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Most systematic reviews of adverse effects did not include unpublished data

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Abstract

Objectives: We sought to identify the proportion of systematic reviews of adverse effects which search for unpublished data and the success rates of identifying unpublished data for inclusion in a systematic review.

Study Design and Setting: Two reviewers independently screened all records published in 2014 in the Database of Abstracts of Reviews of Effects (DARE) for systematic reviews where the primary aim was to evaluate an adverse effect or effects. Data were extracted on the types of adverse effects and interventions evaluated, sources searched, how many unpublished studies were included, and source or type of unpublished data included.

Results: From 9,129 DARE abstracts, 348 met our inclusion criteria. Most of these reviews evaluated a drug intervention (237/348, 68%) with specified adverse effects (250/348, 72%). Over a third (136/348, 39%) of all the reviews searched, a specific source for unpublished data, such as conference abstracts or trial registries, and nearly half of these reviews (65/136, 48%) included unpublished data. An additional 13 reviews included unpublished data despite not searching specific sources for unpublished studies. Overall, 22% (78/348) of reviews included unpublished data/studies.

Conclusion: Most reviews of adverse effects do not search specifically for unpublished data but, of those that do, nearly half are successful.

Keywords: Adverse effects; Systematic review; Unpublished data; Gray literature; Trial registry; Information retrieval

1. Introduction

Adverse effects are harmful or undesirable outcomes that occur during or after the use of a drug or intervention, for which there is at least a reasonable possibility of a causal relation [1]. Information on the adverse effects of health care interventions is important for decision making by regulators, policy makers, health care professionals, and patients. Serious or important adverse effects may occur rarely, and as such, systematic reviews and meta-analyses that synthesize harms data from numerous sources (potentially involving both published and unpublished data sets) can provide useful insights. However, because adverse effects data are poorly reported in published clinical trials [2–9], systematic reviews of adverse effects may be incomplete if they rely on peer-reviewed journal publications alone, or if the reviewers conduct only a relatively limited search for unpublished sources.

A consensus on a clear definition of "published" and "unpublished" data is difficult to reach. For practical reasons and to maintain consistency with our previous research work [10], "published" will refer to peer-reviewed journal articles and "unpublished" data will refer to all other material. It is acknowledged, however, that unpublished data can be publically available (e.g., through Web registries or regulatory agencies), but these do not undergo the processes of peer-reviewing, editing, formatting, and document identification that are part and parcel of established journal publications.

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What is new?

Key findings

- 39% of systematic reviews of adverse effects specifically search for unpublished data.
- 22% of systematic reviews of adverse effects include unpublished data.

What this adds to what was known?

- The most popular sources searched for unpublished data are conference scanning/databases, contacting authors or searching ClinicalTrials.gov.
- The success rate of searching in specific sources for unpublished data ranged from 0% to 38% with contacting authors and conference abstract searches being most successful.

What is the implication and what should change now?

- We need more research into the most effective sources for searching for unpublished data.

Serious concerns have emerged regarding publication bias or selective omission of outcomes data whereby negative results are less likely to be published than positive results and where adverse effects are underreported [11]. One way to attempt to overcome these biases is to include unpublished studies or data. Current guidance for all types of systematic reviews (irrespective of outcome) recommends searching unpublished sources [12−14] such as contacting authors or manufacturers, seeking conference abstracts, and searching trial registries (including industry trial registries). For reviews of adverse effects, the Cochrane Handbook also recommends searching regulatory authorities web sites such as the US Food and Drug Administration (FDA), the Medicines & Healthcare products Regulatory Agency, and the European Medicines Agency (EMA) [12]. Such guidance may have led to more systematic reviewers searching for unpublished data.

Nevertheless, previous research of systematic reviews of adverse effects from 1994 to 2011 has indicated that few attempts are made to search for unpublished data or industry-funded data [10,15]. This may be due to an expected low return or the difficulties of searching for unpublished data or in obtaining and incorporating unpublished data into systematic reviews [16] or a concern that unpublished data are not peer reviewed. In addition, it is unknown whether this situation is improving.

In contrast, research has indicated that much of the data on adverse effects are unpublished accounting for between 43% and 100% of the number of adverse effects and also a wider range of types of adverse effects are reported in the unpublished literature [9,17−25]. A considerable amount of otherwise "missing" adverse effects data therefore may potentially be retrieved from a diverse range of other sources such as trial registries, regulatory agencies, or authors. This has particularly important implications for evaluations of adverse effects because conclusions based on only published studies may not present a true picture of the adverse effects.

A lack of searching for and identification of unpublished data may pose serious threats to the validity of systematic reviews of adverse effects. Yet little is known as to whether (1) systematic reviewers fail to search for unpublished data or (2) whether they fail to identify unpublished data when they search and (3) which data sources are most fruitful for searching for unpublished data. Hence, we aimed to estimate the extent to which unpublished data are sought and identified within systematic reviews of adverse effects by carrying out a retrospective analysis of systematic reviews published in 2014.

2. Methods

2.1. Search strategy

Systematic reviews of adverse effects were identified by screening all records published in 2014 in the Database of Abstracts of Reviews of Effects (DARE) (via the Centre for Reviews and Dissemination web site, April 2015). No search strategy was implemented, as previous research has indicated that even very broad search strings would miss relevant records [26]. The DARE database was chosen because it was the most accessible major collection of systematic reviews of health care interventions. DARE was compiled through rigorous monthly searches of bibliographic databases, including MEDLINE and EMBASE, as well as handsearching of key journals, gray literature, and regular searches of the Internet. It also contains all Cochrane reviews, both new and updated. DARE ceased production in March 2015 but continues to be available in archive format.

2.2. Inclusion/exclusion criteria

A review was included if the primary aim was to evaluate an adverse effect or effects, known to be, or suspected to be, associated with an intervention, regardless of whether the review author's hypothesis or conclusions stated that the intervention increased the outcome. Articles that investigated the complete safety profile of an intervention were included if this was their primary aim. The author and another researcher independently screened titles and abstracts and selected full articles for inclusion. Any discrepancies between the researchers were resolved by discussion and consensus.