Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies
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Authors' objectives
To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients.

Searching
The following electronic databases were searched: MEDLINE (1966-1996), Excerpta Medica (1980-1996), International Pharmaceutical Abstracts (1970-1996), Science Citation Index (1989-1996). 'adverse drug' or 'adverse reaction' or 'drug-related' or 'drug-induced' and 'hospital' were used as keywords along with the following MeSH terms where appropriate 'hospitalisation', 'drugs' and 'drug therapy/adverse effects'. The reference sections of all retrieved articles were manually searched and letters were sent to researchers in the field to request unpublished data, in order to try and reduce the possibility of publication bias occurring. Studies were only included if English translations were available.

Study selection
Study designs of evaluations included in the review
All prospective studies which reported sufficient information to calculate the incidence of ADRs. Only studies conducted in the USA were included in the meta-analysis.

Specific interventions included in the review
All drug treatments.

Participants included in the review
The participants were not selected for particular conditions or specific drug exposures. All hospital patients who were either hospitalised because of an ADR or who suffered an ADR whilst been treated in hospital were included.

Outcomes assessed in the review
The incidence of fatal, serious and all severity ADRs (% number of patients experiencing an ADR) were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report a method for assessing validity. A formal assessment of validity was not carried out but the authors tried to increase the overall quality of the database of selected studies by excluding the lowest quality studies (ie retrospective studies) and excluding ADRs that were classified as ‘possible’ (ie an ADR which follows a reasonable temporal sequence and for which the ADR is a known response for the drug, but which may also be explained by the patient's clinical state)

Data extraction
A random selection of studies were checked for agreement by two authors independently. The intraclass correlation coefficients ranged from 0.89 to 0.92 for the data extracted including the incidences of serious, fatal and all severity ADRs. The following information was extracted: year of study, ward and hospital type, mean age, average length of time in hospital, average number of drug exposures, information on non-serious, serious and fatal ADRs.
Methods of synthesis

How were the studies combined?
The studies were combined and the data analysed in terms of the incidence of in-patient (ADRIn) and admission (ADRad) ADRs. In addition separate analyses of serious, fatal and all severity ADRs were performed. The studies were combined using a random-effects model and the results presented in terms of mean incidences with 95% confidence intervals.

How were differences between studies investigated?
Steps taken by the authors to reduce the incidence and effects of heterogeneity were discussed. Four factors (age, gender, drug exposure and the length of stay) thought to affect ADR incidence were used in a linear regression version of the random-effects model to assess whether they accounted for the observed heterogeneity.

Results of the review

There were 39 prospective studies: 18 in-patient studies including 34,463 participants, and 21 admission studies including 28,017 participants.

Linear regression showed that for ADRIn, the number of drug exposures and the length of hospital stay jointly accounted for 43% of the variance ($r=0.65$, $P=0.009$, $n=18$). If age was included for ARDAd, in addition to the aforementioned factors, the variance was reduced to 27% ($r=0.52$, $P=0.04$, $n=14$). The combined sample used in the meta-analysis differed significantly from the US hospital population as a whole with a respect to length of stay and gender. There was no significant correlation between the year of publication and the incidences of ADRIn ($r=0.27$, $P=0.14$, $n=18$) and ARDAd ($r=0.23$, $P=0.34$, $n=21$). Medical wards were over represented in the included studies, and unfortunately there was insufficient power to determine the possible effects that ward-type distribution may have on the results. Teaching hospitals were also over represented, however there were no significant differences with regard to teaching and non-teaching hospitals in terms of ADR incidences.

In-patient ADRs (ADRIn): Incidence of ADRs - Serious ADRs (n=12 studies; 22,502 participants) 2.1% (95% CI: 1.9, 2.3); Fatal ADRs (n=10 studies; 28,872 participants) 0.19% (95% CI: 1.13, 0.26); All severity (ie non-serious, serious and fatal) ADRs (n=18 studies; 34,463 participants) 10.9% (95% CI: 7.9, 13.9). Estimated number of hospital patients in 1994 with ADRs in thousands - Serious 702 (95% CI: 635, 770); Fatal 63 (95% CI: 41, 81); All severity 3607 (95% CI: 2618, 4596).

Admission ADRs (ADRad):

Incidence of ADRs - Serious ADRs (n=21 studies; 28017 participants) 4.7% (95% CI: 3.1-6.2); Fatal ADRs (n=6 studies; 17,753 participants) 0.13% (95% CI: 0.04, 0.21); All severity ADRs (not reported as by definition all ADRs are serious otherwise the patient would not have been admitted to hospital). Estimated number of hospital patients in 1994 with ADRs in thousands - Serious 1547 (95% CI: 1033, 2060); Fatal 43 (95% CI: 15, 71); All severity 3607 (95% CI: 1033, 2060). 8/21 ADRAd studies included the proportion of type A (dose-dependent ADRs) and type B (idiosyncratic and/or allergic ADRs). For All severity 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.

In-patient ADRs (ADRIn) and Admission ADRs (ADRad) combined:

Incidence of ADRs - Serious ADRs (n=33 studies; 50,519 participants) 6.7% (95% CI: 5.2, 8.2); Fatal ADRs (n=16 studies; 46,625 participants) 0.32% (95% CI: 0.23, 0.41); All severity ADRs (n=39 studies; 62,480 participants) 15.1% (95% CI: 12.0, 18.1). Estimated number of hospital patients in 1994 with ADRs in thousands - Serious ADRs 2216 (95% CI: 1721, 2711); Fatal ADRs 106 (95% CI: 76, 137; All severity ADRs 4986 (95% CI: 3976, 5995).

Authors' 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.
CRD commentary
This is a clearly described study that uses an extensive literature search with defined search terms and well-defined inclusion criteria. Some relevant information may have been excluded however, as only studies with English language translations were assessed. The methods used to extract data from the included studies are described, but the authors fail to state how decisions were made about the relevance of the studies and their quality. Additional information in the results tables regarding the age of study participants, the study setting and length of the study period, would have been useful. Heterogeneity is inevitable in this meta-analysis due to the all-inclusive inclusion criteria with regards to the type of participants and drug treatments studied. The authors describe the steps taken to reduce the heterogeneity including using a random-effects model and 95% CI intervals to highlight the issue. In view of these limitations and the results presented, the authors' cautious conclusions would appear to be valid.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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