

## Has the pharmaceutical industry commandeered evidence-based medicine? 2) Solutions

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### ABSTRACT

Evidence-based medicine, rather than providing a mechanism to challenge questionable claims has become another tool through which covert advertising and promotion furthers the industry's aims, rather than benefiting patients. This paper will review how some of the techniques used by pharmaceutical companies affect evidence based medicine, before suggesting potential solutions to some of these challenges.

It may be some time before confidence can be fully restored in academic medicine, and clinicians and patients can be reassured that published study outcomes are free from influence. There are changes occurring which are moving towards greater transparency, and some pharmaceutical companies are speaking the right language, but only time will tell whether the pharmaceutical industry are prepared to shake off their chequered past and change for good.

**Key Words:** pharmaceutical company; research malpractice; Big Pharma

### Introduction

In the first paper we saw how some of the claims made by the pharmaceutical industry don't stand up to scrutiny. Some additional issues have the potential to impact significantly on the safety of our medicines. First, selective publication leads to an exaggeration of benefits whilst harms are downplayed. This has led to cases where licensed drugs were only found to be harmful long after deaths were occurring. Second, regulatory authorities are not given (or are not demanding) enough information to make fully-informed decisions on the medicines they are approving – full, detailed, patient-level data is held by the drug companies and rarely released. This makes it impossible for researchers to determine the true benefits and risks of particular treatments.

Before discussing some solutions, it makes sense to discuss some other techniques that are used to 'muddy the waters' when trying to determine the safety and efficacy of medicines.

### Subversion of Evidence-Based Medicine

#### Off-Label Marketing

Off-label marketing, the promotion of drugs for conditions that the drug doesn't have a license for, is relatively common. Indeed, a significant proportion of drug company financial penalties relates to off-label marketing and some of the largest corporate fines include penalties for off-label promotion (1).

Although it is not-permitted, off-label marketing can generate significant additional revenue for the company. Whilst a company cannot easily promote study findings outside of its marketing license, conference presentations and posters provide a platform for the display of data relating to non-licensed indications and can still be cited in advertising for the drug (2). Continuing Professional Development, and educational seminars, provides another way in which companies can propagate off-label data by asking key-opinion leaders (KOLs) to talk about their experience of the drug to fellow professionals (3).

The release of company-confidential material as part of litigation proceedings in the US has highlighted the role that off-label marketing plays in the overall release of a new drug; in many cases, it will be an active part of the promotional strategy. For example, off-label promotion formed part of the advertising strategy for Quetiapine<sup>1</sup> and companies have been fined for the off-label selling of Paroxetine (Paxil®) (4), Olanzapine (Zyprexa®) (5), and Semisodium Valproate (Depakote®) (6).

### Ghost-Writing

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Ghost-writing is the practice whereby a company will typically ask an external medical writing company to draft papers that are favourable to the company's product. They will then invite prominent researchers or key-opinion leaders to become authors, in an attempt to increase the credibility of the paper. The original author(s) are rarely acknowledged, hence their description as 'ghosts'. A variation is 'guest' authorship, when a physician or researcher who has made little contribution to the scientific work is credited as an author.

Ghost-writing is common, but can be difficult to spot. A common clue is the use of the term 'editorial assistance' in the acknowledgements section. Very often, this person will have had a much more prominent role in drafting the paper and will commonly work for a medical writing firm. The large depression study STAR\*D resulted in approximately 124 papers, at least 45 of which acknowledge Jon Kilner (who is also a science fiction author<sup>2</sup>) as providing 'editorial assistance'. Standard rules about authorship do not necessarily protect against ghostwriting (7).

A number of studies have been examined in connection with ghost-writing. One of the most prominent is Study 329, a placebo-controlled study of Paroxetine (Paxil) for depression in adolescents which was later determined to have been written by Sally Laden, who worked for the medical writing firm Scientific Therapeutics Information (STI) (8).

### Fixing the problem

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There are numerous possible solutions to the challenges currently facing evidence-based medicine which hopefully will begin to re-establish trust in academic medicine and clinical research.

#### Improved disclosures of conflicts of interest

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Potential conflicts of interest have been described in the drafting of the Diagnostic and Statistical Manual of Mental Disorders in both the recent versions: DSM-IV and DSM-5 (9, 10). They have also been identified in the groups producing clinical practice guidelines (11-14).

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<sup>1</sup> [http://psychrights.org/research/Digest/NLPs/Seroquel/090520UnsealedSeroquelExhibits/Off-label/Schwartz7\[Redacted\]-SeroquelStrategySummary\(12-18-00\).pdf](http://psychrights.org/research/Digest/NLPs/Seroquel/090520UnsealedSeroquelExhibits/Off-label/Schwartz7[Redacted]-SeroquelStrategySummary(12-18-00).pdf)

<sup>2</sup> <http://kilnerwriter.net/bookspage.htm>

It is not just professionals that have ties with the pharmaceutical industry. Third sector organisations also have significant amounts of their funding coming from industry (15). The overall effect is that it is sometimes difficult to determine where particular interests lie, and how those interests are influencing the scientific literature. Undisclosed interests are particular concerning (16). For example, a group of scientists published a review of research on vagus nerve stimulation (VNS), a controversial treatment for depression (16). However, the authors omitted they are paid advisers to the company that manufactures a device for VNS that was approved in 2007 by the U.S. Food and Drug Administration (16).

In a response to the problem, the US has introduced what is known as the ‘Sunshine Act’ where pharmaceutical companies have to disclose all payments to doctors. These payments will be made available on publicly-accessible websites<sup>3</sup>. However, it is worth bearing in mind that disclosure doesn’t automatically remove a conflict of interest. Furthermore, it is possible that biases may be magnified by disclosure (17), through mechanisms such as “strategic exaggeration” and “moral licensing” (18).

### Comparative trials should be the norm

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Pharmaceutical companies do not have to demonstrate that their new drugs are better than existing treatments, they only have to demonstrate that they are better than placebo. This marker of success is often much easier to achieve. This is particularly true in the USA where placebo-controlled trials are mandated by the FDA. Such an approach, whilst ensuring that drugs demonstrate efficacy, results in a number of consequences.

First, where it is known that a particular type of intervention is better than placebo it raises ethical issues about whether it is appropriate to offer people dummy medication (19). Second, placebo-controlled trials are usually conducted across a number of different sites in different populations. This can result in differences between subgroups being obscured in the overall need to demonstrate efficacy for the average patient. In extreme cases, drugs that appear efficacious for one gender may offer little benefit for the other.

### Better evaluations of the benefits of new medications

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We saw in the first paper that the benefits of new medications often seem small. Over time, we are seeing fewer and fewer completely novel drugs, or drugs that offer major gains over existing agents. In recent years, the French industry journal *Prescrire* has found it increasingly difficult to award drugs that offer genuine incremental advances in care (20). Only 1-in-10 new drugs offers “*a statistically significant difference in primary clinical endpoints*” (21).

Consequently, as drug costs remain high but gains become smaller, there is an increasing need for health services to ensure that public funds are spent in the most effective and efficient way possible.

### Value-based pricing

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Value-based pricing for branded drugs will come into effect in 2014. NICE has always evaluated treatments on the basis of gains in utility – i.e. quality of life and functioning was an important measure when assessing the benefits of an intervention. Under the new rules, when considering new treatments, NICE will look at costs that extend beyond those borne by the NHS to include costs to carers and costs relating to employment (22). This means that if a treatment improves quality of

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<sup>3</sup> <http://www.ama-assn.org/ama/pub/advocacy/topics/sunshine-act-and-physician-financial-transparency-reports.page>

life to a similar degree to other drugs, but improves other outcomes more, it may be considered more favourably by NICE.

Some have voiced concerns that drugs that are second to market (i.e. 'me-toos') may be disadvantaged, but value-based pricing means that they will be unable to charge more than existing drugs unless they can demonstrate additional benefit (23).

### Full disclosure of data from Clinical Study Reports (CSRs)

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Since November 2010, the European Medicines Agency (EMA) has released almost two million pages of clinical trial information in response to requests from research groups and other agencies, as part of its 2010 access-to-documents policy. The policy aims to give access to non-clinical and clinical information (including clinical study reports) that have been submitted by pharmaceutical companies as part of their applications for marketing-authorisation. Such apparent transparency has been welcomed by medical researchers, particularly given EMA's history of being unwilling to disclose data on the grounds of commercial sensitivity (24). However, the moves are being actively resisted by some pharmaceutical companies (see below).

### The AllTrials campaign

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The AllTrials campaign was established in early 2013 as a collaboration between: Bad Science (led by Ben Goldacre), the British Medical Journal, the Centre for Evidence-based Medicine, the Cochrane Collaboration, the James Lind Initiative, Public Library of Science, and Sense About Science. The campaign calls for all clinical trials to be registered and their results reported, and it has produced detailed plans for this aspiration.<sup>4</sup>

The aspiration to ensure full disclosure of clinical study reports is an important step in ensuring that decisions can be made about healthcare interventions. It has been estimated that less than 50% of clinical trial outcomes are in the public domain; i.e. published in peer-reviewed literature (25). Importantly, clinical study reports (CSRs) contain much more detailed information about harms of medication.

We have seen in the first paper that selective publication and withholding of clinically-relevant information leads to poor decision-making. Reboxetine was considered to be an effective and safe antidepressant on the basis of published studies, but it was only when the German equivalent of NICE obtained unpublished data did it emerge that reboxetine was ineffective and potentially harmful (26). The problem was that 75% of patient data had never been published.

### Pharmaceutical company sign-up to the AllTrials campaign

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A few drug companies have publicly announced their support for the *AllTrials* campaign for clinical data transparency. GlaxoSmithKline was one of the first to announce their commitment to providing trial data<sup>5</sup> in early 2013, but it has gone on to be caught up in bribery scandals in China<sup>6</sup>. Roche has also declared a greater willingness to share clinical trial data (27), although there remains some scepticism given Roche's unwillingness to disclose data regarding Oseltamavir (28, 29).

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<sup>4</sup> <http://www.alltrials.net/all-trials/>

<sup>5</sup> <http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html>

<sup>6</sup> <http://www.bbc.co.uk/news/business-23402154>

### Is Big Pharma resisting change?

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Two pharmaceutical companies (AbbVie and Intermune) are challenging the EMA's plans to provide access to clinical information (including CSRs) that were submitted as part of applications for marketing-authorisation. Most, it should be noted, have not launched legal proceedings. At a meeting hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), a representative from AbbVie (a research-based company that split from Abbott in early 2013), claimed that information about adverse effects "*is confidential commercial information because if released other companies could use it to help them get products approved.*" The Head of the Dutch board which evaluates medicines went on to question whether AbbVie really thought that adverse events are commercially sensitive information and Hans Georg Eichler, the EMA's chief medical officer said "*I have been a regulator for many years and I am totally flabbergasted.*"<sup>7</sup>

### A willingness to resist indication creep and expanding disease definitions

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Many people are concerned by the gradual expansion of disease definitions so that previously-normal health states are now considered to be disease and requiring of treatment. As a general rule, medicine tends to expand disease rather than contract it (13). Some examples include hypertension and hypercholesterolaemia (where the benefits of treatment for those in low risk groups have been questioned) (30) and metabolic syndrome and diabetes where the number of potential 'customers' might be huge but benefits unknown (31).

A related phenomena is indication creep – the use or promotion of a drug for off-label indications (32). This has been discussed above, and while not necessarily bad medicine (eg: amitriptyline for neuropathic pain) it may be related to drug companies trying to maximise profits by widening the therapeutic indications for their drugs (eg: Levodopa for restless legs syndrome). Despite being common, it may be very difficult to change current practice (1).

Other related approaches include the use of online and self-diagnosis tools to reach a larger range of consumers, many of whom would never had known that they were unwell until they'd filled in an online form, often on a drug company's website (33).

### An acknowledgement that in many cases lifestyle and behavioural interventions can be just as effective as drugs

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In some conditions where drugs are becoming increasingly used, and in particular those conditions where boundaries between disease states and normality are becoming blurred (e.g. hypercholesterolaemia and hypertension), there is very good evidence that lifestyle changes can be just as effective as drugs (34). This requires a greater effort on behalf of the patient, but the risks associated with such interventions may be lower than those associated with drug treatment.

### Summary and Conclusions

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We have seen that evidence-based medicine is a powerful tool for improving care but it is not perfect and current systems do not offer sufficient protection from influence from companies that have financial interests in ensuring that their message is promoted. The historical record does not support the view that pharmaceutical companies are changing quickly. Systems are changing in response to concerns from academics and other interested parties, but we are still not in a position whereby we can be confident that all the data arising from clinical trials is in the public domain.

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<sup>7</sup> <http://www.alltrials.net/2013/2338/>

It may be some time before confidence can be restored in academic medicine, and clinicians and patients can be reassured that published study outcomes are free from influence. There are changes occurring which are moving towards greater transparency, and some pharmaceutical companies are speaking the right language, but only time will tell whether the pharmaceutical industry are prepared to shake off their chequered past and change for good.

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