Research

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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,[4] and, on average, they may have greater methodological rigour than systematic reviews published in paper based journals.[5 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 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 or classes of drugs; was published in the *Cochrane Database of Systematic Reviews* 2003, issue 1; 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; and had no authors in common with the Cochrane review.

We defined support by the pharmaceutical industry as provision of grants, authorship, or other major assistance such as help with the statistical analysis. We did not consider provision of references or unpublished trial reports as support.

One investigator (AWJ) hand searched all reviews in the *Cochrane Database of Systematic Reviews* 2003, issue 1 for drug comparisons. For each potentially eligible Cochrane review, we sought possibly eligible paper based reviews by searching PubMed (January 1966 to July 2003) for the same diseases and drugs combined with "meta-analysis" or meta-analysis[pt]. From online inspection of titles and abstracts, we selected meta-analyses for examination of the full text. When we found no match in PubMed, we searched Embase (WebSPIRS 5) (1980 to August 2003). When we found more than one match with the same type of support, we chose the one with the closest publication date to the Cochrane review.

AWJ and PCG independently assessed each pair of reviews in random order, by reading the Cochrane review first in half of the pairs. We used a pilot tested data sheet and resolved disagreements by discussion. We were not blinded. We extracted data on the date of the most recent substantive amendment to the Cochrane review and of the publication of the paper based review; 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 assessed the methodological quality of the reviews with Oxman and Guyatt's index, which is a validated tool with nine

P+ *An appendix, three extra tables, and extra references w1-w48 are on bmj.com*
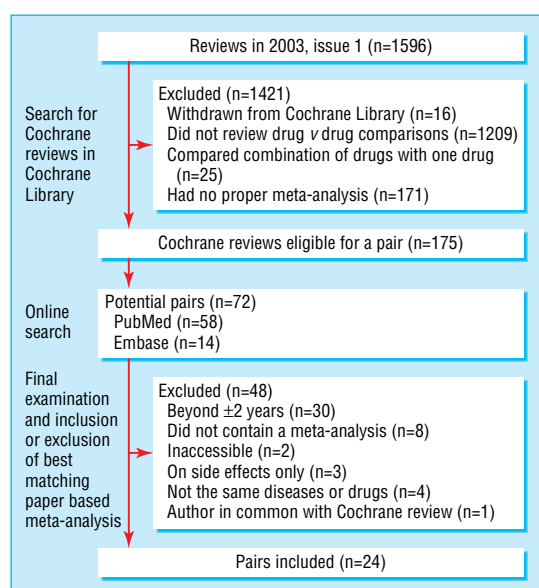
Searches for pairs of reviews (first or most obvious reason for exclusion indicated)

items considering the potential for bias and an overall assessment on a 0-7 scale.[7–9] We judged the review authors' conclusions by assessing whether the experimental intervention was recommended without reservations or whether it was not recommended or recommended only with reservations.[3] As our data were paired, we compared quantitative data with the Wilcoxon-Pratt one sample rank sum test and binary data with a sign test; P values are two sided.

For the industry supported reviews, we also assessed whether the estimated treatment effects were different from those reported in the Cochrane reviews. We used the first reported outcome with data in the industry supported review that was also presented in the Cochrane review, and we also did the corresponding analysis in which we started with the first reported outcome in the Cochrane review. We calculated pooled comparative z scores, after adjustment for the number of patients contributing to the outcome and for the number of patients that were common to the two analyses (see appendix on bmj.com for details).

Results

The *Cochrane Database of Systematic Reviews* 2003, issue 1 contained 1596 Cochrane reviews, of which we excluded 1421, mostly because they did not compare drugs (figure). In 72 of the remaining 175 reviews, the Medline and Embase searches identified potentially eligible paper based reviews, of which we excluded 48, mostly because their publication date differed by more than two years from the last substantive update of the Cochrane review, resulting in 24 matched pairs.[w1-w48] One Cochrane review[w1] was paired with a paper based review with industry support[w2] and also with one with undeclared support;[w3] one of these reviews[w2] presented only a subgroup analysis, and we therefore substituted it with an older review that contained the same trials.[w4] 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 mean years of publication for the three sets of pairs were 2000 versus 2000 for Cochrane reviews versus industry supported reviews, 2000 versus 1999 for Cochrane reviews versus reviews with undeclared support, and 2000 versus 2000 for Cochrane reviews versus reviews with non-profit or no support; 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 supported by industry all 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 (table) 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] and two noted that the effect decreased with increasing sample size.[w5 w9] 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] In contrast to these interpretations, 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 the comparison with 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. One seemed to have included non-randomised studies.[w22] Another 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] A third review presented a highly misleading result in the abstract that was based on an indirect comparison of treatment arms,[w30] and, in contrast to the Cochrane review,[w29] the authors failed to include all eligible studies and failed to detect sample size bias. A fourth review found no differences between the drugs but stated, with reference to an economic analysis: "Coupled with potential cost savings driven by the reduced need for hospitalization and revascularization procedures, it is not dif-

Characteristics of pairs of Cochrane reviews (C) and industry supported paper based reviews (I) of the same drugs

References	Disease	Interventions	No of included trials (both reviews/C only/I only)	No of included patients (C/I)	Significant difference favouring drug of interest		Comments
					Benefits (C/I)	Harms (C/I)	
w1, w4	Acute coronary syndrome	Enoxaparin v unfractionated heparin	2/0/0	7081/7081	Yes/yes	No/no	C: control drug is cheaper; new trials with longer follow-up are needed. I: health economic study shows that enoxaparin lowers total costs of care. Our comment: both reviews found that control drug causes significantly fewer minor bleeds
w5, w6	Schizophrenia or similar psychoses	Amisulpride v typical antipsychotics	14/0/0	1702/1700	Yes/yes	Yes/yes	Both reviews noted that funnel plot suggested publication bias in favour of amisulpride. C: the result must be considered with provisos; amisulpride is expensive. I: dismissed finding, noting that according to manufacturer no further studies had been done; no conclusion. Our comment: bias should not be dismissed; reasons for sample size bias other than selective publication exist
w7, w8	Rheumatoid arthritis	Celecoxib v other NSAIDs	4/1/1	4465/4191	No/no	Yes/yes	C: 12 month results from CLASS study suggest that short term benefit of celecoxib on gastrointestinal ulcers may not persist; this is important as rheumatoid arthritis is a chronic disease and patients are likely to be taking celecoxib for extended periods; increased cost. I: no such reservations
w9, w10	Schizophrenia	Risperidone v haloperidol	6/4/0	2326/1047	Yes/yes	No/yes	C: more weight gain with risperidone, which is costly; included schizophrenia-like psychoses as no evidence that these should be treated differently from schizophrenia; funnel plots showed greater benefit for risperidone in smaller studies. I: all results favoured risperidone; no comment on possible sample size bias. Our comment: inconsistency in inclusion of patients in relation to dose of risperidone in I review; excluded trials had rather negative results
w11, w12	Asthma	Inhaled fluticasone v budesonide and beclometasone	14/16/0	7775/3564	Yes/yes	No/yes	C: plasma cortisol is an unreliable measure of harm. I: plasma cortisol favours experimental drug. Our comment: no information on where studies in I review came from and only those published after 1995 included; C review included 10 such studies that were missing in I review; complete discrepancy between two reviews in studies with cortisol values, and for several studies in I review C authors did not know that cortisol had been measured; authors of I review had access to individual patient data; all requests by authors of C review to get access to further data from authors of trial reports were unsuccessful
w13, w14	Asthma	Salmeterol v theophylline	3/2/6	777/1330	No/yes	Yes/yes	C: trend towards better effect of salmeterol, but inconsistent reporting of data precluded meta-analysis; cost analysis needed. I: significant differences in favour of salmeterol for all efficacy outcomes. Our comment: I review included only studies carried out by company; three missing studies in C review were unpublished, two were abstracts, and one was untraceable as reference in I review was wrong
w15, w16	Depression	Paroxetine v TCAs	15/17/24	5910/3758	NA/no	Yes/yes	C: SSRIs up to 30 times more costly than TCAs. I: no search strategy; company's worldwide clinical database used. Our comment: 12 trials in C review indisputably fulfilled inclusion criteria for I review but were missing; 20 trials included only in I review were "data on file;" C review had missed three small trials, two of which were published only as abstracts
w17, w18	Depression	Venlafaxine v other antidepressants	0/4/5	708/450	No/yes	NA/no	C: costs of SSRIs and limited benefit do not justify routine first line use. I: economic analyses have shown that venlafaxine is cost effective. Our comment: no significant benefit in favour of venlafaxine in C review; I review was obscure; unclear selection criteria ("some selected SSRIs" and "certain TCAs"); impossible to verify which trials were included as references were to trial protocols; inappropriate meta-analysis of study arms

NA=not available; NSAID=non-steroidal anti-inflammatory drug; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

ficult 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]."[w3]

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. In one set, although the same trials were included, the authors had different views on the trade-off between benefits and harms. The Cochrane review strongly supported the use of warfarin in patients with atrial fibrillation with average or greater risk of stroke,[w35] whereas the paper based review strongly favoured antiplatelet drugs.[w36] In another set, the paper review found better control of haemorrhage with octreotide.[w40] The Cochrane review did not find any differences but referred to another meta-analysis when it emphasised that terlipressin is the only drug for which a reduction in mortality has been found compared with no treatment.[w39] We have published a comment with this review, as we doubt that the effect on mortality is reliable.

In the third set, the paper review included only three double blind randomised trials and concluded that methadone should be used for heroin dependence; it noted in an addendum that LAAM (levomethadyl acetate hydrochloride) had been withdrawn from the market because of cardiotoxicity.[w46] The Cochrane review included 18 studies, three of which were cohort studies that were not analysed separately from the randomised trials, and concluded that LAAM seems to be more effective than methadone.[w45] A fourth Cochrane review found a major sample size bias but failed to make reservations in the abstract as regards the mortality benefit, which was based on all trials.[w44]

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, and Cochrane reviews are done according to a handbook[11] that was developed partly by Andy Oxman, who also participated in the development of the validated index that we used for evaluating methodological quality.[9 12] To help readers to make their own judgments, we have provided details on the comparison with industry supported reviews (table) and added items to our data extraction sheet that are indisputably important for the reliability of reviews, such as adequate concealment of allocation.[13 14] Our findings correspond to another recent finding that Cochrane reviews assess methodological quality more often than do other reviews,[15] although because of space constraints some paper based reviews might have been conducted better than was reported.

Industry supported review

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.

We compared pairs of similar reviews published within a narrow time frame. Other such pairwise comparisons have been anecdotal. A meta-analysis found a similar drop-out rate for fluoxetine as for tricyclic antidepressants ($P = 0.4$),[16 17] whereas a company employee reported a marked difference in favour of fluoxetine ($P < 0.001$)[18] in subsequent correspondence. This is surprising, as the industry supported meta-analysis contained fewer patients and included "data on file" reports, which are usually less favourable than published ones.[19 20] In contrast to industry supported authors, authors of Cochrane reviews often cannot get access to such data, as indicated in two of the reviews.[w11 w37]

As another example, a meta-analysis supported by Merck concluded in 2001 that no increased risk of arterial thrombosis existed with the company's drug rofecoxib,[21] but a meta-analysis not supported by industry showed an increased risk,[22] 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. A survey found that none of 56 trials of non-steroidal anti-inflammatory drugs supported by the manufacturer presented results that were unfavourable to the company.[23] Another 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, even after adjustment for the effect size.[3]

Reviews with undeclared support

The conclusions of paper based reviews with undeclared support were more cautious than those for industry supported reviews. We contacted the authors after we had assembled our data. Eight declared that they had not received any external funding or other type of support (which we exemplified as help with the statistical analyses), and one replied that he had not received any other financial support.[w3] We do not know whether these replies were comprehensive, and we suspect that some authors had received undeclared support or had allowed the company to review the paper and insert text, as suggested by the recommendation for low molecular weight heparin above.[w3]

Interpretation of financial support

The interpretation of financial support is not always straightforward. 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 part, and two of the authors had previously received "unrestricted grants" from the manufacturer of octreotide.[w40] The authors of the matching Cochrane review declared that they had no conflicts of interest but added that they had "no permanent financial contracts" with companies producing the comparator, terlipressin.[w39] Finally, one of the Cochrane reviews had industry support, as Upjohn had funded secondary analyses of the author's own trial for use in the review.[w47] The current policy in the Cochrane Collaboration is that industry support of Cochrane reviews is not acceptable.[24]

Other problems with reviews

Less rigorously controlled studies than ours have reported on discrepant conclusions between systematic reviews assessing the same subject. The major reasons were incomplete searches, differential inclusion of trials, insufficient attention to the quality of the trials and to bias detection, and differences in interpretation.[25–32] Some reviews missed more than half of the available trials,[26–28] and a review of meta-analyses of analgesic interventions found that those with positive conclusions had lower quality scores on the Oxman and Guyatt index.[8] A recent study of antihypertensive drugs found that the conclusions of meta-analyses were positive in 91% of the papers with financial ties and in 72% of other papers.[33] However, the conclusions of Cochrane reviews also tend to be too positive.[34]

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. We believe that details of concealment of allocation, blinding, inclusion and exclusion criteria for trials, search strategies, and estimated effects in each included trial need to be reported to allow readers to judge the reliability of reviews. To improve transparency, access to the protocol should be available. Protocols for Cochrane reviews are published in the Cochrane Library, and protocols for other systematic reviews can be registered free of charge at the UK national research register through the Centre for Reviews and Dissemination in York, UK.

compared estimated treatment effects. All authors commented on the final manuscript. PCG is the guarantor.

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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