Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis

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CRD summary
The authors concluded that the review findings were useful as a broad categorisation of in-hospital adverse drug reactions and their frequency but the estimates were crude indicators and should be evaluated with caution due to large differences between the included studies. This appeared to be a well-conducted review and the authors' cautious conclusion seems appropriate.

Authors' objectives
To evaluate the frequency of adverse drug reactions in hospitalised patients.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), SCOPUS, EBSCO, Web of Knowledge, LILACS, DARE, Scirus, NHS EED and ClinicalTrials.gov databases and Google Scholar were searched. Various conference proceedings and abstracts were accessed. Experts were contacted for grey literature and unpublished data. The last search date was on April 2010. Reference lists of included studies and relevant reviews were scanned. A full search strategy was reported to be available. Studies written in English, Portuguese, Spanish, French and German were included.

Study selection
Eligible studies were prospective studies from 1972 onwards with the primary objective of detecting adverse drug reactions in hospitalised patients (followed from admission to discharge) and where investigators could interview physicians, patients or nurses at least once a week. Studies had to have an adequately planned and described methodology for detection of adverse drug reactions including standardised application to patients (the accepted methodologies/combinations of methods for this review were provided in detail in the paper). The outcome of interest was the frequency of adverse drug reactions using the 1972 World Health Organisation (WHO) definition of adverse drug reaction; other definitions were accepted only if they were consistent with WHO criteria. Studies that focused only on patients with a specific pathology or drug exposure were excluded.

The included studies were conducted worldwide (none in United Kingdom). There was wide variation in study characteristics, particularly in terms of study quality, population, hospital ward and method of detection for adverse drug reaction (spontaneous reporting, solicited reporting, intensive monitoring, prospective monitoring, computerised system with investigation of every alert to validate adverse drug reaction, codification/codes and chart review). Study duration ranged between 1.2 months and 36 months.

Two reviewers independently selected the studies. Disagreements were resolved by consensus.

Assessment of study quality
Study quality was assessed using criteria adapted from published checklists for: description of prospective study design; number of hospitals under investigation; adequate selection criteria; definition and assessment of causality/avoidance of adverse drug reaction; rationale for study size and description of statistical methods, description of patients; attempts to avoid information/selection and other biases; intensive monitoring; and presentation of complete summary measures. Low risk of bias was awarded to studies that contained five or fewer parameters with medium, unclear or high risk of bias. Medium risk of bias was assumed where there were six to nine parameters; and high risk of bias where there were 10 or more parameters of this nature.

Two reviewers independently assessed study quality. Disagreements were resolved by consensus.

Data extraction
Data were extracted to enable presentation of cumulative incidence of in-hospital adverse drug reactions (number of
patients with in-hospital adverse drug reaction divided by the number of patients exposed to any drug), along with 95% confidence intervals (CI). Authors were contacted for data clarification or missing information, where necessary.

Two reviewers independently extracted these data.

**Methods of synthesis**
Studies were pooled in a random-effects meta-analysis. Statistical heterogeneity was assessed using $X^2$ and $I^2$ measures. Planned subgroup analyses were carried out to explore: the influence of study location (continent or country); definition of adverse drug reaction and method of detection; hospital and ward type; risk of bias; population age group; and study duration. Publication bias was assessed with a funnel plot (not shown).

**Results of the review**
Twenty-two studies (18,818 patients; 3,553 identified adverse drug reactions) were included in the review. Five studies were considered to be at low risk of bias overall and 13 studies had a medium risk. All studies were at low risk of bias for description of study design. Half of the studies attempted to prevent selection bias. Most studies did not report strategies to prevent information bias. Only one study calculated the intended study size.

The pooled cumulative incidence suggested that adverse drug reactions might occur in 16.88% (95% CI 13.56 to 20.12; $I^2=99\%$) of patients during hospitalisation.

Subgroup analyses revealed that the most influential moderators were risk of bias, population, ward type and adverse drug reaction detection method. Studies with moderate and high risk of bias were highly heterogeneous ($I^2=99\%$) and this did not alter when adjustments were made for population age (paediatric or adult). Low heterogeneity ($I^2=54\%$) disappeared in studies with low risk of bias when adjusted for population age. There was significant heterogeneity in each ward type (internal medicine, paediatric, geriatric, others; $I^2=96\%$). Statistically significant differences were reported between wards ($p=0.03$) and in the analysis of study location (between continents; $p=0.01$). Subgroups of detection method showed that all were highly heterogeneous ($I^2=98\%$ to $I^2=99\%$); there were no statistically significant differences between the detection methods. Further subgroup results were reported in the paper.

The funnel plot reportedly indicated that publication bias could not be ruled out.

**Authors' conclusions**
The review findings are useful as a broad categorisation of in-hospital adverse drug reactions and their frequency. The estimates are crude indicators and should be evaluated with caution due to high heterogeneity amongst the included studies.

**CRD commentary**
The review question was clear. Inclusion criteria were specified in sufficient detail to allow replication. A wide range of data sources were used to identify studies. The search included attempts to retrieve unpublished studies and those written in various languages, which maximised the chance of gathering all relevant studies. The review process was conducted with adequate efforts to minimise error and bias. Appropriate quality assessment criteria were applied to the included studies and the results of this were fully reported and taken into account in the review findings. Study details were presented. Statistical and clinical heterogeneity were commented upon substantially. High heterogeneity made the appropriateness of statistical pooling debatable but the authors made extensive efforts to investigate and report sources of variation.

This appeared to be a well-conducted review and the authors' cautious conclusion seems appropriate.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future studies should seek to reduce risk of bias at the planning stage. Studies should use standardised methods of detection for adverse drug reactions (standardisation of intensive monitoring with strict criteria), use clear definitions of adverse drug reaction (WHO), causality (Naranjo et al.) and preventability assessments.
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