measures, we examined the remaining heterogeneity. We determined whether 4 factors thought to affect ADR incidence (age, gender, drug exposure, and length of stay) contributed to the remaining heterogeneity in our data using a linear regression version of the random-effects model.[15] For ADRIn, we found that number of drug exposures and length of hospital stay jointly accounted for 43% of the variance (r=0.65, P=.009, n=18). For the rate of ADRAd, when age was included in the model, the variance was reduced by 27% (r=0.52, P=.04, n=14). Gender did not contribute to the variance. Thus, a great deal of the heterogeneity could be attributed to factors well known to affect ADR rates: number of drug exposures per patient, length of hospital stay, and the age of patients. This result indicates that much of the heterogeneity is due to variation in the populations examined in the various articles and, hence, only a portion of the variation could merely be attributed to inconsistent methods among the individual studies. For example, if the different investigators use different methods of ascertainment regarding what represents an ADR, they will find different rates. Another example of inconsistent methodology is the problem that some articles did not separate out administration errors. Methodological variation such as this is a limitation of meta-analysis.

Representativeness of Our Sample

In the "Results" section, we found that for the 5 factors examined 3 were possible sources of bias: length of stay, gender, and ward type. Thus, we have attempted to estimate the size of the sampling bias due to these 3 factors as follows. As seen in Table 5, we had a higher average length of hospital stay than the US national average (10.6 days vs 7.6 days).[18] While the literature qualitatively reports a relationship between the incidence of ADRIn and length of stay,[21,45,46] there are no quantitative estimates. Therefore, we performed a linear regression analysis on our own data using a random-effects model[15] regressing the incidence of ADRIn of all severities on average length of stay to obtain a slope of 0.007 (P=.008) and deduced that increasing the length of hospital stay from 7.6 to 10.6 days would possibly cause the incidence of ADRIn of all severities to rise from the adjusted value of 8.7% to our value of 10.9%.

Also, as shown in Table 5, the proportion of female patients in our sample was lower than the national average (50% vs 60%). Using several studies reporting an increased incidence of ADRs among females, we were able to determine that, at most, the risk ratio for women vs men could be as high as 1.5 for both ADRIn and ADRAd. Assuming the worst-case scenario, the adjusted value for the overall incidence of ADRs of all severities in the United States becomes 15.7% (95% CI, 12.7%-18.8%) compared with our value of 15.1% (95% CI, 12.0%-18.1%).

Finally, with regard to ward type, there was insufficient power in 39 studies to determine precisely the effect of ward-type discrepancies. Instead, we made a crude determination of the worst-case scenario of ward bias. If we assumed (1) that obstetrical wards have zero ADRs and (2) that we sampled zero obstetrical patients, and, since there are about 4 million obstetrical ward patients each year in the United States[59] of 33 million total hospital admissions,[18] then the total number of ADRs occurring in the United States would be 4/33 lower than our estimates. Thus the overall number of fatal ADRs in the United States would drop from 106 000 (95% CI, 76 000-137 000) to 93 000 (95% CI, 67 000-121 000), which would make ADRs between the fourth and seventh leading cause of death in the United States rather than between the fourth and sixth leading cause as reported above. Regarding other ward types, psychiatric wards tend to have a higher ADR incidence and pediatric wards a lower ADR incidence than medical wards,[53,54] so these 2 biases might cancel out. Thus, altogether, there probably is a small net upward bias in our ADR incidence due to our overrepresentation of medical wards.

It is important to note that we have taken a conservative approach, and this keeps the ADR estimates low by excluding errors in administration, overdose, drug abuse, therapeutic failures, and possible ADRs. Hence, we are probably not overestimating the incidence of ADRs despite the 3 small sampling biases discussed earlier.

CONCLUSIONS

Perhaps, our most surprising result was the large number of fatal ADRs. We estimated that in 1994 in the United States 106 000 (95% CI, 76 000-137 000) hospital patients died from an ADR. Thus, we deduced that ADRs may rank from the fourth to sixth leading cause of death. Even if the lower confidence limit of 76 000 fatalities was used to be conservative, we estimated that ADRs could still constitute the sixth leading cause of death in the United States, after heart disease (743 460), cancer (529 904), stroke (150 108), pulmonary disease (101 077), and accidents (90 523); this would rank ADRs ahead of pneumonia (75 719) and diabetes (53 894).[18] Moreover, when we used the mean value of 106 000 fatalities, we estimated that ADRs could rank fourth, after heart disease, cancer, and stroke as a leading cause of death. While our results must be viewed with some circumspection because of the heterogeneity among the studies and small biases in the sample, these data suggest that ADRs represent an important clinical issue.

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A complete list of the 104 papers excluded from our meta-analysis is available on request from the authors.

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