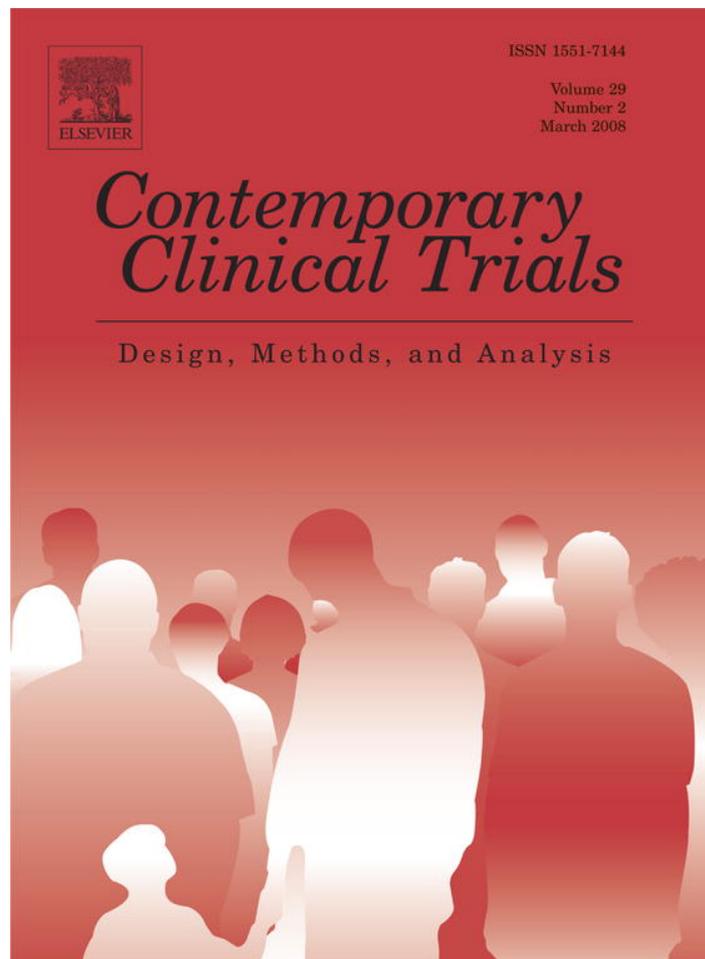


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article was published in an Elsevier journal. The attached copy is furnished to the author for non-commercial research and education use, including for instruction at the author's institution, sharing with colleagues and providing to institution administration.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Short communication

Pharmaceutical company funding and its consequences: A qualitative systematic review[☆]

Sergio Sismondo^{*}*Department of Philosophy, Queen's University, Kingston, Canada K7L 3N6*

Received 4 April 2007; accepted 7 August 2007

Abstract

This article systematically reviews published studies of the association of pharmaceutical industry funding and clinical trial results, as well as a few closely related studies. It reviews two earlier results, and surveys the recent literature. Results are clear: Pharmaceutical company sponsorship is strongly associated with results that favor the sponsors' interests.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Industry funding; Sponsorship; Pharmaceutical companies; Bias

1. Background, and two earlier reviews

Interactions between the pharmaceutical industry and academic medical researchers, which have raised questions for almost a century, are more important now than ever. This article reviews the effects of funding on the published results of clinical trials, finding that pharmaceutical company funding is strongly associated with results that favor those companies' interests. This is important, as the industry funds approximately 70% of all clinical trials [1], and biases created by funding sources influence the medical literature, its condensation in evidence-based medicine, and its representation in journalism.

In 2003, Bekelman et al. performed a systematic survey of quantitative analyses (published between 1980 and 2002) of financial conflict of interest and its relationship to clinical trial results. They found eight analyses comparing outcomes for trials funded by industry (mostly, but not all pharmaceutical) and other sources [2]. A meta-analysis revealed that industry funding greatly increased the chances of pro-industry results, with an odds ratio of 3.60 (95% confidence interval 2.63–4.91). Bekelman et al. also showed that funding has associations with methodological choices, in particular the use of inactive or less active controls. However, using either blinded review or validated quality-assessment measures—such as Jadad scores [3]—most investigations found no association between sponsorship and overall methodological quality; this suggests that funding introduces a systematic bias that cannot be corrected by simple methodological strictures.

[☆] This study was supported by a Standard Research Grant from the Social Sciences and Humanities Research Council of Canada.

^{*} Tel.: +1 613 533 2182; fax: +1 613 533 6545.

E-mail address: sismondo@queensu.ca.

In the same year, Lexchin et al. performed a similar systematic review, of the quantitative analyses of the relationships between research funding and outcomes, methodology, or publication; this review was broader in dates (1966–2002) and in languages of publication [4]. 16 analyses examined the relationship between research funding and outcomes of clinical trials and meta-analyses; of these, 13 showed an association between industry funding and pro-industry outcomes. A further seven looked at the relationship between funding and pharmacoeconomic analyses. Pooling data where possible produced a summary odds ratio of 4.05 (95% confidence interval 2.98 to 5.51). Thus Lexchin et al.'s review agrees very closely with that of Bekelman et al. In a slight difference, industry funding was associated with higher methodological quality in the data examined by Lexchin et al., measured as higher quality in four of nine analyses for which statistics were available.

Despite these strong results, the issue continues to be studied piecemeal, and many researchers and commentators write as though it is not settled. Moreover, as argued briefly below, no substantial action has been taken that directly and substantially reduces funding biases [5]. What follows is a qualitative systematic review of the literature asking similar questions between 2003 and 2006, summarized in Table 1. Articles were identified on the basis of citation searches of

Table 1

Authors	Description	Representative bias result
<i>Positive studies</i>		
Als-Nielsen et al. [10]	213 trials included in sample of Cochrane reviews	Sponsored trials significantly more likely to recommend treatment, odds ratio (OR)=5.3
Baker et al. [18]	44 pharmacoeconomic reports of SSRIs	Sponsored studies were significantly more likely to report favorable results
Bell et al. [19]	Systematic review of cost effectiveness literature expressed in QALYs.	Sponsored studies more than twice as likely to report favorable outcomes
Beutels [20]	Detailed case study of two very similar economic evaluations of a vaccine	Sponsored study more favorable on vaccine
Finucane and Boulton [6]	48 trials reported at meeting	100% of sponsored trials favorable, 67% of non-sponsored
Friedman and Richter [8]	119 trials with and without conflict of interest (COI) published in JAMA and NEJM	85% with COI favorable, 41% without COI favorable.
Fries and Krishnan [7]	45 sponsored trials reported at American College of Rheumatology meeting	100% favorable
Heres et al. [12]	42 head-to-head trials of antipsychotics	90% of trials favorable to sponsor's drug
Kelly et al. [11]	406 trials reported in major psychiatry journals	78% of sponsored trials favorable, 48% of non-sponsored favorable
Liss [17]	100 reports of drug studies in pulmonary/allergy literature	98% of sponsored trials favorable, 32% of non-sponsored
Miners et al. [21]	54 comparisons of cost effectiveness appraisals submitted to the National Institute for Clinical Excellence	Pharmaceutical company estimates of cost effectiveness ratios consistently favorable or neutral, and more favorable than independent estimates
Moncrieff [14]	10 trials of clozapine, an antipsychotic	Sponsored trials reported significantly greater benefit of drug
Montgomery et al. [13]	59 trials of antipsychotics	Sponsored trials significantly more likely to recommend treatment
Perlis et al. [16]	162 placebo-controlled trials with and without COI, reported in major psychiatry journals	92% of trials with reported COI present favorable outcome, 70% of non-COI
Perlis et al. [22]	179 trials with and without COI, reported in major dermatology journals	Sponsorship a strong predictor of positive outcomes, OR=4.54
Procyshyn et al. [15]	124 sponsored trials of three antipsychotics	88% report positive outcome, none report negative outcome
Ridker and Torres [9]	241 trials on cardiovascular treatments, reported in JAMA, Lancet, and NEJM	67% of sponsored trials favorable, 49% of non-sponsored favorable
<i>Negative studies</i>		
Barden et al. [27]	143 head-to-head trials of analgesics as test and comparator	No association of sponsorship and outcome
Brown et al. [30]	135 trials reported in major GI journals	No statistically significant association of sponsorship and outcome.

prominent earlier references, and subsequent advice from researchers familiar with the area. As well as corroborating the earlier reviews, this qualitative review reveals a broad range of situations in which funding has effects.

2. Research between 2003 and 2006: Positive results

At a clinically-oriented professional meeting, Finucane and Boulton found that of sponsored trials, 100% presented positive results, whereas of other trials, only 67% presented positive results [6]. Interestingly, of their 30 industry-supported trials only 3 acknowledged that support; others had authors who were pharmaceutical company employees, or received indirect funding from those companies—thus, without strict reporting requirements funding's effects are unseen. With different goals, Fries and Krishnan looked at industry-supported abstracts at the 2001 meeting of the American College of Rheumatology: of 45 abstracts, all 45 reported pro-industry results [7].

Biases are not restricted to lower-status venues. Friedman and Richter looked at conflicts of interest and outcomes in articles published in *NEJM* and *JAMA* [8]. They found strong and significant associations, with odds ratios ranging from 2.35 to 7.32 depending on the breadth of the definition of conflict. Similarly, in a detailed analysis of cardiovascular trial reports, including both drug and device trials, appearing in *JAMA*, *NEJM*, and *The Lancet*, trials funded by for-profit companies were significantly more likely to recommend the new treatment over the standard of care than were trials funded by not-for-profit organizations (67% to 49%) [9].

Funding has effects on the interpretation of data and the writing of articles. On the basis of a grading of conclusions—on a six point scale with “experimental intervention highly preferred” scoring highest—Als-Nielsen et al. found that for trials included in Cochrane reviews the source of funding is a better predictor of strength of published conclusions than is treatment effect [10].

Investigators have focused on particular fields and subfields, with a cluster studying trials in psychiatry. Kelly et al. examined 542 abstracts of articles—more frequently read than full articles—published in 1992 and 2002 in four major psychiatry journals [11]. 78% of sponsored studies favored the sponsor's drug, versus only 48% of those without apparent industry sponsorship. Of studies funded by a competing drug's company, 28% were read as favorable. Heres et al. examined head-to-head trials of second-generation antipsychotics, of which 90% showed that the sponsoring pharmaceutical company's drug was superior overall [12]. Heres et al.'s title, recalling the game of rock paper scissors, tells the story succinctly: “Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine.” Montgomery et al. reach a very similar result comparing trials of second- and first-generation antipsychotics [13]. In a review and meta-analysis of trials of the antipsychotic drug clozapine, Moncrieff found that support from a drug company was a good predictor of the observed benefits of clozapine, a finding echoed by Procyshyn et al.'s (2004) study of trials of clozapine, risperidone, and olanzapine [14,15]. In placebo-controlled trials reported in the four most cited psychiatry journals between 2001 and 2003, papers acknowledging or displaying conflicts of interest have an odds ratio of 4.9 (though not statistically significant) in favor of positive results, and papers both acknowledging industry funding and displaying conflict of interest report positive results with a statistically significant odds ratio of 8.4 [16].

In a sample of 100 articles published in the pulmonary/allergy literature, 98% sponsored by the pharmaceutical industry reported results favorable to the drug being studied, versus 32% of the other articles [17]. Other areas in which analyses have found associations between funding and positive results include cost effectiveness [18–21] and dermatology [22].

We find corroborations of the above in recent analyses of the effects of research funding by medical device companies (rather than the pharmaceutical industry) [23,24].

Results since 2003 support the association of industry funding with higher measures of methodological quality. With the exception of a comparison of industry and Cochrane meta-analyses [25], recent studies report that in other ways industry-funded trials are of equal or higher methodological quality than non-industry-funded trials [9,13,15,16,26].

3. Research between 2003 and 2006: Negative results

Barden et al. found no significant association in the articles comparing pain relievers in head-to-head comparisons: Drugs owned by the sponsoring companies do not fare better in the data from these trials [27]. There are important differences between this analysis and most of the others. First, Barden et al. did not compare articles but rather reported

data, and to the extent that industry sponsorship affects interpretation and rhetoric, looking at the data alone would not have revealed any association [10,28]. Second, some of the drugs investigated have long been available as generics, affecting the interests in particular results.

Brown et al. provide another negative result [26]. In their sample of articles in gastrointestinal clinical research, published in four major journals, the difference between the results funded by industry (primarily pharmaceutical, but also medical device) and those funded by other sources was not statistically significant. The authors point to an extremely high percentage of articles reporting positive results, reducing the chances of significant associations.

A third published analysis, of clinical trials of two drugs to treat overactive bladder, was also negative, but it was too underpowered to be revealing [29].

4. Conclusion and discussion

Given their widely varying methodologies, a meta-analysis of the above results would be misleading. However, by way of summary, 17 analyses published since 2003 have shown an association, typically a strong one, between industry support and published pro-industry results, and 2 have not. Taken in conjunction with the earlier systematic reviews that found 20 of 23 reports of positive associations, it is unequivocally the case that sponsorship influences published results.

Do we need more research along this line? Not to establish that funding affects published results. Pharmaceutical company funding systematically biases the clinical trials literature in favor of new drugs, and this fact casts a shadow over much medical knowledge and practice. The causes of this bias are complicated, ranging from ghost-management of the literature by pharmaceutical companies to subtle actions provoked by relationships between companies and researchers [5]. Such actions have been demonstrated to create publication biases through over-publication of positive results and under-publication of negative ones, to create design biases, to duplicate known positive results, to affect the interpretation of data, and may also prompt more serious cases of scientific misconduct [5]. It can easily be seen that these causal connections between funding and outcomes are relatively unaffected by such commonly proposed solutions as: stronger disclosure requirements, rigorous trial reporting standards, and trial registries [5]. Because the bias is not the result of simple methodological problems, radical solutions are called for, that divorce the pharmaceutical industry from published research. In the meantime, the fact that pharmaceutical company funding has such strong effects deserves to be more widely known, and measures to address it more widely explored.

References

- [1] Baird P. Getting it right: industry sponsorship and medical research. *Can Med Assoc J* May 13 2003;168(10):1267–9.
- [2] Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289(4):454–69.
- [3] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- [4] Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167–70.
- [5] Sismondo S. How pharmaceutical company funding affects clinical trial results: causal structures and responses. *Soc Sci Med* in press.
- [6] Finucane TCB. Association of funding and findings of pharmaceutical research at a meeting of a medical professional society. *JAMA* 2004;117:842–5.
- [7] Fries J, Krishnan E. Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. *Arthritis Res Study* 2004;6:250–5.
- [8] Friedman LS, Richter ED. Relationship between conflict of interest and research results. *J Gen Intern Med* 2004;19:51.
- [9] Ridker PM, Torres J. Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000–2005. *JAMA* 2006;295:2270–6.
- [10] Als-Nielsen B. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA* 2003;290(7):921–8.
- [11] Kelly RE, Cohen LJ, Semple RJ, et al. Relationship between drug company funding and outcomes of clinical psychiatric research. *Psychol Med* 2006;36:1647–56.
- [12] Heres S, Davis J, Maino KJE, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006;163:185–94.
- [13] Montgomery J, Byerly M, Carmody T, et al. An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. *Control Clin Trials* 2004;25:598–612.

- [14] Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *Br J Psychiatry* 2003;183:161–6.
- [15] Procyshyn RM, Chau A, Fortin P, Jenkins W. Prevalence and outcomes of pharmaceutical industry-sponsored clinical trials involving clozapine, risperidone, or olanzapine. *Can J Psychiatry* 2004;49:601–6.
- [16] Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg A. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. *Am J Psychiatry* 2005;162:1957–60.
- [17] Liss H. Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship. *Israel Med Assoc J* 2005;8:451–4.
- [18] Baker CB, Johnsrud MT, Crismon ML, Rosenheck RA, Woods SW. Quantitative analysis of sponsorship bias in economic studies of antidepressants. *Br J Psychiatry* 2003;183:498–506.
- [19] Bell CM, Urbach DR, Ray JG, et al. Bias in published cost effectiveness studies: systematic review. *BMJ* 2006;332(699–703):699.
- [20] Beutels P. Potential conflicts of interest in vaccine economics research: a commentary with a case study of pneumococcal conjugate vaccination. *Vaccine* 2004;22:3312–22.
- [21] Miners A, Garau M, Fidan D, Fischer AJ. Comparing estimates of cost effectiveness submitted to the National Institute for Clinical Excellence (NICE) by different organisations: retrospective study. *BMJ* 2005;330:65.
- [22] Perlis CS, Harwood M, Perlis RH. Extent and impact of industry sponsorship conflicts of interest in dermatology research. *J Am Acad Dermatol* 2005;52:967–71.
- [23] Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *Can Med Assoc J* 2004;170(4):477–80.
- [24] Shah R, Albert T, Bruegel-Sanchez V, Vaccaro A, Hilibrand A, Grauer J. Industry support and correlation to study outcome for papers published in spine. *Spine* 2005;30:1099–104.
- [25] Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ* 2006;333:782.
- [26] Brown JR. Money, method and medical research. *Episteme* 2004;1:49–59.
- [27] Barden J, Derry S, McQuay H, Moore A. Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain* 2006;121:207–18.
- [28] Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994;154:157–63.
- [29] Tulikangas P, Ayers A, Sullivan DM. A meta-analysis comparing trials of antimuscarinic medications funded by industry or not. *Br J Urol Int* 2006;98:377–80.
- [30] Brown A, Kraft D, Schmitz SM, et al. Association of industry sponsorship to published outcomes in gastrointestinal clinical research. *Clin Gastroenterol Hepatol* 2006;4(12):1445–51.