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Invited review

Meta-analysis of data from animal studies: A practical guide

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HIGHLIGHTS

- Meta-analysis is an invaluable tool in the life sciences.
- Methods for the application to clinical data are well documented.
- Consideration is required when applying these methods to preclinical data.
- We describe the application to preclinical data.
- We describe effect size calculations and assessing sources of heterogeneity.

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ABSTRACT

Meta-analyses of data from human studies are invaluable resources in the life sciences and the methods to conduct these are well documented. Similarly there are a number of benefits in conducting meta-analyses on data from animal studies; they can be used to inform clinical trial design, or to try and explain discrepancies between preclinical and clinical trial results. However there are inherit differences between animal and human studies and so applying the same techniques for the meta-analysis of preclinical data is not straightforward. For example preclinical studies are frequently small and there is often substantial heterogeneity between studies. This may have an impact on both the method of calculating an effect size and the method of pooling data. Here we describe a practical guide for the meta-analysis of data from animal studies including methods used to explore sources of heterogeneity.

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1. Introduction

Systematic review is a type of literature review that aims to identify all relevant studies to answer a particular research question (Greenhalgh, 1997; Cook et al., 1997). Data from these studies are often used in meta-analysis. The Cochrane collaboration has been pivotal in providing a framework for evidence-based health care to guide clinical decisions and healthcare policies. The use of systematic review and evidence-based healthcare is widely accepted by academia, healthcare professionals and funders, and these reviews receive twice as many citations in peer-reviewed journals as non-systematic reviews (Mickenautsch, 2010).

The systematic synthesis of data from the basic sciences is relatively novel. The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES; www.camarades.info) was established in 2004 to promote and support the use of similar approaches to those used by the Cochrane Collaboration to data from animal studies. Other similar initiatives, such as the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE; www.umcn.nl/Research/Departments/cdl/SYRCLE) research group also actively promote and train individuals in the conduct of systematic reviews of preclinical studies. Whilst the Cochrane methodology is considered gold-standard, their remit is limited to health care interventions tested in humans, and their activity does not extend to in vitro or in vivo laboratory studies. Crucially, there are fundamental differences in the purposes, design and conduct of systematic review and meta-analysis of preclinical and clinical studies which mean that standard methodologies for systematic overviews and meta-analysis need to be adapted to this new setting.

The objectives of this paper are:

- to outline the rationale for the review and synthesis of preclinical data and to explain why the differences between clinical and preclinical reviews may require different approaches to the conduct of systematic review and meta-analysis;
- to present the methodology for a systematic review of preclinical data in a self-contained tutorial.

Although most of the statistical fundamentals used to review data from preclinical data are not novel, to our knowledge this is the first self-contained tutorial on applying these to the review of preclinical data. Unless otherwise stated, the formulae are adapted from those described by Borenstein (2009) which we recommend for further reading.

This paper is organised as follows: in Section 2 we describe why we perform systematic reviews of preclinical data and what makes them different to clinical systematic reviews; in Section 3 we describe the methodological approach to performing a review of the preclinical data; and in Section 4 we describe further considerations which may be helpful to the reader.

2. Why preclinical systematic reviews and what makes them different to clinical systematic reviews

Systematic reviews of data from preclinical literature are important for a number of reasons. First and foremost, although systematic reviews are not bias free, their purpose is to reduce it by outlining transparent aims, objectives and methodology. This approach enables us to identify all of the published literature to answer a particular research question. In turn this may highlight gaps in our knowledge which can be fulfilled by further preclinical experimentation, or it can help us to avoid unnecessary replication which is unethical and of limited benefit. Secondly, clinical trials of novel interventions should not proceed without a rigorous appraisal of the preclinical data. Systematic reviews can tell us the efficacy of any given intervention as well as the limits to efficacy which may aid in clinical trial design. Additionally, we can assess both the internal and external validity of each included study and assess for publication bias which can help to predict outcome in the clinical setting.

There are fundamental differences in the purposes, design and conduct of systematic review and meta-analysis of preclinical and clinical studies. Clinical reviews are intrinsically confirmatory (see The Cochrane Handbook by Higgins and Green, 2009): the aim of a Cochrane review is to provide evidence to allow practitioners and patients to make informed-decisions about the delivery of healthcare. Because certain aspects of experimental design can introduce bias to the results of relevant studies, a central part of a Cochrane review is to include only those studies meeting a certain threshold of internal validity to allow confidence in the results reported. In contrast, preclinical reviews are typically exploratory. Because the summary estimate of the effectiveness of an intervention in animal models is, of itself, not particularly useful information; the practice has been to include all available data. This is useful for identifying if there are any gaps in the data. One important purpose (and perhaps the single most important impact) of systematic reviews of preclinical studies has been to explore the impact of possible sources of bias, and we recommend that this is carried out in all systematic reviews. The important findings from such reviews are differences between different types of experiments (i.e. sources of heterogeneity) rather than a headline figure for how "good" a drug