COUNCIL FOR EVIDENCE-BASED PSYCHIATRY

The majority of psychiatric drug trials are conducted and commissioned by the pharmaceutical industry or those who have extensive ties with them. This industry has a long history burying negative results, and of manipulating research to highlight positive

In 2005 a report by the British government's Health Committee identified some of the practices by which pharmaceutical companies research and present their findings. The practices brought to the attention of the report's authors included:

> *…that clinical trials were not adequately designed – that they could be designed to show the new drug in the best light – and sometimes fail to indicate the true effects of a medicine on health outcomes relevant to the patient. We were informed of several high-profile cases of suppression of trial results. We also heard of selective publication strategies and ghost-writing. The suppression of negative clinical trial findings leads to a body of evidence that does not reflect the true risk/benefit profile of the medicine in question.*[1]

Today the pharmaceutical industry funds most of the clinical trials into their own products. They develop and conduct the trials, and evaluate and often manipulate the results. They are not obligated to publish the results of trials and rarely provide raw data for external review. Moreover, trials with positive outcomes are much more likely to be published, sometimes multiple times. An obvious example of this is Ely Lilly's antipsychotic, Zyprexa. Lilly conducted four clinical trails on this drug, yet turned this in to a total of 234 publications. Furthermore, none of these publications mentioned what these trials revealed: that Zyprexa increased rates of suicide or blood glucose or cholesterol levels.[2]

Such suppression of data is endemic in the industry. For example, according to the authors of a 2008 article published in the New England Journal of Medicine, of the 74 antidepressant trials reviewed in the article, nearly half were deemed by the FDA to have either negative or questionable results. Of this half, only 3 were published accurately, the rest were either entirely buried or published in a way to convey positive outcomes.[3]

Aside from burying negative data, companies deploy other strategies to advantage their products. Many articles published in high profile journals by senior researchers with prestigious university associations are actually ghost-written by the companies. In such instances, drugs companies send the article to a well-known researcher for review and then pay for using his or her name even if the researcher has never seen a single participant and does not have access to the raw data. The percentage of ghost-written clinical trials articles has been estimated at over 50% by a House of Commons Health Committee.[4]

Other questionable strategies include adopting clinical trials protocols that strongly bias the study towards positive outcomes. For example, prospective subjects are often screened to see if they would be good candidates. In one study, only about 30 of the 350 depressed patients would have qualified for a randomized controlled trial.[5] Some of the reasons for exclusion include prolonged depression, poor response to previous antidepressants and a good response to placebo. Moreover, the selected candidates are often not representative of the people who will be taking the drug and the effectiveness is likely to be less than that reported.

Clinical trials results can be further massaged by the choice of methods used to evaluate outcomes. For example, the Hamilton Depression Rating Scale (HAM-D) is often used in antidepressant clinical trials, but this scale gives more importance for a drug that causes sedation thereby reducing insomnia than it does if it causes the participant to have increased suicidal thoughts. Another analysis tactic is to remove participants from the study if they cannot tolerate the drug and must discontinue usage regardless of the symptoms, such as suicidal thoughts. They are not counted as failures for the effectiveness of the drug and are deemed non-compliant.

Another often-criticized strategy used in clinical trials is failing to differentiate clearly between placebos and the drug effect. Since many psychiatric drugs have strong side effects, participants can usually tell and the real drug from the fake pill thereby undermining the validity of controlling for the placebo effect.[6] Moreover, because of their short duration, clinical trials don't allow for a long-term evaluation of a drug's effectiveness or indeed its safety.

These and other strategies were identified by the former chief editor of the British Medical Journal, Dr Richard Smith, in a paper titled *Medical Journals are an Extension of the Marketing arm of Pharmaceutical Companies*. Here he described how pharmaceutical companies have manipulated drug-trial data in ways so initially undecipherable that, as he confessed, it took 'almost a quarter of a century editing for the BMJ to wake up to what was happening'.[7] Here are some of the strategies Smith identified:

- Conduct a trial of your drug against a treatment known to be inferior (your drug therefore looks superior).
- Trial your drugs against too low a dose of a competitor drug (your drugs looks superior).
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs (concealing that your drug could be inferior).
- Use multiple endpoints in the trial and select for publication those that give favourable results (thus discarding results that are unfavourable).
- Do multi-centre trials and select for publication results from centres that are favourable (again discarding negative results).
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress – for example, reduction in relative rather than absolute risk.[8]

Legal action

What further undermines trust in industry-conducted research is that many of the major manufacturers of psychiatric drugs have either been prosecuted or settled out of court for burying data. Here are just three examples[9].

1. The British pharmaceutical giant GlaxoSmithKline (GSK), which manufactures the antidepressant paroxetine (marketed as Seroxat in the UK and Paxil in the US). GSK conducted three trials to investigate whether this drug could reduce major depression in adolescents. But the trial results were highly inconclusive. One trial showed mixed results, another showed that Paxil/Seroxat was no more effective than a placebo, while the third suggested that the placebo might be more effective with some children. GSK published only the most positive study as evidence that the drug is effective for major depression in children. This would have gone unnoticed had not an internal company document been leaked to the Canadian Medical Association. This showed that GSK officials had actively suppressed negative results from one study because, as they said: 'It would be commercially unacceptable to include a statement that the efficacy had not been demonstrated, as this would undermine the profile of paroxetine.' Once this information came to light, a lawsuit was filed against GSK in 2004 for intentionally hiding negative findings. This was settled out of court two months later when the company paid $2.5 million for charges of consumer fraud – a meagre sum considering that it made $4.97 billion in worldwide sales from the drug in 2003 alone.[10]
2. A separate class action in 2010 revealed that the international pharmaceutical company AstraZeneca buried negative data from a study it commissioned on its

antipsychotic Seroquel. This study investigated whether Seroquel worked better than an older drug when treating schizophrenia. The results showed that Seroquel was only mildly better than the older drug in improving cognitive functions such as memory and attention. But in total it was far worse than the older drug. After a year patients on Seroquel had more relapses and worse ratings on some symptom scales. They also gained on average five kilograms in weight, which put them at increased risk of diabetes. But again, AstraZeneca simply buried these negative findings, and published only the positive results, leading to the drug's approval for general use. But so many thousands of patients suffered such awful side effects that in 2010 AstraZeneca was finally forced to pay up £125 million to settle a class action out of court.[11]

3. In 2010 an article in the British Medical Journal revealed that the drug reboxetine, marketed as Edronax by the drug giant Pfizer, was no more effective in treating major depression than a placebo sugar pill. Data on 74 per cent of the patients in Pfizer's studies of the drug were never published. If these data had been included, the evidence would have showed that the risks of taking the drug far exceeded the benefits.[12] Yet reboxetine has been approved for marketing in many European countries (for example, the UK and Germany) since 1997, and is still being taken by thousands of people in the UK today.

Long-term use vs short-term trials

There is very little data on the long-term effectiveness of the drugs commonly prescribed by psychiatrists. However, the data that is now emerging does not favour long-term use. (See Worse Long-term Outcomes at cepuk.org).

This is not surprising since clinical trials usually last only a few weeks or months, while many patients take psychiatric drugs for years or even decades. The effects of a drug over the short term can be very different to the cumulative effect of taking the same drug for years, and the only means of determining whether a drug is safe for long-term use is to commission research into cohorts of patients who have taken the drug long-term. For some psychiatric drugs such as SSRIs – despite the fact that each year hundreds of millions of prescriptions are given out worldwide – this work has never been done, and it is reasonable to conclude that long-term users of many modern psychiatric drugs are part of an ongoing experiment.

There are numerous examples in medical history of drugs which were initially believed to be safe and which are subsequently revealed to have caused harm. For example, benzodiazepines were touted as an entirely safe replacement for barbiturates, and millions of people took the drugs regularly during the 60s and 70s. Despite evidence of physical dependence and withdrawal symptoms appearing in the early 1970s it was not until the 1988 that UK Committee on Safety of Medicines first insisted that they should be used for a maximum of two to four weeks only to minimize the risk of addiction.[13] Today, withdrawal charities report numerous cases of people experiencing similar lasting negative withdrawal effects after stopping antidepressants, and yet these drugs continue to be prescribed for long-term use without firm evidence that such long-term use is in fact safe.

The multiple failings of the current clinical trial system recently led Marcia Angell to conclude: 'It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.'[14]

COUNCIL FOR EVIDENCE-BASED PSYCHIATRY

CEP believes that the current clinical trial system is broken, and that conflicts of interest and the manipulation of trial data have led to significant patient harm. In order to rebuild public trust, trials need to operate without any industry influence, overseen by independent academic institutions.

To contact us or for more information please visit cepuk.org.

(Last revised: 15 March 2014)

---

[1] House of Commons Health Committee Report (2004-5) *The Influence of the Pharmaceutical Industry*

[2] Healy D. *Pharmageddon* (University of California Press, 2012, pg. 125)

[3] Turner E.H, Matthews A.M., et al., 2008, Selective Publication of Antidepressant Trials and its Influence on Apparent Efficacy, New England Journal of Medicine, 358; 3 252-260

[4] McHenry L., 2010, Of Sophists and Spin-Doctors: Industry-Sponsored Ghostwriting and the Crisis of Academic Medicine, *Mens Sana Monogr*, Jan-Dec; 8(1): 129-145

[5] Zetin M, Hoepner C T., 2007, Relevance of exclusion criteria in antidepressant clinical trials: a replication study, Jun;27(3): 295-301

[6] Kirsch I., *The Emperor's New Drugs - Exploding the Antidepressant Myth* (Basic Books 2010 Ch.5)

[7] Quoted in, Spielmans, G. I. & Parry, P. I., 2010, From Evidence-based Medicine to Marketing-based Medicine: evidence from internal industry documents, *Bioethical Inquiry*, 7:13–29

[8] Smith R., 2005, Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies. *PLoS Med,* 2(5): e138

[9] The following three cases are quoted directly from Davies, J., 2013, *Cracked: why psychiatry is doing more harm than good (*London: Icon Books)

[10] Kondro W, Sibbald B., 2004, Drug company experts advised to withhold data about SSRI use in children, *Canadian Medical Association Journal,*170: 783

[11] Goldacre B., Drug companies hiding negative data are unfit to experiment on people, The Guardian 14 August 2010

[12] Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T et al., 2010, Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials, *British Medical Journal*, 341: c4737.

[13] Committee of Safety of Medicines, *Current Problems*, January 1988, Number 21

[14] Angell M., Drug companies and doctors: A story of corruption, January 15, 2009. *The New York Review of Books* 56.