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Quantifying Adverse Drug Events
Are Systematic Reviews the Answer?

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Abstract

Quantifying adverse drug events (ADEs) is critical to clinicians, consumers and policy makers. Most ADE information comes from large clinical trials. Systematic reviews have become a popular tool in quantifying the efficacy of different therapeutic interventions and ADE data collected in randomised trials may be helpful in quantifying the risk associated with a specific pharmacological agent. However, clinicians who are interested in conducting systematic reviews of ADEs may face many challenges. These challenges are geared towards two main areas: poor quality of ADE reporting in randomised trials and poor indexing of ADEs in medical databases.

In this review, we will discuss these challenges in detail using some examples from the literature. Where possible, we also discuss strategies that may overcome these problems. More rigourous standards of reporting ADEs in randomised trials, as well as better indexing of ADE terminology in medical databases, could one day make systematic reviews of ADEs a powerful tool for practising clinicians.

Information on adverse drug events (ADEs) is an invaluable tool in the clinical decision-making process. When two drugs of the same class are believed to be equally efficacious, clinicians usually choose to prescribe the drug with the safer adverse event profile for their patients.

Quantifying adverse drug data may be a challenging task to practising clinicians. Systematic reviews are a popular method of summarising clinical evidence.[1,2] Although most systematic reviews address the efficacy of different medical interventions, such reviews may also be helpful in quantifying ADEs.[3]

This paper will discuss the potential role of systematic reviews as a tool in quantifying ADEs, as well as examining the obstacles that clinician scientists may face when conducting such reviews.

1. Why is Information on Adverse Drug Events (ADEs) Important?

The direct medical costs associated with ADEs have been estimated to be in the range of $US30 billion to $US130 billion annually in the US alone.[4] These estimates are even more meaningful when compared with other high cost conditions or diseases, such as diabetes mellitus ($US45.2 billion),[5] obesity ($US70 billion)[6] and cardiovascular diseases ($US199.5 billion).[7] Drug-related mortality has been estimated to claim 218 000 lives annually.[8]

The importance of quantifying ADEs is particularly apparent in the case of drug treatment for children, women of child-bearing age, and the elderly. Because these population groups are exposed to medications almost entirely in the postmarketing phase of drug use, there is no systematic examination of the outcomes of medication use as would exist if the medication were given as part of a clinical trial.

2. ADE Reporting to Regulatory Authorities

Federal government agencies in North America (the US FDA and Health Canada) have voluntary ADE reporting systems for healthcare professionals and mandatory reporting systems for pharmaceutical companies. It is unclear what proportion of ADEs are reported by practising clinicians directly to the FDA, but it is believed to be less than the proportion that are reported through the pharmaceutical industry.[9] Between mid-1997 and mid-1998, physicians reported 2083 ADEs to the FDA.[10] If one assumes that 1997 is a typical reporting year, US physicians report an ADE to the FDA once every 336 years,[11] based on the number of licensed physicians in the US. During the same reporting period, pharmacists in the US reported 7406 ADEs to the FDA.[10] US pharmacists fare a bit better in the frequency analysis, reporting an ADE to the FDA once every 26 years, based on the number of licensed pharmacists in the US.[11] Health-related accreditation bodies estimate that as many as 95% of all ADEs are not reported, supporting the need to stimulate reporting on a large-scale basis.[12] Spontaneous reporting systems may not be efficient in informing clinicians about ADEs. Systematic reviews specifically of ADE data that are published in randomised controlled trials (RCTs) may be used as a supplementary tool to guide clinicians in quantifying ADEs.

National public health agencies are in a unique position to conduct systematic reviews of ADEs. These agencies have access to published and unpublished ADE data, which will strengthen the validity of such reviews.[13]

3. Why Conduct Systematic Reviews of ADEs?

Systematic reviews are a useful tool in quantifying outcomes of interest in clinical medicine. Although most systematic reviews are geared towards exploring the benefit of a specific pharmacological therapy,[14] systematic reviews that assess ADEs may be equally important to clinicians.[15] Although ADE data collected from RCTs may not reflect ADEs that may be seen in a real clinical setting (as clinical trials are conducted in a more controlled setting), randomisation and blinding in these studies usually alleviate biases and confounding that may exist in observational pharmacovigilance studies.

Such reviews can quantify the risk associated with a particular pharmacological agent. A recent systematic review of pramipexole and ropinirole, a relatively new class of drugs used in the treatment of Parkinson's disease, revealed that these agents may double the risk of somnolence compared with levodopa, an older agent.[16] The importance of this review was further enhanced when case reports associated the use of these drugs with numerous motor vehicle accidents that were recently published.[17]

In addition, adverse event data collected in randomised trials may actually be used to study the potential beneficial effects of a specific drug class or generate a hypothesis for a new drug indication. For example, a recent systematic review that assessed the frequency of an adverse event, headache, revealed that angiotensin receptor antagonists, a relatively new class of cardiovascular agents, may

actually prevent headache.[18] Recently, a RCT was conducted to test this hypothesis. The results of this study showed that angiotensin receptor antagonists reduced the frequency of migraine headaches by approximately 30% in patients with migraine.[19]

Systematic reviews may also be valuable in answering drug-related questions where RCT data is not readily available. This is especially the case when comparing the adverse event profiles of two drugs of the same class. Although a large-scale head-to-head RCT is the optimal design for answering this question, such trials may not have been conducted. Bucher and colleagues have recently proposed a method for estimating the risk of an adverse event occurring with two drugs by conducting a systematic review using data from a RCT of each drug compared with placebo.[20,21]

Recently, clinicians and scientists have come to realise that systematic reviews of RCTs can be a valuable tool for combining both efficacy and toxicity data in RCTs. However, the majority of published systematic reviews are those of efficacy data and the number of published reviews on ADEs is small.[22] We conducted a Medline search (from 1966 until September 2003) using the terms 'adverse drug events', 'adverse drug reactions', 'drug toxicity', and combining them with 'meta-analysis' or 'systematic reviews'. Our search only resulted in 21 systematic reviews of ADEs.

4. Limitations of Conducting Systematic Reviews of ADEs

Conducting systematic reviews is a challenging task. These challenges lie in two main areas. First, the methodology in conducting such reviews is difficult, mostly due to poor indexing of adverse events in medical databases. Secondly, the poor quality of ADE reporting in RCTs may make their interpretation difficult for the purposes of systematic review.

Searching for relevant articles is another challenge.[23] This is because ADEs are not always indexed in the title or abstract of an article. Databases, including Medline and Embase, are unable to find words relating to ADEs in the abstract of an article. Consider a cardiologist who is eager to know whether the prevalence of cough differs amongst ACE inhibitors. Entering the four most commonly prescribed ACE inhibitors (captopril, enalapril, lisinopril and ramipril) as subject heading and text words in Medline (from 1966 until September 2003) and combining the search with the term 'cough' yielded 19 potential articles (restricted to RCTs). This number is far less than the true number of trials that have measured cough as an ACE inhibitor-associated ADE since many large RCTs of ACE inhibitors, including the Heart Outcomes Prevention Evaluation (HOPE) trial, were not included in the search results.[24] One solution may be for the US National Library of Medicine to systematically index ADEs in clinical trials where these events are reported in the publication.

In addition, the Cochrane collaboration, a leader in the conduct and dissemination of systematic reviews, is in a position to conduct systematic reviews of ADEs. We contacted the different review groups, including cardiovascular, rheumatology and respiratory groups. Almost all the groups stated that assessing ADEs is part of every review. We believe that systematic reviews of ADEs should be conducted in conjunction with systematic reviews of efficacy studies. For example, a clinician who is interested in the efficacy of corticosteroids in preventing asthma symptoms may want to understand the risk of clinically important ADEs associated with these agents, including the potential risk of diabetes mellitus.[25] Although some systematic reviews report data on ADEs, it is apparent that strict criteria on ADE reporting have not been developed by the various Cochrane groups. Section 4.2.3 of the Cochrane Reviewers' handbook only briefly discusses the importance of reporting adverse events, secondary to different pharmacological interventions.[26]

The quality of reporting of ADEs in large RCTs can severely affect the integrity of a systematic review.[27,28] This is because the validity of any systematic review is related to the quality of the studies that it incorporates.[29] In a recent study, Ioannidis and Lau evaluated the reporting of ADEs in 192 RCTs of drug therapy in seven different therapeutic areas.[30] The authors found that only

39% of the trials reported ADEs. One approach in overcoming this problem is to develop strict criteria for reporting ADEs in clinical trials. Such criteria must concentrate on an active organ system-based reporting of ADEs. Some of these criteria have been developed, but are still not widely used.[31] The development of the Consolidated Standard of Reporting Trials (CONSORT) statement may be another solution. A recent study compared the quality of RCTs published in four medical journals (the *British Medical Journal, Journal of the American Medical Association, Lancet* and *New England Journal of Medicine*). The study demonstrated that the RCT quality was significantly higher in those journals using CONSORT.[32] Currently, CONSORT statements for the reporting of ADEs in RCTs are being developed.

5. Conclusion

Systematic reviews of ADEs have the potential to be a valuable resource to clinicians. However, poor quality of ADE reporting in RCTs has made it difficult to use systematic reviews as an effective and efficient tool in quantifying ADEs. Stricter guidelines on the reporting of ADEs in clinical trials will enable future clinician scientists to use systematic reviews of ADEs in their clinical decision-making process.

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