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The association between funding by commercial interests and study outcome in randomized controlled drug trials

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Background. Previous studies limited to specific drugs or journal types have shown an association between the source of funding of research and the published results.

Objective. The aim of the present study was to determine the association between source of support of research and published outcomes of randomized controlled drug trials in general interest medical journals.

Methods. Randomized controlled drug trials ($n = 314$) published in five general interest medical journals over a 2-year period were reviewed. Study outcome was classified as positive or negative. Support was classified as pharmaceutical industry or non-industry. Association between source of support and outcome was tested with the chi-squared statistic.

Results. Positive findings were found in 77% of studies, negative findings in 20% and an uncertain outcome in 3%. Support from commercial sources was found in 68% of trials. Negative findings were found in 13% of industry-supported studies and in 35% of non-industry-supported studies (chi-squared = 18.36, $P < 0.0001$, odds ratio = 3.54, 95% confidence interval 1.90–6.62).

Conclusions. An association was found between the source of study support and the published outcome. Though the reason for this association cannot be determined from the data collected, future studies may clarify the importance of this finding for readers concerned with the relationship of funding bodies to the publication of research outcomes.

Keywords. Publication bias, randomized controlled trials.

Introduction

The medical literature is an important source of information about prescription drugs. The objectivity of published studies is critical for clinicians, medical researchers and other medical professionals. In published studies, the potential for bias varies greatly based upon the study design and the editorial process, including publication in a peer-reviewed or non-peer-reviewed journal. It has been suggested that pharmaceutical industry support for research may affect study outcomes.

Previous investigations have found an association between funding by pharmaceutical companies and support for new therapies tested,[1] between manufacturer support and a positive outcome of trials in published drug symposia[2] and between industry support and positive outcome in trials of non-steroidal anti-inflammatory drugs (NSAIDs).[3] In these three studies, a total of 320 articles were evaluated. A fourth study[4] of clinical research projects submitted to a hospital ethics committee found that an external source of funding was associated with publication of a trial but that pharmaceutical industry funding was not predictive of publication. In this study, we examine the association between manufacturer support and study outcome in papers published in five high profile, general interest medical journals.

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Methods

Inclusion and exclusion criteria

All randomized controlled trials (RCTs) of drugs or food products with therapeutic properties appearing in *Annals of Internal Medicine*, *The British Medical Journal*, *The Journal of the American Medical Association*, *The Lancet* and *The New England Journal of Medicine* between October 8, 1992 and October 1, 1994 were reviewed. The journals were hand searched. Studies of medical instruments or surgical procedures, duplicate publications of trials, secondary analyses of earlier data sets, meta-analyses and studies in which two regimens of the same drug were compared (different dose regimens of the same drug, different durations of treatment) were excluded. Studies were identified as RCTs by reviewing the methods section of each paper to determine if the study used a control group for comparison with the study-drug group and if patients were assigned randomly to the study or control arms of the trial.

Review protocol

The study team consisted of four physicians. Two reviewers evaluated each article to determine whether a drug company had supported the research and whether the reported outcome was favourable to the drug in question. The pair of reviewers then met and compared their assessments. We found complete agreement between pairs of reviewers regarding outcome and sources of support. The studies with an 'uncertain' outcome or source of support were presented to the forum of four reviewers in an attempt to achieve a consensus on the source of funding or the outcome of the study. The physicians read the full published version of each study and thus were not blinded with regard to commercial support when assessing the study outcome.

Classification of study support

Study support was classified as stemming from either industry or non-industry sources. Each article was reviewed to determine whether the company, which manufactured the product being tested, contributed to the research. Three types of commercial involvement were recorded: funding, provision of study materials (drug, look-alike placebo, food product or assay kits) and manpower (authorship or statistical analysis). We determined whether there had been commercial support on the basis of information provided in the article from statements of author affiliation, the methods section, statements of sources of support and acknowledgements. In cases where the relationship between a supporting company and the drug being tested was unclear, we referred to the American Hospital Formulary Service Drug Information[5] and the Martindale Pharmacopoeia[6] to determine the name of the manufacturer of the study drug.

Classification of study outcome

Study outcomes were classified as positive or negative according to the general criterion that the result would or would not promote use of the drug of interest. The following specific criteria were used.

(i) If the study drug was claimed to be effective, and side effects were acceptable according to the researchers, the study outcome was considered positive.
(ii) If the study drug was claimed to be no more effective than placebo or the comparison regimen, or if it was effective, but with unacceptable side effects, the study outcome was considered negative.
(iii) If a study reported both a positive effect on an intermediate or surrogate outcome measure and no positive effect on a clinically significant outcome measure, the outcome was considered uncertain.

Statistical analysis

Data were entered and analysed using Epi-Info version 6 software.[7] Associations were tested using the chi-squared statistic with significance set at $P < 0.05$. The null hypothesis is that there is no difference in the proportions of positive and negative studies between the industry-funded and non-industry-funded studies.

Results

A total of 314 articles that met the study criteria were found in the five journals (Table 1). Positive outcomes were found in 243 (77%) studies and negative outcomes in 62 (20%). In nine (3%) studies, the reviewers were unable to determine if the outcome was positive or negative, and these were classified as 'uncertain'. Evidence of pharmaceutical industry support was found in 215 studies (68%). Support was financial in 125 (40%), manpower (authors or statistical help) in 103 studies (33%) and supply of drugs in 67 studies (21%). Negative outcomes were found in 34% of non-industry-supported trials and in 13% of those with pharmaceutical company support. (Table 2; chi-squared = 16.7, $P < 0.0001$, odds

TABLE 1 *Distribution of randomized controlled drug studies by journal, 1992–1994* (n = *314*)

Journal	No. of studies	Studies with industry funding
New England Journal of Medicine	116	70 (60%)
Lancet	90	61 (67%)
Annals of Internal Medicine	54	38 (70%)
British Medical Journal	28	21 (75%)
Journal of the American Medical Association	26	19 (73%)

TABLE 2 *Outcome of randomized controlled drug trials in five general interest medical journals 1992–1994 by source of funding (*n = *305)*

	No. of studies (with raw percentages)	
	Positive outcome	Negative outcome
Industry funding	181 (87%)	28 (13%)
Non-industry funding	62 (65%)	34 (35%)

This table excludes the nine studies from Table 1 with 'uncertain' outcome.

ratio = 3.54, 95% confidence interval 1.90–6.62). Reclassifying the nine studies with an 'uncertain outcome' as all positive or all negative did not change the significance of the findings. Tests of association between the subtype of support provided (money, manpower or drugs) and study outcome were not found to be statistically significant nor were differences between individual journals in the ratio of negative industry-supported to negative non-industry-supported studies.

Discussion

Our findings show an association between financial support of published RCTs by commercial interests and outcomes favouring the use of the products being tested. We concur with the results of previously published papers that examine the question of drug company support for research and its relationship to outcome. Davidson,[1] in a single-author paper, analysed 107 controlled clinical trials that were classified as favouring a new therapy or a traditional therapy. Of those favouring a new therapy, pharmaceutical companies funded 43%. Of those trials favouring traditional therapy, pharmaceutical companies funded only 13%. Cho and Bero[2] looked at the quality of studies that were published in drug symposia. They included observational and controlled studies that were published in peer-reviewed and non-peer-reviewed journals. They found that manufacturer-supported studies were more likely to result in outcomes that were favourable to the drug of interest (98% versus 79%). Rochon *et al*.[3] looked only at RCTs that evaluated the use of NSAIDs in the treatment of arthritis during a two and a half-year period. They found that all of the 56 manufacturer-supported studies were favourable for the study drug. In addition, there were many cases of comparisons of drug doses that were mismatched and claims of a better toxicity profile that were justified in only 12 of 22 trials. In all, 320 articles underwent evaluation in these three studies taken together, while our study alone examined 314 articles.

Rochon *et al*. conclude their structured abstract as follows: "The manufacturer-associated NSAID is almost always reported as being equal or superior in efficacy and toxicity to the comparison drug . . . These data raise concerns about selective publication or biased interpretation of results in manufacturer-associated trials."[3]

Can our findings be explained without concluding that funding adversely affects interpretation of data? It has been pointed out that the higher frequency of good outcomes in industry-supported trials may stem from a decision to fund the testing of drugs at a more advanced stage of development.[1] Furthermore, comparison of a new drug with placebo, required for Food and Drug Administration approval of the drug, might be more likely in industry-sponsored studies than in non-industry-supported studies. Comparison with placebo may produce more positive results than comparison with alternative active treatment.[2]

Our method could not identify publication bias, a tendency on the part of journals to reject null results or a tendency on the part of authors not to submit them. A review by Easterbrook *et al*.[8] took research projects as its subject and attempted to determine which reports were submitted and, of those, which accepted. The authors emphasize the importance of this kind of bias which may cause the conclusions of literature reviews or meta-analyses based only on published studies to be misleading. On the other hand, journal editors' proclivity to accept positive studies cannot account for the imbalance we found between negative industry-supported studies and negative studies with other sources of support.

A further possible explanation for our results might be a tendency on the part of journals to favour those negative studies funded by prestigious granting agencies such as the Medical Research Council in the UK and the National Institutes of Health in the USA. If such favouritism does exist, it could lead to the publication of more negative trials receiving support from public bodies than from drug companies. Two other possibilities suggested by Davidson[1] are the cessation of trials by commercial bodies as negative results accumulate in order to conserve funds, and the reticence of investigators to submit negative findings for publication, fearing discontinuation of future funding.

Lexchin,[9] in his review of studies that address the issue of bias in industry-supported research, produced a similar list of publications in his search and came to the same conclusions as the present study regarding the presence of an association, without establishing a causal link.

Potential bias from commercial associations has also been assessed in other areas in medical writing. In a study of articles debating the value of calcium channel blockers, Stelfox[10] found that authors who supported their use were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of these drugs. Friedberg *et al*.,[11] in an unblinded study with a design similar to our own, found an association between source of funding and outcome

in 44 studies of the potential economic benefit from new drugs used in oncology.

Our findings add to the evidence for an association between the outcome of clinical trials and the provision of support by one or more drug companies. It is the largest carried out to date, restricts itself to RCTs published in leading journals and uses a method of consensus development designed to minimize the individual prejudices of the investigators. Its chief weakness lies in the fact that the review process did not include blinding with regard to support status when outcome was determined. However, it reached the same conclusion as did the study by Davidson where the author was unaware of the source of funding when he made his decision concerning the trial's recommendations.

Our study, like its predecessors, has a design that dichotomizes clinical trials into positive and negative outcomes crossed by funding source. Thus it cannot prove the existence of support bias, although the findings here, taken together with the results from the earlier studies, raises the suspicion that there is such a thing. Sir George Pickering once said that science progresses by means of simplification which later turns out to be oversimplification. There is little doubt our design oversimplifies the issue and there is need for further studies that will enlist the help of journal editors in obtaining information on rejected clinical trials. Granting agencies providing public funds for research will also have to be contacted so that future investigators of support bias will learn of the trials that were carried out but not submitted for publication. Examination of studies uncovered in the recent amnesty for unpublished trials[12] will contribute to our understanding of publication bias. A positive step has been taken by the pharmaceutical industry in registering clinical trials and making data from drug trials available on the Internet before publication.[13] When the results of such steps become available for further study, we will have a better understanding of the influence of funding on outcome and the reliability of the sources on which we base our clinical decisions.

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