Manipulation of knowledge

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Introduction

I use the term ‘manipulation of knowledge’ to refer to biasing of information that is made available to the academic community and the public. Those who engage in manipulation typically create a more favourable impression of current knowledge than would be justified by complete and unbiased information. This may occur for any of several reasons. In the health care industry, there may be a desire to create or retain market share for a particular product, creating incentives to exaggerate its efficacy or safety. In the case of product liability, such as unexpected safety or toxicity concerns, the goal may be to avoid blame and especially lawsuits.

From the perspective of a researcher or academician, there may be an incentive to put a positive ‘spin’ on findings in order to keep funding sources happy. Furthermore, academicians may want to defend a pet theory, help build or protect a reputation, or assure academic promotion and success. The motivations of academic researchers are harder to identify or quantify, so much of the present discussion will focus on industry-sponsored research, and the interaction between industry and universities.

Several strategies have become common for making research results seem as favourable as possible. The simplest and easiest to understand is simply withholding or suppressing unfavourable research studies. Conversely, a researcher or sponsor may wish to publish favourable results multiple times, creating the appearance of a larger body of supportive research data than actually exists. Selective reporting is another concern, in which a researcher reports only measurements showing favourable results, and suppresses those that do not. In the world of medical research, ‘ghost-writing’ has become commonplace. In this practice, professional writers, typically employed by a public-relations firm, prepare scientific articles and editorials, then invite a prominent academician to be identified as the author. Yet another strategy is simply to eliminate independent research funding sources or to eliminate the editors of professional journals who publish unflattering results. We will consider each of these in more detail.

Withholding unfavourable studies

U.S. researchers described a clear example of suppressing unfavourable results in a recent study of antidepressant drug trials [1]. The lead author, Dr Erick Turner,
had worked both in the pharmaceutical industry and at the U.S. FDA (Food and Drug Administration), and was therefore familiar with practices of both manufacturers and regulators. His research team identified 74 industry-sponsored studies of antidepressant drugs that manufacturers had registered with the FDA. Of these, just 38, slightly over half, showed positive results, favouring the antidepressant drug over placebo. The remaining trials were negative, meaning they failed to show a clear advantage of the new drug over a placebo.

Nonetheless, when Turner’s team examined the published literature on these drugs, 94% of the published trials were positive. The reason was that 22 of the trials the FDA judged to be negative or questionable were never published. Another 11 negative studies were published, but with a positive spin that made it appear that the results were favourable. As an example, the primary outcome measure identified prior to the research was no longer reported as the primary outcome, and instead a secondary outcome measure with a more favourable result was presented as the primary measure. Only three of the 36 negative trials were ever published as negative studies [1]. The net result of this publication bias is to create a more favourable impression of antidepressant drug efficacy than may truly be warranted. This has the potential to mislead both doctors and patients considering this type of therapy.

As this example shows, research sponsored by industry may simply never be published. One might imagine that research conducted by university investigators, however, would certainly appear in the public literature. Some striking examples to the contrary emphasize the risk that those with a financial interest may suppress even university-conducted research.

An example in the United States began in the 1980s, when a particular brand of thyroid hormone replacement (Synthroid) dominated the market for thyroid hormone replacement. However, a high price was eroding its market share, as many buyers moved to less expensive preparations. The manufacturer, Boots Pharmaceuticals, wanted to prove that Synthroid was superior to competing generic drugs in potency, consistency and ‘bioavailability’ [2,3].

The company hand-selected Dr Betty Dong at the UCSF (University of California-San Francisco) to conduct the study, in part because she had previously published comments that were favourable to Synthroid. The company designed the research protocol and monitored its conduct closely throughout the trial. However, the results surprised both Dr Dong and the company. The four drugs they compared, Synthroid and three generic preparations, proved fully equivalent. Citing contract language, the company threatened a lawsuit if the results were published and prompted two investigations. Both investigations found only minor problems with the study and concluded that it was generally well-conducted. One investigator described the company as being self-serving in its allegations [3].

The researchers finally submitted a paper for publication at the *Journal of the American Medical Association* in 1994. However, they withdrew the manuscript after the journal accepted it, when university attorneys changed their previous position, and indicated that they would not defend the researchers in
case of a lawsuit. In the meantime, company officials published the research team’s data, identifying themselves as the authors, using a different analysis and a different conclusion. In many circumstances, such publication of the data might preclude further publication. However, a national newspaper, The Wall Street Journal, uncovered the story. The Journal ran an article with the headline:

“How a drug firm paid for university study, then undermined it; research on thyroid tablets found cheap ones were just as good as sponsor’s; article pulled at last minute” [3]

As these events unfolded, Boots sold its drug division to Germany’s BASF AG in 1995 for $1.4 billion. Synthroid was a key product in the sale, and the company subsequently became known as Knoll Pharmaceuticals. Finally, in the face of bad publicity, Knoll relented in its threat of lawsuits. Journal of the American Medical Association published Dong’s article in 1997, seven years after the study was completed [4]. Knoll subsequently faced a class action lawsuit from consumers alleging that they were overcharged for thyroid replacement hormones and were misled. Knoll ultimately settled for $135 million, although Dr Dong estimated that if less expensive generic drugs had been widely used, consumers might have saved $356 million per year.

The story of Dr Dong may seem exceptional, but other examples suggest that suppressing unwelcome results may be business as usual. Dr Herb Needleman was harassed by the lead paint industry after demonstrating the neurotoxicity of lead in children. Dr James Kahn conducted trials of an AIDS therapeutic vaccine that proved ineffective and was threatened with lawsuits by the manufacturer who funded the research. Dr David Kern studied the lung toxicity of nylon flocking in a manufacturing plant and had his job threatened by the company that requested the investigation. Dr Gurkipal Singh, a Stanford University rheumatologist, felt intimidated by statements to his academic supervisor when he raised concerns about the cardiovascular risks of Rofecoxib (Vioxx) in his continuing education lectures. The company cancelled his lectures and, according to the supervisor, hinted at repercussions for him and Stanford if Singh did not stop his ‘wild and irresponsible statements’. The manufacturer insisted that it was just maintaining balance in a vigorous public debate [5,6].

Partly in response to such stories, some universities have tried to improve safeguards to limit conflicts of interest in publishing data or in having certain findings withheld. Nonetheless, industry sponsorship of clinical research has increased dramatically, from 32% in 1980 to 62% in 2000. Studies suggest that industry-sponsored research is approximately three times more likely to yield pro-industry conclusions than non-industry sponsored research [7]. Furthermore, one-third of researchers in biomedicine have a personal financial interest in their research, such as patents, equity or membership on a board of directors. Surveys indicate that delays in publication are more frequent with industry sponsorship, and 12–34% of academic researchers report that they have been denied access to research results by company sponsors. Despite these concerns, many universities have not yet implemented strong safeguards to limit conflicts of interest [7].
Selective reporting of favourable outcomes in published reports

Even if a research report is published, it may misrepresent information by presenting only favourable results and failing to report unfavourable measurements. For example, investigators studied outcome measures that were reported in 102 clinical trials conducted in Denmark, and compared those reports with protocols, related articles and a survey of authors. The investigators found that only 50% of outcomes related to treatment efficacy and only 35% of measures of harm were completely reported in these studies. They noted that statistically significant outcomes were more likely to be reported than non-significant outcomes. Furthermore, 62% of these trials had at least one primary outcome measure that was changed, introduced or omitted in comparison with the original protocol. In the author survey 86% of responders denied omitting outcomes despite documentation to the contrary [8].

Partly in response to such problems, The International Committee of Medical Journal Editors began, in 2005, to require pre-registration of randomized clinical trials. The idea was that any randomized human trial should have its protocol specified in advance, so that published reports could be compared with the stated intentions prior to initiating the research. Web-based repositories for these protocols were designated. One goal was to assure that published reports included all the specified outcome measures, rather than only selected results. However, by 2009, in a study of 323 trials, a team headed by French researchers found that only 45% had been fully registered before the end of the trial with a primary outcome specified; 28% of the trials were never registered. Of the adequately registered trials, 31% showed a discrepancy between the outcomes that were registered and those the authors eventually reported. Once again, the published outcomes favoured those that were statistically significant [9].

The most recent study of suppressed data examined clinical trials that were registered at clinicaltrials.gov and found that less than half of the registered trials were ever reported in published form and only 66% reported the primary outcome [10]. By publishing only the favourable results and suppressing the unfavourable results, such studies again create an impression of greater treatment efficacy than the complete evidence supports.

In a study that examined published trials of competing antipsychotic drugs, German researchers noted the paradox that 90% of industry-sponsored trials favoured the sponsor’s drug, even when the competitor’s trials showed the opposite. As an example, among comparative studies sponsored by the maker of Olanzapine, five out of five trials favoured Olanzapine over Risperidone. In contrast, among studies sponsored by the manufacturer of Risperidone, three out of four trials favoured Risperidone over Olanzapine [11].

The authors tried to determine how conflicting results could occur in seemingly well-designed randomized trials, and found that the explanations were subtle. They concluded that several design and reporting features might contribute to the paradoxical findings. For example, suboptimal dosing might be employed in the comparison group. The statistical methods might favour the sponsor’s drug when there were ambiguities about the proper analytical...
approach. Such ambiguities include uncertainty about defining two drugs as equivalent, and how to handle multiple comparisons or missing data. The authors also noted the likelihood of selective reporting of the most favourable efficacy and safety measures. Finally, they noted that the wording of findings and conclusions might itself be slanted, leading the reader to a desired conclusion [11]. Given such problems, a former editor of the British Medical Journal has declared:

“Medical journals are an extension of the marketing arm of pharmaceutical companies” ([12], p. e138).

Publishing favourable results many times

Canadian investigators undertook a literature synthesis to study the effectiveness of Risperidone for treating schizophrenia. After “vexing”, “bewildering” and “intolerably time-consuming” efforts, they identified 20 articles and several unpublished reports that actually represented only seven small studies and two large ones. One larger study had been reported in six different publications with different authorship and often with no reference to the others [13]. Similar redundant reports have been identified for other drugs, such as Ondansetron, Fluconazole, and some non-steroidal anti-inflammatory drugs [14–16]. Multiple reports of the same research have the effect of inflating the apparent quantity of evidence in favour of such treatments.

Ghost-writing in medical journals

Ghost-writing is a term used to describe research reports, editorials and review articles that a professional writer prepares, typically under hire by a drug company or a public-relations firm under its direction. In this circumstance, the company invites a prominent medical authority, typically from academia, to be identified as the author. The medical authority gives final approval to the manuscript, but the ghost-writer’s name does not appear. As an example, writer Ronni Sandroff of New York reported being hired to write two articles about cancer pain for peer-reviewed journals. She reported that she was:

“told exactly what the drug company expected, and given explicit instructions about what to play up and what to play down…”

As she noted:

“once it’s published… it looks like established fact” ([17], p 136)

Court documents indicate that dozens of articles related to the drug Rofecoxib (Vioxx) were prepared in just this fashion [18]. Vioxx was recalled from the market after, by one estimate, 140 000 avoidable heart attacks and some 38 000 deaths [19]. An evaluation of patients who received this drug suggested that most would have done as well with older and less expensive drugs, such as Ibuprofen [20]. Nonetheless, successful marketing had led to a $2.5 billion dollar per year market prior to the recall.
Investigators from Denmark, the U.K. and Canada studied a group of industry-sponsored clinical trials that were conducted in Denmark. They defined ghost authorship as occurring if individuals who wrote the trial protocol, performed the statistical analyses or wrote the manuscript were not listed as authors, or at least acknowledged. Out of 44 industry-initiated trials, the investigators found evidence of ghost authorship for 33, or 75%. The prevalence of ghost authorship increased to 91% if they included cases in which a person qualifying for authorship was acknowledged rather than appearing as an author. The investigators concluded that ghost authorship in industry-initiated trials is common and that guidelines regarding authorship are often not followed [21]. Indeed, critics argue that guidelines such as those drawn up by the International Committee on Medical Journal Editors have been relatively ineffective, and many smaller medical journals have not fully adopted the guidelines.

Some 15 years ago, Dr Troyen Brennan described the experience of being approached to be guest author of a ghost-written article. A public relations firm in New York invited him to be identified as author of an editorial for a medical journal. The company noted that the editorial might be timed to coincide with new clinical developments and that writing would be funded by a drug manufacturer. He was told that a professional writer would compose the article after talking with Dr Brennan [22]. At his request, Brennan subsequently received a packet of information describing the public-relations firm and its activities. These materials indicated that the firm solved negative publicity with advertising, medical symposiums and strategies for managing the press. They enclosed sample editorials, some of which did not disclose drug companies’ support. The company offered Brennan $2,500 for his guest authorship, but he declined. He argued that this practice blurred the distinction between the best interests of patients and financial gain of the sponsors [22].

Other strategies for suppressing bad news: Attacking research funding agencies and editors

In the 1990s, our research team was funded by the U.S. federal AHCPR (Agency for Health Care Policy and Research), to study outcomes of alternative approaches to managing lower-back pain. Among other topics, we studied spinal fusion surgery, which we found to be the most rapidly increasing type of back surgery. In this technique, adjacent vertebrae are ‘welded’ together with bone grafts, often with added metal plates and screws. A relatively new and popular technique was the use of so-called ‘pedicle screws’, devices that today add about $13,000 in cost to a single operation and have created a market of over $4 billion per year.

Our work included a literature synthesis suggesting that, outside of a small number of uncommon conditions, there were few validated indications for performing spinal fusion surgery. An analysis of data from insurance claims suggested that fusion surgery was associated with higher costs and complication rates than simpler forms of spine surgery, intended only to decompress nerve roots. We recommended randomized controlled trials to establish the efficacy and safety of fusion surgery for its common indications. This work emerged at a time
of numerous lawsuits over pedicle screw implants, from patients alleging poor results. Consultants described the spine surgery market as being “stagnant, after several years of dynamic growth”. Pedicle screw sales fell by 10–20% in 1994, perhaps due to a combination of lawsuits and growing questions about efficacy and safety of the devices.

The same agency that funded our research also supported a clinical guideline panel on acute lower-back problems in adults. This was part of a Congressional mandate to prepare clinical guidelines. The panel on acute lower-back pain included 23 members, with four surgeons and representatives of nearly every specialty involved in the care of patients with back pain. The guideline advocated non-surgical therapy for most acute back problems and did not address the more controversial challenges of chronic back pain. Nonetheless, the research and guideline efforts prompted a backlash from the North American Spine Society, a professional organization comprising mainly orthopaedic surgeons and supported heavily by device manufacturers. The society was displeased with the lack of support for spinal fusion surgery in the research and guidelines, and especially the absence of support for use of pedicle screws. The society mounted a letter-writing campaign to Congress suggesting that the funding agency be eliminated for supporting biased research and guidelines [23].

A surgeon member of the society’s board founded a lobbying group dubbed the ‘Center for Patient Advocacy’, with the explicit agenda of eliminating the AHCPR and restricting the authority of the FDA, which had never fully approved the use of pedicle screws in the spine. In addition, a spinal device manufacturer sought a court injunction to block release of the guidelines [23]. The lobbying efforts were partly successful: in its 1996 budget, the House of Representatives suggested eliminating the AHCPR. The Senate restored the agency after intense lobbying in its support by other professional societies, including the American Hospital Association and the American Medical Association. Nonetheless, the intimidation led the agency to end its guideline work and resulted in a 25% budget cut. This meant the agency could fund no new research for several years and currently funded projects, like ours, sustained substantial budget cuts [23].

A decade later, in 2006, the same agency (with a new name, the Agency for Healthcare Research and Quality) issued a draft literature synthesis on spinal fusion, concluding that fusion surgery for degenerative spine disorders:

“does not conclusively demonstrate short-term or long-term benefits compared with non-surgical treatment…” ([24], p. 2)

Nonetheless, we documented that spinal fusion surgery had increased rapidly over that decade [25]. Also in 2006, the manufacturer who tried to block release of the guidelines agreed to pay the U.S. government a $40 million fine to settle accusations of “sham consulting agreements, sham royalty agreements and lavish trips” for physicians who worked with the company ([26], Section C, p. 4). Other companies were also under investigation for alleged kick-backs to surgeons.

This attack on a funding agency may seem exceptional, but there are other examples in the U.S. The Injury Prevention Branch at the Centers for Disease Control, another federal agency, came under attack from gun advocates
They sought to eliminate the Injury Prevention Branch because its research had suggested that rates of suicide and homicide were greater in homes with gun ownership. In the 1970s, Congress eliminated the National Center for Health Care Technology after lobbying from drug and medical device makers, who were concerned that the Center’s evaluations might hurt their markets [28]. Congress eliminated its own Office of Technology Assessment following accusations that it was ideologically motivated. It had issued an unpopular report indicating that ‘Star Wars’ laser anti-missile technology was unlikely to be effective, but had also come under attack for its reviews of drugs and medical advances.

Another form of intimidation is directed at editors of scientific journals. Perhaps the best known example involved Dr Suzanne and Dr Robert Fletcher, editors of the *Annals of Internal Medicine* and members of the Harvard Medical School faculty. In 1992, under their editorship, the *Annals* published an article that was critical of drug advertising. A researcher had sent print advertisements to experts for review in the same fashion as a peer-reviewed article. The experts found faults in the accuracy of the adverts, compliance with FDA standards, and educational value of the adverts. Following the article's publication, there was a dramatic fall in drug advertising in the *Annals*; it was estimated that the journal lost between $1 million and $1.5 million in revenues. This drop was immediate following the publication of the critical article, and lasted until January 1994, when a new editor was appointed [29].

**Common themes and consequences**

In many of the situations related here, responses to unfavourable information bypassed the genteel scientific debate that generally occurs in scientific meetings or journals. Instead, many responses were non-scientific, and were aimed at discrediting findings, suppressing publication, intimidating investigators, pre-empting the time and resources of investigators or eliminating funding agencies.

Unfortunately, there are important consequences for manipulating knowledge in this way. First, patients may be exposed to unnecessary risks if efficacy is inflated or safety concerns are minimized. Similar concerns would arise with broader environmental or toxic exposures. Secondly, costs of care may increase without increasing quality of care. Thirdly, intimidation or suppression of data discourages research in controversial areas: often those most in need of good scientific evidence. The result is that vested interests are sometimes able to determine acceptable questions and results. Finally, eliminating public peer-reviewed research funding risks slowing production of new knowledge and pushing investigators towards funding that is more likely to have conflicts of interest [23].

**Lessons for society**

Because of opportunities to manipulate knowledge, it is important to protect valid scientific findings. The peer-review system should resist efforts to block
publication of articles; editors should avoid selecting reviewers with conflicts of interest; and journals must be protected from threats of advertisers. Investigators themselves may come under attack from vested interests, which can include industry, but also professional and advocacy groups. In some cases, new university policies may be necessary to support such faculty and to identify vested interests more rapidly.

When funding agencies come under attack by special interests, prompt and unambiguous support from universities, professional journals and professional societies is needed. Consumers of research, including nearly all of us, should support public and other disinterested funding of research. The peer-review process for scientific research proposals should be insulated from politics, marketing or consultants with financial interests [23].

Investigators should understand that research on marketed products is likely to be more politicized than basic science. Such research should strive for impeccable science that can be readily defended. In some cases, it may be possible to anticipate opponents to the research prior to conducting the work and to invite their support for the research design even before it begins. Nonetheless, investigators should expect a political, legal and marketing discourse if they discover findings with important financial implications. Researchers should become familiar with media interviews, because it is important to provide their perspectives and context for new scientific findings. Those of us involved in research should be transparent about our own conflicts of interests.

Furthermore, researchers should have thick skin. Research involving products already in the marketplace is a ‘contact sport’ and getting pushed around is part of the game. When researchers work on policy-relevant problems that are likely to make an important difference to society, they may expect complaints from vested interests. We should perhaps bear in mind the caution of Piet Hein, the Danish scientist, mathematician, and poet, who wrote:

“Problems worthy of attack
Prove their worth
By attacking back” [30]

References


