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Do Financial Conflicts of Interest Bias Research? An Inquiry into the ''Funding Effect'' Hypothesis

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Abstract

In the mid-1980s, social scientists compared outcome measures of related drug studies, some funded by private companies and others by nonprofit organizations or government agencies. The concept of a ''funding effect'' was coined when it was discovered that study outcomes could be statistically correlated with funding sources, largely in drug safety and efficacy studies. Also identified in tobacco research and chemical toxicity studies, the ''funding effect'' is often attributed, implicitly or explicitly, to research bias. This article discusses the meaning of scientific bias in research, examines the strongest evidence for the ''funding effect,'' and explores the question of whether the ''funding effect'' is an indicator of biased research that is driven

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by the financial interests of the for-profit sponsor. This article argues that the "funding effect" is merely a symptom of the factors that could be responsible for outcome disparities in product assessment. Social scientists should not suspend their skepticism and choose as a default hypothesis that bias is always or typically the cause.

Keywords
conflicts of interest, funding effect, scientific bias, clinical trials, scientific objectivity

Introduction

The philosopher Charles Sanders Peirce claimed that of all ways of fixing our beliefs, science is the most dependable. He wrote in 1877, "Scientific investigation has had the most wonderful triumphs in the way of settling opinion" (Peirce 1877). Not only have we come to believe in the "dependability" of scientific claims, we have come to depend upon them for making important life decisions. It is generally understood that the production of scientific knowledge is accompanied by quality controls that are designed to filter out errors and bias. By errors I shall mean those assertions or calculations in a study that are factually incorrect and which would be recognized as such by anyone trained in the discipline. These can include errors in statistical analysis, citations, recording of data, or the application of measuring devices. Bias, on the other, is a more complex term.

As distinguished from error, bias is not as simple as an oversight or a mistake. Bias can be conscious or unconscious. It can be structural (by the choice of method) or nonstructural (by the interpretation of data). By "structural bias," I mean the adoption of certain norms or methods that would distort (over- or underreport) the effects being studied. This term has been used in media studies where a structural bias is said to be the result of a preference of journalists for some type of story or frame that leads them to pay more attention to some events over others (van Dalen 2011).

Bias could involve proper or improper (scientific misconduct) behavior. In his book The Bias of Science, Brian Martin considers "biased" research as synonymous with "value-laden" research "conditioned by social and political forces and dependent on judgments and human choices" (Martin 1979, 7). Under this definition, science, according to Martin, might never be unbiased or value-free. Resnik (1998, 85) argues that a bias is an invalid

assumption: ''The person who conducts biased research is more like the person who defends a hypothesis that is later proven wrong than a person who makes a mistake or attempts to deceive his audience.''

I am using ''bias'' in a different sense. By research bias, I shall mean the use of a method, data collection, data analysis, or interpretation of results that, in the consensus view of scientists of a discipline, tends to yield results that distort the truth of a hypothesis under consideration, diminishing or negating the reliability of the knowledge claim. Bias must be viewed in terms of the current operating norms of science. Since ''bias'' distorts the truth, scientists must be aware of its presence and where possible prevent or diminish it. I leave open the question of whether research considered unbiased in one time period could be viewed as biased by scientists during another time period.

The function of our system of peer review is to identify error or bias before scientific studies are accepted for publication. After a study is published, it may still be criticized or corrected. Moreover, if an empirical finding cannot be replicated, the article may be withdrawn by the journal editors. Unlike other sources of establishing belief, science is considered to be a self-correcting enterprise where truth claims are kept open to new evidence. No one doubts, however, that bias can enter into published scientific work. While bias can be built into scientific methodology (structural), sometimes its subtlety can elude even the most careful reviewer and journal editor.

Only recently have government and journals turned their attention to Conflict of Interest (COI) as a source of bias. The first federal guidelines on scientific COI, issued simultaneously by the Department of Health and Human Services' (DHHS) Public Health Service (PHS) and the National Science Foundation were titled ''Objectivity in Research.'' The stated purpose of the regulation was ''to ensure that the design, conduct, or reporting of research funded under PHS grants, cooperative agreements or contracts will not be biased by any conflicting financial interest of those investigators responsible for the research'' (DHHS 1995). And while the DHHS focused on financial COIs (FCOIs), it is generally recognized that interests other than direct financial interests can also play a potentially biasing role in science (Levinsky 2002). Writing in the journal Cell Stem Cell about the ethics of stem cells, Jeremy Sugarman (2008, 532) noted: ''Both nonfinancial and financial conflicts of interest may adversely affect good judgment regarding stem cell research.'' But Sugarman also wrote that ''financial conflicts of interest in research may be easier to identify, simply because financial interests can be measured and more easily described than those

associated with nonfinancial interests, such as the advancement of scientific and professional concerns'' (Sugarman 2008, 532).

Following the maxim ''study what you can measure,'' social scientists began investigating the relationship between FCOIs and bias in the mid-1980s, when author disclosures of author FCOIs were still in their infancy. Most of the studies investigating a link between author FCOIs and private funding of science were carried out in the field of medicine, specifically medical pharmacology. The concept of a ''funding effect'' was coined after a body of research revealed that study outcomes were significantly different in privately funded versus publicly funded drug studies (Krimsky 2006 2010). The funding effect was also identified in tobacco, pharmacoeconomic, and chemical toxicity research (Als-Nielsen et al. 2003). This article examines the strongest evidence for the ''funding effect,'' and explores the question of whether the ''funding effect'' is an indicator of scientific research bias, based on a previously stated criterion of ''bias.'' To begin, I shall discuss sources of evidence behind the ''funding effect.'' I shall argue that the ''funding effect'' is a symptom of the factors that are responsible for outcome disparities in product assessments and that social scientists should not, without further investigation and the elimination of other explanations, chose bias as the default hypothesis.

Evidence of the ''Funding Effect'' in Science

Beginning in the mid-1980s, scientists began testing the hypothesis that the source of funding from for-profit companies compared to nonprofit institutions and government can be correlated with the outcome of research, such as safety and efficacy in drug studies. This has been called ''the funding effect'' in science (Krimsky, 2005). The assumption has been that where there is a ''funding effect'' there must be bias. I shall begin with the evidence for the ''funding effect,'' largely from a group of studies in drug trials, and then discuss the possible causes of the effect.

Badil Als-Nielsen et al. (2003) tested the hypothesis that industry-sponsored drug trials tend to draw pro-industry conclusions. The authors selected a random sample of 167 Cochrane reviews and found 25 with meta-analyses that met their criteria. From the meta-analyses, they studied 370 drug trials. After coding and numerically scoring the trials' conclusions and applying a logistic regression analysis, the authors found that ''conclusions were significantly more likely to recommend the experimental drug as treatment of choice in trials funded by for-profit organizations alone compared with trials funded by non-profit organizations'' (Als-Nielsen et al.

2003, 925). The authors ruled out as an explanation of industry favored outcomes both the magnitude of the treatment effect and the occurrence of adverse events reported. They also noted that the clinical trial methods between for-profit and nonprofit organizations were not of the same quality. ''Trials funded by for-profit organizations had better methodological quality than trials funded by nonprofit organizations regarding allocation concealment and double blinding'' (Als-Nielsen et al. 2003, 925). The authors do not report on the sponsor involvement and influence on the conduct and reporting of a trial. Such information could help us understand whether the external funder influences the scientist running the trial. The effects they observed between funding and outcome occurred whether the sponsor's contribution was minimal (provided the drug) or maximal (funded the study).

The authors distinguish between potential biases in the empirical trial results (collection of data) and in the interpretation of those results, particularly in the recommendations they make about the experimental drug. As previously noted, bias can enter into any or all the stages of a study: the methodology, execution of the study, interpretation of results and recommendations (whether the experimental drug is better than the existing drug).

It is also possible that industry-funded studies, having been identified as being of higher quality, have gone through more internal (company-sponsored) study and analyses, than one would expect of a nonprofit organization. This study found statistically significant outcome differences in a class of studies, but not necessarily bias—although systemic bias is one hypothesis.

John Yaphe et al. (2001) selected for their study randomized controlled trials (RCTs) published between 1992 and 1994 of drugs or food products with therapeutic properties appearing in five journals: Annals of Internal Medicine, BMJ, JAMA, Lancet, and NEJM. A total of 314 articles met their inclusion criteria. Of the 209 industry-funded studies, 181 (87 percent) and 28 (13 percent) had positive and negative findings, respectively, while of 96 nonindustry-funded studies, 62 (65 percent) and 34 (35 percent) had positive and negative findings, respectively. What can account for this disparity in the outcomes of industry and nonindustry trials? Clearly, the bias of an investigator internalizing the financial interests of the sponsor is one potential hypothesis.

Paula Rochon et al. investigated the relationship between reported drug performance and manufacturer association. They adopted a broad definition of ''manufacturer association,'' which included supplying the drug or

sponsoring a journal supplement where the publication of the study appeared. The authors selected as their study sample randomized drug trials (identified in MEDLINE between 1997 and 1990) of nonsteroidal anti-inflammatory drugs used in the treatment of arthritis (Rochon et al. 1994). The authors found 1,008 articles published within that period but only 61 articles representing 69 individuals met their inclusion criteria. All the trials in their study had a ''manufacturer association,'' because they reported there was a scarcity of nonmanufacturer-associated trials. Therefore, they could not compare trials funded/supported by private companies with those funded/supported by nonprofit organizations. The authors also used several rating systems to estimate drug efficacy. The critical outcome measure was whether the drug being tested was superior, the same, or inferior to a comparison drug.

The results of the study showed the ''the manufacturer-associated drug is always reported as being either superior to or comparable with the comparison drug'' and that ''these claims of superiority, especially with regard to side-effect profiles, are often not supported by trial data'' (Rochon et al. 1994, 158). It is logically possible that head-to head testing of new versus old drugs always shows the new drug superior. After all, that is the impetus for developing new drugs. But in this case, the framing of the tests can bias the outcome. Marcia Angell explains the process with an illustration from statins—drugs that lower blood cholesterol levels. ''There is little reason to think one is any better than another at comparable doses. But to get a toehold in the market, me-too statins were sometimes tested for slightly different outcomes in slightly different kinds of patients, and then promoted as especially effective for those uses'' (Angell 2004, 81).

In a study by Benjamin Djulbegovic et al. (2000), the investigators explored whether the reports of pharmaceutical-industry sponsored randomized trials result in biased findings. They selected 113 articles published from 1996 to 1998 that described 136 randomized trials on multiple myeloma (Djulbegovic et al. 2000, 637). The authors compared the new therapy versus the standard therapy in the trials and then analyzed the outcome according to whether the sponsors were nonprofit or for-profit organizations. Nonprofit organizations showed a 53 percent versus 47 percent support for new therapies, but when the trials were sponsored by for-profit organizations the ratio was 74 percent to 26 percent, a statistically significant difference.

Friedman and Richer (2004) investigated whether sources of funding could be correlated to reported findings. The authors analyzed original contributions in NEJM and JAMA published in 2001. They classified the

presentation of results as positive (statistically significant clinical benefit from a treatment or absence of suspected side effects), mixed (clinical benefits but adverse side effects), negative (absence of clinical benefits), or other (unclear significance). They located 193 original articles in NEJM, 76 (39.4 percent) with a COI and 205 articles in JAMA, 76 (37.1 percent) with COI. The authors found 119 studies that investigated drug treatments and 174 studies for all treatments. They observed a ''strong association between positive results and COI among all treatment studies'' with an odds ratio of 2.35 and for drug studies alone an odds ratio of 2.64. The odds ratio is the ratio of probability of an event occurring in one group to the probability of it occurring in another group. An odds ratio of 2.35 for the drug studies is the probability of a positive result in a drug treatment study conducted by individuals with a FCOI divided by the probability of a positive result from a similar drug treatment conducted by individuals without a financial conflict of interest. In other words, an odds ratio of 2.35 means that investigators with an FCOI are more than twice as likely to produce positive results in a drug treatment study.

Another interesting finding is that the probability of reporting negative results in cases where an author had a FCOI was very low. One negative study of the 60 drug studies with FCOIs versus 21 negative studies of the 59 drug studies without FCOIs were reported. The authors conclude that ''the odds are extremely small that negative results would be published by authors with COI'' (Friedman and Richter 2004, 53).

The authors cannot provide an explanation for their observed association between FCOI and reported findings in medical treatments. They can only theorize about the cause. ''One could surmise that drug companies are selective and only want to invest in treatments proven to produce positive results and that early clinical trials filter out the most promising treatments, which could explain the small number of studies funded by private corporations presenting negative findings'' (Friedman and Richter 2004, 55). But they also consider the possibility of bias and ''spin.'' The question arises as to whether an investigator with a conflict of interest may be more inclined to present findings in order to gain favor with the sponsor or achieve any other extraneous objective—for example, to ''spin'' (Friedman and Richter 2004, 55). Notwithstanding the fact that the cause of the association is not apparent in their data, they state that:

> The observation that negative findings are less commonly reported among studies funded by private corporations raises troublesome ethical questions. Researchers appear to be failing to promote both the benefits and negative

> side effects of commercial products they review or simply failing to submit negative studies for publication because they are viewed as uninteresting. (Friedman and Richter 2004, 55)

For social scientists studying the funding effect, the issue in this case is less a question of bias in the reported studies than it is an issue of bias in a failure of reporting negative studies, that is, in subverting the complete scientific record.

Not all studies testing a hypothesis that there is an association between trial outcome or study quality and funding source reached positive findings. Tammy Clifford, Barrowman, and Moher (2002) selected a convenience sample of RCTs published between 1999 and 2000 by hand-searching five high impact general medical journals—Annals of Internal Medicine, BMJ, JAMA, The Lancet, and NEJM. The quality of the trial report was evaluated according to the Jadad scale, which included randomization, allocation concealment, and withdrawals. The authors classified the trials according to funding source in four categories: entirely industry, entirely non-for-profit, mixed, and not reported. Sixty-six of the hundred trials reviewed were funded in whole or in part by industry; 6 did not disclose their source of funding. Of the 100 trials, 67 favored the new therapy, 6 favored conventional treatments, 19 reported neutral findings, and for 8 the outcome was unclear. Of the 67 trials that favored the new treatment, 30 came from "industry only," 15 came from "not-for-profit only," and 16 came from mixed sources; of the 6 trials that favored the conventional treatment, 4 came from "industry only," 1 came from "not-for-profit only," and 1 came from mixed sources.

The numbers for "favored conventional" were so low that statistical findings were not relevant. Also, this study only focused on funding and not on the financial ties of individual faculty associated with the trials. The authors noted limitations of their results. "Our failure to detect any significant association may result from a type 2 error that indicates inadequate statistical power. Although our results do not even hint at a trend . . . the potential for type 2 error is real" (Clifford, Barrowman, and Moher 2002, 21). Perhaps one conclusion can be drawn: of the 100 trials, 66 percent were funded in whole or in part by industry and 67 percent favored the new therapy. Thus, it appears that industry trials are dominant and driving the advocacy of new drugs over old treatments even without adding author FCOI.

Finally, I shall summarize the first meta-analysis that explored the "funding effect." Bekelman et al. culled 1,664 original research articles and ended up with 37 studies that met their criteria. They concluded: "Although

only 37 articles met [our] inclusion criteria, evidence suggests that the financial ties that intertwine industry, investigators, and academic institutions can influence the research process. Strong and consistent evidence shows that industry sponsored-research tends to draw pro-industry conclusions'' (Bekelman, Li, and Gross 2003, 463). Bekelman et al. were convinced that the ''funding effect'' is real.

I shall now turn to the relationship between FCOI and pharmacoeconomics, defined as the discipline that evaluates the clinical, economic, and humanistic aspects of pharmaceutical products, services, and programs.

Pharmacoeconomic Studies

A few studies have examined whether the results of economic analyses of drugs are correlated with the funding source. Because there is greater discretion in developing the methodology for economic studies of drugs, any inferences of bias must be addressed through the modeling, the stakeholder interests, and the specific parameters used in cost–benefit analysis rather than the omission or manipulation of clinical data. Johnson and Coons (1995, 165) note that ''Many different guidelines have been proposed for conducting pharmacoeconomic studies. The differences among the various versions reflect the diverse and sometimes conflicting views of those who specialize in economic evaluations.''

Mark Friedberg et al. (2010) searched the Medline and Health Star databases for articles published between 1985 and 1998 on cost or cost-effectiveness analyses of six oncology drugs. The found forty-four eligible articles whose texts were analyzed for qualitative and quantitative conclusions and the funding source, based on predetermined criteria. Of the forty-four articles, twenty-four were funded by nonprofit organizations and twenty were funded by drug manufacturers. The authors found a statistically significant relationship between funding source and qualitative conclusions. Unfavorable conclusions were found in 38 percent (9/24) of the nonprofit-sponsored studies and 5 percent (1/20) of company-sponsored studies.

Studies funded by pharmaceutical companies were almost 8 times less likely to reach unfavorable qualitative conclusions than nonprofit-funded studies and 1.4 times more likely to reach favorable qualitative conclusions.

C. M. Bell et al. (2006) undertook a systematic review of published papers on cost-utility analyses. The authors found that industry-funded studies were more than twice as likely to report a cost-utility ratio below $20,000 per quality adjusted life year (QALY) as compared to studies sponsored by nonindustry sources. A similar study reported in the International

Journal of Technology Assessment in Health Care assessed the relation between industry funding and findings of pharmacoeconomic analyses (Garattini, Rolova, and Casasdei 2010). The authors searched Pub Med for articles on cost-effectiveness and cost utility, performed during 2004-2009 on single drug treatments. They found 200 articles that met their criteria. They divided the articles into two groups based on whether or not the authors had financial support from the pharmaceutical industry. ''Studies co-signed by at least one author affiliated to a pharmaceutical company and/or studies that declared any type of company funding were considered sponsored'' (Garattini, Rolova, and Casasdei 2010, 331). The authors also classified the main conclusions as favorable, doubtful, or unfavorable toward the drug. Of the 200 articles, 138 (69 percent) were sponsored by a pharmaceutical company. Sponsored articles reported a favorable conclusion 95 percent of the time as against 50 percent of the time for nonsponsored articles. They claimed that ''the presence of a pharmaceutical sponsorship is highly predictive of a positive conclusion'' (Garattini, Rolova, and Casasdei 2010, 331). According to Krimsky 1999, 1475):

> The differences observed between [pharmacoeconomic] studies funded by industry and nonprofit organizations may be the result of methods chosen, prescreening, or bias due to the source of funding. By following the traditions of professional societies, such as those of engineering and psychiatry in setting guidelines of practice, pharmacoeconomists can attain a special role in the health care policy community in developing independent studies that are based on accepted canons that meet the highest standards of the profession. Canada and the United Kingdom have developed national guidelines for cost effectiveness studies.

K. S. Knox et al. (2000) reported on data collected in Friedberg et al. in comparing practices of pharmaceutical-sponsored and nonprofit-sponsored pharmacoeconomic studies. They found that nonprofit studies more likely make an explicit statement of the significance of the findings (38 percent vs. 20 percent), provide a source of cost data (67 percent vs. 45 percent), and make a clear statement about the reproducibility of the findings in other settings (58 percent vs. 35 percent). As in Friedberg et al., Knox et al. considered only one type of economic relationship between industry and researchers, namely, direct funding of a study and omitted many other types of financial relationships. Had they broadened their criteria, some of the 42 pharmacoeconomic analyses they studied might be reclassified as ''pharmaceutical associated'' thus changing the statistical results.

Some of the authors who found a ''funding effect'' were cautious about inferring a bias from the data, although it was included in the list of hypotheses they considered. The next section explores alternative explanations.

Explanations of the "Funding Effect" Other than Bias

In Yaphe et al., the authors note 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'' (Yaphe et al. 2001, 567). In other words, industry has already done a lot of internal studies weeding out ineffective drugs. Thus, by the time a private company funds a trial, it would likely do better than a drug has not gone through its internal review. To fully understand this process, we need to know the extent to which companies test and reject drugs internally before funding a study by an academic group and whether the outcome results of ''new drugs are always better'' would be found in trials of the same drugs but funded by nonprofit organizations.

The methodologies of industry-funded as compared to nonprofit-funded trials may differ. For example, comparison of new drugs with a placebo may be more prevalent among industry-financed studies compared to nonindustry-financed studies. ''Comparison with placebo may produce more positive results than comparison with alternative active treatment'' (Yaphe et al. 2001, 567). Unless we have a profit organization and nonprofit organization using the same or very similar methods to test the same drugs, drawing an inference about bias can yield false conclusions. The appearance of low negative outcomes from private sponsors could be the result of company screening for low probability drugs before they sponsor the trial or the ''reticence of investigators to submit negative findings for publication, fearing discontinuation of future funding'' (Yaphe et al. 2001, 567). These caveats speak against a conclusion that bias can be inferred from the data that show outcome differences.

Some tests use different doses of the new drugs and compare them to lower doses of the old drugs. This is corroborated by Rochon et al. in their study. ''When we evaluated the relative range of dosing of the manufacturer-associated drug and the comparison agents in the trials on the basis of the recommended dosage suggested in standard tests, there was a considerable mismatch. In the majority of cases where the doses were not equivalent, the drug given at the higher dose was that of the supporting manufacturer'' (Rochon et al. 1994, 161).

The authors surmise that higher doses ''bias the study results on efficacy in favor of the manufacturer-associated drug'' (Rochon et al. 1994, 161). This illustrates that bias may enter into the ''funding effect'' in subtle and complex ways that deal with how the trial is organized.

Some authors try to explain the ''funding effect'' by maintaining that most industry studies use a placebo and as a result are more likely to show a positive outcome. Also, the method of drug delivery used by companies may have been different than that used in nonprofit sponsor trials.

Others have questioned whether industry trials are of lower quality and thus are likely to produce more favorable results. Djulbegovic et al. rated the trial quality and concluded that ''trials funded solely or in part by commercial organizations had a trend toward higher quality . . . than those supported by the governmental or other non-profit organizations'' (Djulbegovic et al. 2000, 637). Thus, the outcome effect found in the industry-funded work of this group was not related to poor quality trials.

In Frieberg's pharmacoeconomic study, the authors offer several possible explanations for the ''funding effect.'' First, for-profit companies are more likely than nonprofit companies to get ''early looks'' at the drugs, preliminary trial results, and economic data, weeding out those that would fail a cost-effectiveness standard. Companies might censor unfavorable studies by not funding them. Second, they surmise that funded studies with unfavorable results are less likely to be submitted for peer review and published. A third explanation for the disproportionate favorable results could arise from ''unconscious bias that could influence study conclusions'' from scientists who have a financial conflict of inter- est—such as being paid by the company or holding an equity interest in the drug. As previously noted, the economists engaged in the study may internalize the values of the study sponsor, which could translate into a methodology that is more likely to yield a positive economic analysis.

And the final explanation suggested by the authors is that ''the pharmaceutical companies can collaborate directly with investigators in devising protocols for economic analyses and indirectly shape the economic evaluation criteria'' (Friedberg et al. 2010, 1475). The assessment of bias requires a standard or norm for pharmacoeconomic analysis against which one can compare different outcomes (Krimsky 1999). Several studies have addressed the quality of pharmacoeconomic analysis of drugs (Sacristan, Soto, and Galende 1993; Jefferson et al. 1988). Currently, no standardization or best practice for pharmacoeconomic analyses exists. Because the choice of method can have a significant effect on outcome, a method that

systematically yields outcomes consistent with the private sponsor's financial interest may be biased.

Single Product Assessment: Tobacco

The studies of funding effects in pharmaceutical products include many types of drugs in order to develop aggregate statistics. Companies may do in-house studies before sponsoring extramural studies. The type of drug studied is generally considered not relevant to the findings of a funding effect. However, investigators may have different histories with the products they are testing. Nonprofit investigators may have seen the product for the first time. By eliminating product variability, investigators of the funding effect can more precisely judge the possible linkage between the source of funding and outcome findings such as product quality, safety, or economic efficiency. Two product studies for a funding effect meet these criteria: tobacco and the chemical bisphenol A (BPA). I shall begin with a discussion of tobacco research.

Turner and Spilich (1997) investigated whether there was a relationship between tobacco industry support of basic research and the conclusions reached by authors of the study. They utilized a comprehensive review of the literature on tobacco and cognitive development and used that to obtain their reference studies. Beginning with 171 citations, the authors selected 91 studies fulfilling their selection criteria that investigated the effects of tobacco and nicotine upon cognitive performance. They coded the conclusions of the papers as positive, negative, or neutral on the question of whether tobacco enhances performance and segmented the papers into those that acknowledged corporate sponsorship and those that did not. When one or more of the authors was an employee of a tobacco company, the article was coded as industry-supported. All other articles were coded as "noncorporate sponsorship," even in cases where one or more of the authors had previously received industry support.

For those papers reporting a negative relationship between tobacco and cognitive performance, sixteen were coded "nonindustry supported," and one was coded "industry-supported." For those reporting a positive relationship, twenty-nine came from nonindustry supported papers and twenty-seven from tobacco industry-supported papers. Among those papers reporting a neutral effect, eleven were from nonindustry studies and seven from industry-supported studies. In this study, the industry/nonindustry demarcation in the papers shows a disparity in negative results compared to positive results. Why did so few studies funded by the tobacco industry

report negative effects on performance from tobacco use? Because the study methodologies were different, we cannot say that investigator bias played a role. It may just be that the industry-funded studies used a method that yielded fewer negative outcomes compared with an alternative method(s) used by the nonindustry-funded studies. There is a phenomenon known as "bias in the study design," but that was not examined in the study. As previously mentioned, systematic bias in a study design seeking to test the toxicity of a chemical would be introduced by animal models that are inherently insensitive to the chemical in question (Bailar 2006).

Deborah Barnes and Lisa Bero (1998) investigated whether review articles on the health effects of passive smoking reached conclusions that are correlated with the authors' affiliations with the tobacco companies. Since tobacco is a relatively homogenous product, differences in outcome cannot be attributed to product variability or company pre-testing. Just as in pharmacoeconomic studies, there is no canonical method in undertaking a review article. Authors make a selection of articles that become part of the review. Some reviewers make their selection algorithm transparent. Others may not. Any two studies may use a different selection algorithm and they may weigh studies differently. "Ultimately, the conclusion of any review article must be based on the judgment and interpretation of the author" (Barnes and Bero 1998, 1570).

For this study, the authors adopted a search strategy use by the Cochrane Collaboration to select review articles from 1980 to 1995 on the health effects of passive smoking from the databases MEDLINE and EMBASE. They located additional review articles from a database of symposium articles on passive smoking. Articles were evaluated on quality and were classified as concluding that passive smoking was either harmful or not harmful. The authors found that 94 percent (29/31) of reviews by tobacco-industry affiliated authors concluded that passive smoking is not harmful compared with 13 percent (10/75) of reviews without tobacco-industry affiliations. The influence of tobacco-industry affiliation on the finding of "safety of passive smoking" was very strong. "The odds that a review article with tobacco with tobacco industry-affiliated authors would conclude that passive smoking is not harmful were 88.4 times higher than the odds for a review article with nontobacco affiliated authors, when controlling for article quality, peer review status, article topic, and year of publication" (Barnes and Bero 1998, 1569). The authors reported that the "only factor that predicted a review article's conclusion was whether its author was affiliated with the tobacco industry" (Barnes and Bero 1998, 1570). In this study, the authors had no alternative hypotheses other than

the inherent bias of authors with industry affiliation. Because there is a great deal of discrepancy among authors in how a review is carried out, including the selection and weighting of articles that form the basis of the review, there are a number of ways that the conclusion can be made to favor the funder's interests, not the least of which is to set a high bar for establishing evidence of causality. The authors impute conscious intentionality of bias to the funders in their statement that "the tobacco industry may be attempting to influence scientific opinion by flooding the scientific literature with large numbers of review articles supporting its position [which they paid for] that passive smoking is not harmful to health" (Barnes and Bero 1998, 1569). From tobacco, I shall now turn to an industrial chemical used in many products—bisphenol A.

Single Product Assessment: BPA

While there are different variants of tobacco that depend on where the tobacco plant is grown, and even greater variation in cigarettes because of chemicals added to the tobacco and the paper, there is still greater homogeneity in studying tobacco than in studying different types of drugs. BPA, on the other hand, is a synthetic chemical that has a precise chemical structure. It was first reported synthesized in 1905 by a German chemist. In 1953, scientists in Germany and the United States developed new manufacturing processes for a plastic material, polycarbonate, using BPA as the starting material. In the 1990s, scientists began studying the toxicological effects of BPA leaching from plastic food and water containers. Despite the fact that some scientists claimed there was extensive evidence that BPA can disrupt mouse, rat, and human cell function at low part per trillion doses and that disruption at the same low doses is also found in snails [and] has profound implications for human health (vom Saal et al 2005, 249), other scientists disagreed. Vom Saal and Welshons (2006, 61) divided the studies into those funded by industry and those funded by nonprofit organizations. Of the 119 studies funded by the federal government, 109 showed harmful toxicological outcomes while 10 had outcomes which showed no harm. Of the studies funded by the chemical companies, there were zero with outcomes showing harm and 11 with outcomes of no harm.

The authors write: "Evidence of bias in industry-funded research on BPA." Is it systematic bias and if so what form does it take? Is industry using a different methodology than most of the federally-supported studies? If so, is their methodology sound or is it designed to get a "no harm" outcome?

Vom Saal and Welshons argue that industry-funded studies have a built in bias [what I have referred to as structural bias] against finding positive effects of BPA. They maintain that "To interpret whether there is a positive or negative effect of a test chemical, such as BPA, appropriate negative and positive controls also have to be examined" (vom Saal and Welshons 2006, 62). Vom Saal argues that the industry-supported tests omitted a positive control and without positive control findings, one cannot interpret a reason for purely negative results. The authors also noted that some industry-funded BPA studies used test animals that had very low sensitivity to exogenous estradiol and thus would not be expected to exhibit effects from BPA. Other industry-funded investigators used a type of animal feed, which because of its estrogenic activity, would give a false result. "Inclusion of an appropriate positive control . . . would have allowed a determination of whether the failure to find effects of BPA was due to the lack of activity of BPA or to a lack of sensitivity of the animal model and/or estrogenic contamination of the feed that was used" (vom Saal and Welshons 2006, 63).

In his classic work, The Logic of Scientific Discovery, Karl Popper (1968) developed the philosophical foundations of scientific methodology. Science, Popper argued, is not an inductivist enterprise, where truth is built up from data that are consistent with a hypothesis. Scientists must seek to falsify a hypothesis, and only when a hypothesis is recalcitrant against a rigorous attempt at falsification can it be accepted as truth. The critical point is that deduction and not induction is the logical grounding of empirical science. In the latter case, scientists would be given: A_1 is B, A_2 is B . . . A_n is B therefore All A is B. In the former case, scientists seek to falsify "All A is B" by trying to find a disconfirming instance (A_x is not B).

For example, one can reach the conclusion that "all crows are black" by observing crops in certain parts of Africa. Or you could imagine a geographical location that would most likely nurture a nonblack crow—such as the North or South Pole. If after all the seeking for a falsifying instance none appears, then, under the Popperian program, you can claim that the hypothesis "all crows are black" is confirmed. Vom Saal and Welshons illustrate this point in the toxicology of BPA.

> . . . it is a common event in toxicological studies conducted by the chemical industry for purposes of reporting about chemical safety to regulatory agencies to provide only negative results from a study in which no positive control was included but from which positive conclusions of safety of the test chemical are drawn. (von Saal and Welshons 2006, 63)

As Peirce noted, ‘‘We are, doubtless, in the main logical animals, but are not perfectly so’’ (Peirce 1877). Both he and Popper understood that knowledge claims drawn inductively can be easily distorted by the social context of scientists. This is most notably the case in the field of toxicology, which is composed of academic scientists and contract toxicologists working on behalf of for-profit companies. These scientists are usually paid by chemical companies to fulfill the information needs of their regulatory requirements. The standards for doing toxicological research may vary, especially in new subfields like low-dose, endocrine toxicology. Thus, until the norms of good scientific practices are adopted across the subfield and by the government regulators, contract toxicologists may perform studies that have structural biases because they are more likely than not to produce false negatives. This is the take-home message from the criticism by vom Saal and Welshons of private-company-sponsored studies. They are looking to confirm the null (no effect) hypothesis rather than trying to falsify the null hypothesis, which would provide more confidence in the claim that the chemical is not harmful.

Conclusion

This analytical review of studies of studies that investigate an association between funding source and study conclusions has revealed several important results. First, there is sufficient evidence in drug efficacy and safety studies to conclude that the funding effect is real. Industry-sponsored trials are more likely than trials sponsored by nonprofit organizations, including government agencies, to yield results that are consistent with the sponsor’s commercial interests. Second, there is some circumstantial evidence that this effect arises from two possible causes. Either the drugs sponsored by industry have gone through more internal testing and less-effective drugs are screened out, or the methods used in industry-sponsored drug testing have a structural bias that is more likely to yield positive outcomes.

Third, a small number of pharmacoeconomic studies also show evidence of a funding effect. Without standardization of economic studies or the use of third-party ‘‘economic auditors’’ who have no economic ties to a company, it is difficult to account for the factors that explain this effect.

A person who files his income tax is likely to use whatever discretionary decisions at his disposal to reduce his tax obligation. Similarly, a company that performs its own economic analysis of a new drug is likely to choose a model and use inputs that are advantageous to it. When a company hires an independent agent to undertake the economic analysis, little is known about

what influence the company has in shaping the study. Also, little is known about drugs that are kept out of the testing pool by companies because they have already done the economic analysis.

When we turn to studies of the funding effect on individualized commodities, the results are less ambiguous. There is an extensive body of research on tobacco, both primary (smokers) and secondary (secondhand smoke) exposures. This research shows a clear demarcation between studies funded by the cigarette industry and studies funded by nonprofit and governmental organizations. From this body of research, it is reasonable to conclude that the tobacco industry hired scientists to play a similar role as their contracted lawyers, namely, to develop a brief, in this case a scientific argument, that provides the best case or their interest. If that interpretation of tobacco-funded research is correct, it could explain the funding effect in tobacco studies.

The second homogenous product discussed in this article is BPA. However, with only one study of this compound found that addresses the funding effect, a generalization cannot be drawn. But the scientists who published the study help the reader understand why a funding effect is a probable outcome. They show the systemic bias involved in the industry-funded studies that ordinarily do not appear in studies funded by nonprofit organizations.

What I have argued in this article is that the ''funding effect,'' namely the correlation between research outcome and funding source, is not definitive evidence of bias, but is prima facie evidence that bias may exist. Additional analyses of the methodology of the studies, interpretation of the data, interviews with investigators, and comparison of the products studied can resolve whether the existence of a funding effect is driven by scientific bias. Social scientists should follow Robert Merton's norm of ''organized skepticism'' when they frame an initial hypothesis about the cause behind the ''funding effect'' phenomenon (Merton 1968, 608). The notion of bias based on possessing a financial conflict of interest is certainly one viable hypothesis. But there are others. Social scientists must be equipped to compare the methods used across a cluster of studies funded by for-profit and not-for profit companies to determine whether a particular method biases the results toward ''no detectable outcome'' while other more sensitive methods yield positive results. Certain chemical effects may show up in animal fetuses and not on the adult animals.

In addition, social scientists must gain an understanding of the entities being tested across a series of studies to determine whether the differences in the entities can account for the ''funding effect.'' Calcium channel

blockers represent a class of drugs. It is important to understand whether the partition of studies between for-profit and not-for-profit funders coincides with a random distribution of the entities being studied. Drugs that have passed a prescreening test are more likely to show more favorable outcomes than similar drugs that have not. This potential confounder can be eliminated when the entities are relatively homogenous, like tobacco or a chemical like BPA.

In some cases, ethnographic studies can determine whether for-profit companies have made internal decisions about drugs before they send them out to academic laboratories for study and how that compares with drug studies funded by not-for-profit organizations. Ethnography can also help social scientists ascertain when investigators reach beyond the data when they interpret results and whether the frequency of such overinterpretation (claiming benefits not found in the data) is more likely in studies funded by for-profit funders. Interviews with academic investigators, who are funded by private for-profit companies, and company executives, can reveal whether and how the funding organization helps frame the study, contributes to the interpretation of the data, and plays a role in deciding whether the results get sent for publication. The ''funding effect'' is merely a symptom of the factors that could be driving outcome disparities. Social scientists should not suspend skepticism and choose as the default hypothesis that ''bias'' is always the cause.

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