Medical journals and pharmaceutical companies: uneasy bedfellows

Richard Smith

Many medical journals have a substantial income from pharmaceutical companies from the purchasing of advertising and reprints and the sponsoring of supplements. Is this funding corrupting journals?

BMJ, London WC1H 9JR
Richard Smith *editor*
rsmith@bmj.com

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Summary points

- Free newspapers for doctors depend completely on income from pharmaceutical advertising, but many journals also depend heavily on such advertising
- The advertising is often misleading
- Editorial coverage is much more valuable to drug companies than advertising, and scientific studies can be manipulated in many ways to give results favourable to companies
- Many medical journals have a substantial income from supplements and reprints paid for by drug companies

One of my first experiences of the relation between medical journals and pharmaceutical companies occurred in the early 1980s after the *BMJ* had published papers suggesting that a new non-steroidal anti-inflammatory drug, benoxaprofen, might have serious side effects. We were visited by three stern men from Eli Lilly, the makers of the drug. Tony Smith, the deputy editor, conducted the meeting and asked me to join him. The men, whom I remember (probably wrongly) as having gold teeth, threatened us with legal action, at which point Tony said: "In that case we'll see you in court." They backtracked hastily and asked simply to be able to publish a prompt response.

Those papers led eventually to benoxaprofen being banned, but the drug's rapid demise may well have been caused by its rapid ascent. The summer before the meeting with the men with gold teeth, I had visited Eli Lilly's headquarters in Indianapolis. I had won a prize from the Medical Journalists Association, and the money had to spent on a journalistic investigation. I was interested in compensation for drug injury and decided to visit the United States to look at its system. The prize money came from Lilly, and as Lilly had been involved in one of the biggest cases of drug injury—from diethylstilbestrol—it made sense to visit them. My wife and I were put up in a grand hotel at the company's expense and treated very well.

Lilly showed me films that were to be used to promote benoxaprofen when it was launched. I thought them wildly over the top: patients with severe arthritis were shown before they took the drug and then afterwards dancing. The message was that benoxaprofen didn't simply relieve the symptoms of the disease; it actually reversed the disease. I was sceptical of this claim, and even if it had some truth I thought the films excessive.

When the drug was later launched in Britain Eli Lilly made these extravagant claims. The *Liverpool Echo* carried a report of "a miracle drug." Heavy marketing meant that the drug began rapidly to be widely prescribed. This meant—ironically—that reports of side effects also appeared rapidly, culminating in the papers in the *BMJ*. Research published later showed that benoxaprofen probably didn't cause any more side effects than similar drugs—but it didn't reverse the process. Benoxaprofen may have died from being overhyped.

This story had a formative influence on me and caused me to fret about the relationship between doctors and the pharmaceutical industry. Firstly, it taught me something about conflict of interest: your opinion may not be bought, but it seems rude to say critical things about people who have hosted you so well. Secondly, there's a tendency to see the industry as villains and doctors as innocent victims—but that's oversimplified. In doing their best for patients, doctors will need to use the products the pharmaceutical industry makes, and it's reasonable that the industry should be able to promote its products. But surely doctors should be looking also to independent sources of information, and how did we reach a point where so many doctors won't attend an educational meeting unless it's accompanied by free food and a bag of "goodies"? Something's wrong, and medical journals are part of what's wrong.

Pharmaceutical advertising in journals

Advertising is the most obvious and straightforward way in which pharmaceutical companies use medical journals. In most countries companies can advertise drugs only to doctors. This creates a lucrative market for publications to doctors, and many countries have many publications that are sent free to doctors and entirely paid for by advertising.

To attract advertising these publications have to be read by the doctors whom the advertisers want to reach. So the free publications work hard at making themselves attractive, relevant, interesting, and easy to read—in contrast to journals, which are often delivering complex, difficult to read material of limited relevance.

Journals compete with free publications for advertising. Doctors in Britain receive the *BMJ* free in part because of the support the journal receives from pharmaceutical advertising. *BMJUSA*, which circulates monthly to 90 000 doctors in the United States, is paid for entirely by advertising. Because of advertising the

New England Journal of Medicine is sent free to many hospital doctors in Britain and *JAMA* to many doctors in the United States.

Pharmaceutical advertising almost certainly does affect prescribing,[1] though no randomised trials have been done and most doctors say that they are not influenced by advertising. Nevertheless, publishers have calculated a return on investment of drug advertising and argued that it produces a better return than spending money on drug company representatives.

Is advertising misleading?

We have good evidence to show that much drug advertising is misleading. A US congressional inquiry reported that from August 1997 to August 2002 the Food and Drug Administration (FDA) issued 88 letters accusing drug companies of advertising violations. In many cases companies overstated the effectiveness of the drug or minimised its risks.[1]

These violations pursued by the FDA are almost certainly, however, the tip of the iceberg. A 1992 study, which included all 109 full page advertisements from 10 leading medical journals, found many more problems.[2] The authors were able to find four fifths of the references cited in the advertisements. They then sent the advertisements and the references to specialist reviewers, asking them to evaluate the advertisements using FDA criteria. In a third of cases two or more reviewers disagreed with the advertiser's claim that the drug was the "drug of choice." In 40% of advertisements the reviewers thought that information on efficacy was not balanced with that on side effects and contraindications. Overall, reviewers would not have recommended publication of 28% of the advertisements and would have required major revisions in a third. A recent Spanish study found that promotional statements made in nearly half of almost 300 advertisements were not supported by the reference they cited.[3]

Should journals refuse to publish drug advertisements?

As advertisements influence prescribing yet are often misleading, the question arises whether medical journals should publish them and, if they do, whether they should peer review them. Few editors (and fewer owners) refuse advertisements. Many review advertisements and turn down those that they think misleading. The *BMJ*'s policy is given in the box.

BMJ policy on advertisements

At the *BMJ* we don't attempt to review the claims made by advertisements. We do review advertisements for taste but rarely turn any down. The logic of this position, which many find extreme, is as follows.

- Strict British and European laws control the claims that can be made in advertisements
- The UK industry has a code regulating advertisements, and companies are quick to report each other for breaking the code
- We know that readers discount advertising (though this conflicts with evidence that advertising changes prescribing)
- It makes sense for us to concentrate our resources on improving editorial, not advertising, pages.
- We encourage readers to criticise advertisements just as they criticise editorial pages, and we encourage them to complain to the authorities if they think the offence serious enough.

This policy is against the backcloth that we want the income from advertising. Like many editors, we believe that, paradoxically perhaps, such income buys us independence. Advertisers have little power to influence what is published—partly because there are many of them. But if owners have to support a journal financially they will want the journal to promote their view of the world. We also know that if readers are given a choice of paying for a journal without advertising or receiving free a journal with advertising, nearly all opt for the free journal.

Editorial material favourable to drug companies

Advertisers would always prefer favourable editorial coverage to an advertisement—because they too know that readers discount advertising. So, most crassly, advertisers may offer to buy advertising if it can be accompanied by favourable editorial mentions of their products. Next, advertisers seek to publish "advertorials," advertising that is mostly words that they hope may not be distinguishable from editorial material.

Most commonly, however, advertisers want to know what is to be published in a journal so they can position their advertising alongside editorial material favourable to their products. Many journals seem to sell advertising space on this basis.

Ultimately, however, medical journals are probably more useful to pharmaceutical companies for publishing trials than they are for advertising. Though the free publications may be better read than journals, they cannot provide the worldwide approval that accompanies a major trial in an international journal.

A major randomised trial that is favourable for a drug is a major step in creating the "blockbuster drug" that all companies want. This means that the marketing people in a pharmaceutical company will often be more interested in clinical trials than are researchers—because many trials are scientifically uninteresting. What is happening is that this major scientific invention—the randomised trial—is being debased for marketing reasons. And medical journals are very much part of this process because they are the outlets for these trials—and the impact of a trial is much magnified if it is in a major journal.

A quick guide to corrupting science to promote drugs

The best trial asks a simple, medically important question, is properly randomised (to avoid bias), and is conducted on a large scale (to avoid getting the wrong answer by chance). There are many ways to debase the process for marketing purposes.

Seeding and switching trials—Sometimes companies will conduct trials simply to get doctors to prescribe their drug. These "seeding trials" are often scientifically meaningless. They have no clear question and no controls. But they are conducted on a large scale, and "investigators" (often ordinary doctors, not research-

ers) are paid substantial sums to enter patients into the trial. A variant is a "switching trial" in which a doctor is paid to switch patients from their usual treatment to the new treatment. These sorts of trials will rarely make it into major journals, but many may be published somewhere—and then used to promote the drug with doctors, most of whom are scientifically naive.

Postmarketing surveillance—Yet another variant—with perhaps more scientific justification—is postmarketing surveillance. Many adverse effects of drugs do not emerge until after they are on the market, so it makes scientific sense to gather data on patients taking new drugs, but it can also make marketing sense as a way of getting doctors to prescribe the drug. Again doctors may be paid substantial sums "for expenses." My guess is that they rarely explain this to patients. Instead, patients may be flattered to think that they are getting the newest (with a false implication of best) treatment. These trials will often be published, sometimes in major journals—because they give important data on adverse effects.

Placebo controlled trials—Pharmaceutical companies are usually required to conduct a trial of their new drug against a placebo to get a licence for the drug. This requirement may conflict with the Declaration of Helsinki, which deems it unethical to give patients a placebo if an evidence based treatment is available. As most new drugs are not completely new but "me toos," this conflict arises often. What patients and doctors want to know is whether the new drug is better than existing treatments. But pharmaceutical companies have a horror of "head to head" trials, where treatments are tested against each other in trials that are big enough to give a clear answer. A clear but unfavourable answer would be dreadful for a company that had spent hundreds of millions of dollars bringing the drug to market and tens of millions on trials.

Equivalence trials—Companies thus prefer a trial against placebo or a trial that shows that their drug is as good as another. These "equivalence" or "non-inferiority" trials are particularly hard to interpret. In essence, the trial is not big enough to be able to show that one treatment is better than another, but not so small as to be meaningless. Most trials funded by pharmaceutical companies are in these categories, which is why it is possible for none of the 61 trials of non-steroidal anti-inflammatory drugs funded by pharmaceutical companies to come up with a result unfavourable to the company.[4] It's less a matter of suppressing unfavourable results and more a (less dishonest?) matter of making sure you don't fund a trial that will work against you.

Doses—There are other ways to make it more likely that results will be favourable. You can use a dose of the competitor drug that is lower than optimal. Or use the competitor drug in a dose that is higher than optimal and so will have more side effects. This may have happened with trials of new antidepressants, where the selling point is not that they are more effective but that they are less toxic.

Sorting it out

This is not an exhaustive list, and there is a similar array of methods of getting favourable results from systematic reviews and economic evaluations. Indeed, economic evaluations, which are relatively unfamiliar to editors and readers and highly complex, may be particularly easy to manipulate. It's difficult with all of this to sort out dishonesty, honest bias, and clever use of legitimate methods, but we journals need to try and do so—not least because three quarters of randomised trials reported in major journals are funded by the pharmaceutical industry.[5] Often too the trials are conducted not by academic researchers (who at least in theory will not be beholden to the industry) but by contract firms who are paid a fee to get the job done. These firms will not object—as academics might—if the company chooses not to publish the results, perhaps because they are unfavourable.

The International Committee of Medical Journal Editors has made a small stand against such practices by saying that journals should publish papers only if the authors control the right to publication.[6] This is tokenism, though: if the sponsors controlled publication and didn't like the results, the papers won't be sent to these journals for publication.

The lucre of reprints and supplements

The major journals try to counterbalance the might of the pharmaceutical industry, but it is an unequal battle—not least because journals themselves profit from publishing studies funded by the industry. Major trials are very good for journals in that doctors around the world want to see them and so are more likely to subscribe to journals that publish them. Such trials also create lots of publicity, and journals like publicity. Finally, companies purchase large numbers of reprints of these trials. Sometimes they will spend more than $1m on reprints of a single study, and the profit margin to the publisher is huge. These reprints are then used to market the drugs to doctors, and the journal's name on the reprint is a vital part of that sell.

Another way in which journals become entangled is through publishing supplements. The big weekly journals do not publish supplements, but many specialist journals do—and they can be very profitable. Some journals have a supplement with every issue, and generally the poorer the scientific quality of the supplement and the more favourable it is to the company that funds it, the bigger the profit. If a journal is willing to publish every paper presented at a sympo-

sium that was funded by a single company and that dealt with one drug, then it can charge a substantial fee. Often these papers will be set pieces by, to be crude for a moment, "paid industry hacks" and will have been published many times. If, however, the journal wants to peer review every study and take only those that are original and pass review then the fee will be smaller. Studies have shown that papers published in supplements are of poorer quality than those published in the main journal.[7 8]

Conclusion

In one sense, all journals are bought—or at least cleverly used—by the pharmaceutical industry. The industry dominates health care, and most doctors have been wined and dined by it. It's not surprising, therefore, that medical journals too should be heavily influenced by industry. But health care, doctors, journals, and—I believe—the pharmaceutical industry would all benefit from relationships being less grubby and kept more at arm's length and businesslike.

This is a drastically shortened chapter from a book by RS provisionally called "The Trouble with Medical Journals" and due to be published by Cambridge University Press next year.

Competing interests: RS is editor of the BMJ and chief executive of the BMJ Publishing Group Ltd. He is responsible for journals that include advertising, sell reprints, and publish supplements. He is paid a fixed salary. For further information on his competing interests access http://bmj.com/aboutsite/comp_editorial.shtml

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Unhealthy spin

Bob Burton, Andy Rowell

Public relations companies are experts at "third party technique"—helping the drug industry separate the message from what could be seen as a self interested messenger. But most journalists have a sketchy idea about how the public relations industry works, and thereby are vulnerable to uncritically accepting the disguised messages of the drug industry

Few doctors have heard of the world's leading medical public relations companies—Edelman, Ruder Finn, Noonan/Russo Presence, the Shire Health Group, and Medical Action Communications, among others. Yet barely a day passes without most doctors or their patients being exposed to messages that have been carefully crafted by these public relations companies, aimed at boosting sales of their clients' drugs.

According to the public relations industry's trade press, the top five companies in "healthcare PR" raked in over $300m (£186m, €260m) last year for everything from planning pre-launch media coverage of new drugs and cultivating doctors to publishing medical journals and wooing patients' groups.

Business tactics

At the heart of most public relations strategies is what is referred to as the "third party technique." Edelman's associate director health in London, Paul Keirnan, explained the technique as separating the message from what could be seen as a self interested messenger. A pharmaceutical company defending a controversial product, he said, "would have much less credibility than if an opinion leader or a prescriber said it. It is not putting words in the mouths of opinion leaders. It is basically using a third party to put forward what are the

Summary points

In the "third party technique," instead of using a company representative from the drug company (who would have low credibility) as spokesperson, an apparently independent messenger with a higher credibility rating in the eyes of the target audience is used

A lack of proactive disclosure by third party messengers is often reinforced by the failure of doctors, patients, and journalists to demand that potential conflicts of interests be revealed

"Healthcare" public relations has traditionally focused on influencing prescribing decisions, but now attention is increasingly directed to potential patients

Patient groups are increasingly being sponsored by drug companies, and this is fuelling debate about standards of disclosure by non-profit groups

Expert reporting on the public relations industry is lacking, allowing tactics aimed at shaping important decisions on health care to flourish

POBox 157, O'Connor, ACT2602, Australia
Bob Burton
freelance journalist
Devon TQ10 9JL
Andy Rowell
freelance journalist
bobburton@ozemail.com.au

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