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Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review

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Abstract

Objective To compare the methodological quality and conclusions in Cochrane reviews with those in industry supported meta-analyses and other meta-analyses of the same drugs.

Design Systematic review comparing pairs of meta-analyses that studied the same two drugs in the same disease and were published within two years of each other.

Data sources Cochrane Database of Systematic Reviews (2003, issue 1), PubMed, and Embase.

Data extraction Two observers independently extracted data and used a validated scale to judge the methodological quality of the reviews.

Results 175 of 1596 Cochrane reviews had a meta-analysis that compared two drugs. Twenty four meta-analyses that matched the Cochrane reviews were found: eight were industry supported, nine had undeclared support, and seven had no support or were supported by non-industry sources. On a 0-7 scale, the median quality score was 7 for Cochrane reviews and 3 for other reviews ($P < 0.01$). Compared with industry supported reviews and reviews with undeclared support, Cochrane reviews had more often considered the potential for bias in the review—for example, by describing the method of concealment of allocation and describing excluded patients or studies. The seven industry supported reviews that had conclusions recommended the experimental drug without reservations, compared with none of the Cochrane reviews ($P = 0.02$), although the estimated treatment effect was similar on average ($z = 0.46$, $P = 0.64$). Reviews with undeclared support and reviews with not for profit support or no support had conclusions that were similar in cautiousness to the Cochrane reviews.

Conclusions Industry supported reviews of drugs should be read with caution as they were less transparent, had few reservations about methodological limitations of the included trials, and had more favourable conclusions than the corresponding Cochrane reviews.

Introduction

Bias in drug trials is common and often favours the sponsor's product.¹⁻³ Critical, systematic reviews that aggregate the available information in a neutral manner are therefore essential. Cochrane reviews aim to minimise bias and avoid conflicts of interest and, on average, may have greater methodological rigour than systematic reviews published in paper based journals.⁴⁻⁶ We therefore hypothesised that Cochrane reviews would be more transparent and less biased than industry supported systematic reviews. We aimed to compare Cochrane reviews with other meta-analyses of the same drugs, which we divided into those that had industry support, those with undeclared support, and those that had non-profit support or no support.

Methods

We searched for review pairs that consisted of a Cochrane review and a similar review in a paper based journal. A Cochrane review was eligible if it used meta-analysis to compare at least two different drugs; was

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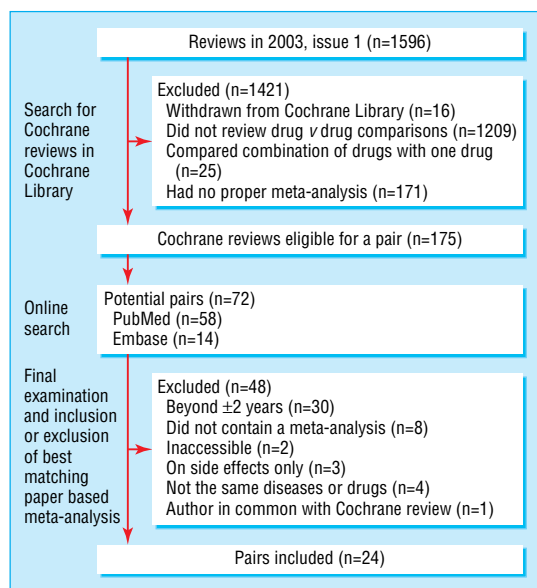
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An appendix, three extra tables, and extra references w1-w48 are on bmj.com



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Searches for pairs of reviews (first or most obvious reason for exclusion indicated)

published in the *Cochrane Database of Systematic Reviews* 2003, issue 1; and could be matched with a meta-analysis of the same drugs and diseases published in full in a paper based journal within two years before or after the most recent substantive amendment of the Cochrane review.

One investigator hand searched reviews in the *Cochrane Database of Systematic Reviews* for drug comparisons. For each potentially eligible Cochrane review, we sought possibly eligible paper based reviews in PubMed (January 1966 to July 2003) and Embase (1980 to August 2003). Two researchers independently assessed each pair of reviews. We resolved disagreements by discussion. We were not blinded. We extracted data on names of relevant drugs and diseases; types of support; number and type of sources used to identify trials for the review; searches for unpublished trials; and descriptions of concealment of allocation, details of blinding, and excluded patients and trials. We defined support by the pharmaceutical industry as provision of grants, authorship, or other major assistance such as help with the statistical analysis.

We assessed the methodological quality of the reviews with a validated tool.⁷⁻⁹ We assessed whether the experimental intervention was recommended, with or without reservations.³ For the industry supported reviews, we also assessed whether the estimated treatment effects were different from those reported in the Cochrane reviews.

Results

The *Cochrane Database of Systematic Reviews* contained 1596 Cochrane reviews. After exclusions we obtained 24 matched review pairs (figure).^{w1-w48} In eight of the 24 pairs the paper based reviews had industry support,^{w1 w4-w18} in nine they had undeclared support,^{w1 w3 w19-w34} and in seven they had non-profit or no support.^{w35-w48}

The overall median quality score was 7 for the 24 Cochrane reviews and 3 for the other reviews

($P < 0.001$; table A on bmj.com). The median differences in number of included trials were 0, 1, and 1 (table B on bmj.com).

Cochrane reviews versus industry supported reviews (eight pairs)

Cochrane reviews were of higher quality than industry supported reviews ($P < 0.01$). They also more often stated the search methods used to find studies ($P = 0.06$), searched comprehensively ($P = 0.06$), avoided bias in the selection of studies ($P = 0.03$), reported criteria for assessing the validity of the studies ($P = 0.03$), used appropriate criteria in assessing the studies ($P < 0.01$) (table A), described methods of concealment of allocation ($P = 0.02$), and described excluded patients ($P = 0.03$) and studies ($P = 0.03$), and they used more sources to identify studies ($P = 0.02$) (table B).

One of the industry supported reviews had no conclusion, as it referred to physiological characteristics of the drug.^{w6} The other seven reviews recommended the experimental drug without reservations, compared with none of the Cochrane reviews ($P < 0.01$). This difference was related to interpretation of the data (see bmj.com) and consideration of costs. The authors of six of the eight Cochrane reviews had reservations about the quality or relevance of the trials or their findings.^{w1 w5 w7 w9 w11 w17} Seven mentioned the higher cost of the experimental drug as a problem compared with none of the industry supported reviews, of which two claimed that economic analyses had shown that the experimental drug was cost effective.^{w4 w18} The estimated treatment effect was similar, on average, in the pairs of reviews (pooled $z = 0.46$, $P = 0.64$; appendix and table C on bmj.com). However, the scatter of the comparative z scores was high ($\chi^2 = 19.4$, $df = 6$, $P = 0.004$), which partly reflects differential inclusion of trials and patients despite our close matching (table C) and partly could be caused by selective or biased handling of data.

Cochrane reviews versus reviews with undeclared support (nine pairs)

The results for reviews with undeclared support were similar to those for the industry supported reviews (table A), except that no significant differences existed for the stated search methods ($P = 1.00$) or efforts to avoid bias in the selection of studies ($P = 0.22$) and the recommendations were without reservations in one Cochrane review and in two other reviews ($P = 1.00$). The paper based reviews were often biased and poorly done. For example, one study included retrospective studies, had arbitrary entry criteria, and seemed to have preferentially selected those studies and data that were in favour of the experimental drug; the outcome was analysed in eight different ways, and the biggest difference was emphasised.^{w26}

Cochrane reviews versus reviews with non-profit or no support (seven pairs)

We found no significant differences between Cochrane reviews and reviews with non-profit or no support (table A). The recommendations were without reservations in two Cochrane reviews and in one other review. However, in three pairs of reviews the conclusions favoured different drugs.

Discussion

We found that although some Cochrane reviews had clear methodological deficiencies, these were fewer, on average, than in reviews published in paper based journals.

Limitations

A minor limitation was that we could not be blinded, as the layout of Cochrane reviews is unique; blinding has little impact on extraction of data for reviews.¹⁰ A more important limitation is that our sample was small and needs to be replicated. Furthermore, we are affiliated with a Cochrane centre. To help readers to make their own judgments, we have provided details on the comparison with industry supported reviews (see bmj.com). Our findings correspond to another recent finding that Cochrane reviews assess methodological quality more often than do other reviews,¹¹ although because of space constraints some paper based reviews might have been conducted better than was reported.

Industry supported reviews

The estimated treatment effects in industry supported reviews were similar to those of Cochrane reviews, but the former had uniformly positive recommendations for the experimental drug, without reservations about methodological limitations of the trials or costs, in contrast to none of the Cochrane reviews. This suggests that the main problem with industry supported reviews lies in how conclusions are formulated.

As an example, a meta-analysis supported by Merck concluded in 2001 that no increased risk of arterial thrombosis existed with the company's drug rofecoxib,¹² but a meta-analysis not supported by industry showed an increased risk,¹³ which was apparent in publications available to the authors of the industry supported meta-analysis. Rofecoxib was withdrawn because of thromboses in 2004. The influence of industry on trial reports is similar to our findings. One survey found that the conclusions recommended the experimental drug as the drug of choice five times as often if the trial was funded by for profit organisations.³

Undeclared support and interpretation of financial support

The conclusions of paper based reviews with undeclared support were more cautious than those for industry supported reviews. We asked the authors if they had received industry support, and none answered affirmatively. However, we suspect that some authors had received undeclared support or had allowed the company to review the paper and insert text, as suggested by a recommendation in one review: "Coupled with potential cost savings driven by the reduced need for hospitalization and revascularization procedures, it is not difficult to understand why clinicians, administrators and medical organizations representing the interests of physicians and the welfare of patients look favourably upon [low molecular weight heparin]."³

The interpretation of financial support is not always straightforward. For example, the authors of a paper based review that we classified as "non-profit support" noted that it was supported in part by public sources but did not describe the nature of the other

What is already known on this topic

Bias commonly occurs in trials of healthcare interventions and often favours the sponsor's product

Anecdotal reports have suggested that industry supported meta-analyses may also be more flawed than other meta-analyses

What this study adds

Industry supported reviews were of lesser quality than Cochrane reviews of the same drugs and always recommended the experimental drug without reservations, which none of the Cochrane reviews did

Industry supported meta-analyses of drugs were less transparent and had few reservations about methodological limitations of included trials

Reviews with undeclared support and those with not for profit support or no support had similarly cautious conclusions to matched Cochrane reviews

part, and two of the authors had previously received "unrestricted grants" from the manufacturer of ocreotide.⁴⁰ In one of the Cochrane reviews, Upjohn had funded secondary analyses of the author's own trial for use in the review.⁴⁷ The current policy in the Cochrane Collaboration is that industry support of Cochrane reviews is not acceptable.¹⁴

Other problems with reviews

Less rigorously controlled studies than ours have reported on discrepant conclusions between systematic reviews assessing the same subject.¹⁵⁻²² Some reviews missed more than half of the available trials,¹⁶⁻¹⁸ and a review of meta-analyses of analgesic interventions found that those with positive conclusions had lower quality scores on the index we used.⁸ Our examination of the comparative z scores revealed more scatter than expected, which indicates that some effect estimates might have been biased, and, furthermore, that the confidence interval in a meta-analysis generally exaggerates the precision in the underlying data.

Conclusions

Industry supported reviews of drugs are less transparent than Cochrane reviews and have few reservations about methodological limitations of the included trials; their conclusions should be read with caution. Details of concealment of allocation, blinding, inclusion and exclusion criteria for trials, search strategies, and estimated effects need to be reported to allow readers to judge the reliability of reviews. To improve transparency, access to the protocol should be available.

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DRUG POINTS

Epileptic seizures can follow high doses of oral vardenafil

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Case report

An otherwise healthy 60 year old man was prescribed 10 mg of vardenafil (Levitra, Bayer) for sexual dysfunction. Because this was ineffective, he increased the dose to 40 mg. Three hours later, he had a tonic-clonic seizure, seen by his relatives. On admission to hospital, neurological examination, brain magnetic resonance imaging, and electroencephalography after sleep deprivation were normal. Stress electrocardiography, echocardiography, and cardiac scan with dipyridamole test as well as carotid doppler ultrasonography did not show concomitant cardiac diseases. The man was told to stop using vardenafil.

Two months later he had a new tonic-clonic seizure, four hours after taking 30 mg of vardenafil. At eight months' follow-up he is seizure-free without treatment.

Discussion

In this man, the seizures were unlikely to be the manifestation of other diseases: a complete screening ruled this out. And in both occasions seizure occurred within a few hours after he took vardenafil.

Vardenafil is a selective oral phosphodiesterase type 5 (PDE5) inhibitor effective in erectile dysfunction.¹ Adverse events include headache, flushing, nasal congestion, and dyspepsia.¹⁻² Convulsions were not reported to Bayer during clinical trials of vardenafil.¹⁻² However, people taking sildenafil (Viagra, Pfizer), another inhibitor of this type, have had seizures.³

PDE5 inhibitors increase nitric oxide leading to increased cyclic guanosine monophosphate (cGMP), with relaxation of the smooth muscle in the corpus

cavernosum and increased blood flow to the penis.¹⁻² Recent evidence indicates that these inhibitors may increase effects mediated by nitric oxide. Although the role of nitric oxide in the pathophysiology of epilepsy remains debated, the effects of nitric oxide and cGMP signalling pathway on seizure threshold⁴ raise the possibility that nitric oxide may mediate mechanisms that alter susceptibility to seizure. Furthermore, sildenafil has shown a pro-convulsant effect on seizure threshold, interacting with exogenously and endogenously released nitric oxide.⁵ However, the exact role of PDE5 in altering susceptibility to seizure via this pathway remains unclear.

After we submitted this drug point, a 78 year old patient presented with partial epileptic seizure after oral intake, for the second time, of 10 mg of vardenafil.⁶ This confirms that epileptic seizures may occur during treatment with phosphodiesterase inhibitors.

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