Threats to Academic Freedom: Beyond Threats from Contracts

David Healy MD FRCPsych – Cambridge.

There has been a good deal of talk about the clear risk to academic freedom made explicit in contracts put in place between universities and commercial companies that limit the freedom of academics to publish the findings of their research. I want to draw your attention to another set of less obvious limits to academic freedom.

In academic medicine, these less obvious factors stem from the drug crisis surrounding Thalidomide and in particular from a set of safeguards ironically put in place to prevent a repeat.

**Factor 1: Product Patents**

After 1962 and the thalidomide crisis there was a switch to product rather than process patents on drugs. Since the TRIPS convention in 1985 product patents apply worldwide. This enables – almost mandates - pharmaceutical companies to make blockbuster products out of their drugs, in a way that was not economic before when process patents and the restriction of patents to a national territory meant that other companies could produce copies of the same drug.

The mark-up for blockbuster drugs, over the cost of their raw ingredients, in some cases rises to several thousand percent, making these drugs literally worth more than their weight in gold. As a result, the fortunes of many companies now depend critically on one or two key drugs, so that they have no option but to hype the benefits and hide the hazards of products, as is brought out by a quotation from Leigh Thompson of Eli Lilly in connection with Prozac.

“I am concerned about reports I get re UK attitude toward Prozac safety. Leber (FDA) suggested a few minutes ago we use CSM database to compare Prozac aggression and suicidal ideation with other antidepressants in UK. Although he is a fan of Prozac and believes a lot of this is garbage, he is clearly a political creature and will have to respond to pressures. I hope Patrick realizes that Lilly can go down the tubes if we lose Prozac and just one event in the UK can cost us that.”

This means that companies have an incentive to and do hide data from studies – up to 50% of trials in a therapeutic domain remain unpublished, and in those that are published in up to 1/3rd of cases the data is distorted to the point that a negative trial may be published as positive.

**Factor 2: Prescription-only Status:**

A second factor is that drugs are now made available on prescription only. This was a system that was introduced in 1914 to control drug addicts. In 1951 the system was extended to cover all new drugs against opposition. In 1962 in response to thalidomide this arrangement was copper fastened in place.

There are a number of aspects to this problem that were not considered at the time. When pharmaceutical companies market drugs they now only have to focus on a very small number of people who are prescribers – a very naive group of consumers. Companies understand these consumers better than these people understand themselves. They also bring to bear on this small group more marketing power per individual consumer (doctors are the true consumers of drugs) than anywhere else on the planet.

Yet there is no academic department of medicine than has a clue about how this marketing operates. No clue that companies have for over decade invested their marketing dollars in the appearances of science – controlled trials, guidelines, and measurement technologies.
Prescription-only status means that companies have to sell products for diseases and this has led to marketing by disease mongering and more recently risk-factor and measurement mongering.

**Factor 3 Controlled Trials:**

Following thalidomide, it was thought that one protection against the risks inherent in all drugs was at least to keep ineffective drugs off the market. Controlled trials were put in place to ensure only effective drugs reached the market.

This system is not fit for purpose. Indeed the belief that it is a good system makes it even more dangerous. There is no better symbol of the inadequacies of the system than the fact that as of 1962 the only drug that had been through a placebo controlled trial before coming to market was thalidomide which appeared a safe and effective hypnotic.

There are a series of allied problems linked to trials hinging on lack of access to the data from these trials and the measurement technologies linked to them.

Companies refuse access to clinical trial data – not even FDA gets to see all the data. What the rest of us see are articles written by ghostwriters. Close to 100% of studies undertaken on on-patent pharmaceuticals are likely to be ghost-written or managed by companies and the apparent authors are invariably some of the most prominent names in medicine with the articles appearing in the best journals – New England Journal of Medicine, Lancet, JAMA etc, with the journals explicitly stating it is not their role to ensure the integrity of the data.

What does lack of access buy? Well if you look at the suicidal acts that happened in the clinical trials that brought Fluoxetine, Sertraline and Paroxetine to the market, you find there is an entirely different distribution of acts in the published literature to what can be found when you get to see the raw data behind the trials (see slides 1 and 2 for an illustration of data manipulation). The control that lack of access gives has allowed many companies to effect similar or other manoeuvres for a range of side effects from heart attacks on Avandia to problems on Vioxx, atypical antipsychotics and other drugs.

Refusing access to the data and producing scientific articles that claimed one thing about the benefits of treatment when the data pointed to just the opposite led to a fraud action against GSK in 2004 and in recent weeks to a $3 Billion settlement between US authorities and GSK. Other companies have been similarly fined. But although both the regulators and many medical academics have known about the dimensions of what is going on for a decade no-one has been held to account, the articles have not been retracted and the treatments continue to earn billions of dollars.

Furthermore in contrast to the easy passage of ghostwritten articles into the very best journals, those same journals routinely refuse to publish anything on the hazards of treatment fearing a legal suit from pharmaceutical companies. The BMJ articles in slides 1 and 2 for instance was held up for over a year by such concerns. I personally have a series of articles that have been accepted after peer-review but then not published owing to legal worries – even when all documents and data are in the public domain.

There is a further problem with trials. Fifty years ago doctors and patients were much more confident in the observations they made about what treatments did for good or bad. Controlled trials have brought to light the biases doctors and patients bring to such observations but the pendulum has swung too far so that few doctors or patients appear able to believe the evidence of their own eyes today. When patients get huge on an antipsychotic if the controlled trial hasn’t shown that happening, then it isn’t happening.
Slide 1

**FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS**

*Occurrence of suicidal acts*

- Screening
- Randomization
- Drug
- Placebo
- Run-in/wash out
- Stop treatment
- Start treatment
- Follow-up

Healy
BMJ
2006

---

Slide 2

**FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS**

*Reporting of suicidal acts*

- Screening
- Randomization
- Drug
- Placebo
- Run-in/wash out
- Stop treatment
- Start treatment
- Follow-up
The statistics associated with RCTs give rise to this argument - individual observations are inherently unreliable. Only large samples can give us reliable observations. Slide 3 showing drugs A and B bring out part of the fallacy of the argument.

Drug A has some benefit. But also a hazard - it causes heart attacks or suicide. The data for the hazard are mapped here - they lie to the right of a line through 1.0, with the point estimate - the highest part of the curve at 2.0 - so it doubles the risk over placebo. Crucially 95% of the data lie to the right of 1.0 - so the data are termed by some statistically significant.

Now Drug B will also produce the same benefit - and hazard. The point estimate for the hazard here show an 8-fold increase in risk but only 90% of the data lie to the right of 1.0.

While only 90% of the data lie to the right of 1.0, by conventional criteria these data are unreliable - and by implication the only rational course of action is to assume they have arisen by chance and if faced with taking Drug A or Drug B to take Drug B as the safer drug. When in fact Drug A although risky is 4 times safer.

Any sane drug company executive would give a family member Drug A rather than B but in public the marketing apparatus gears up to say Drug B is entirely safe - and it will remain so while trials are not powered to settle the issue no matter how many convincing cases of death on B are described by clinicians, patients or others.

Slide 3

What the data show

Drug A     Drug B

![P-value Function](image)
A psychosis has been set up at the heart of medicine that is silencing patients, doctors and policymakers.

Merck, GSK, Lilly and others have traded on this in the case of Vioxx, Avandia, Prozac and other drugs. This is the most sophisticated version ever of the Doubt is our Product strategy pioneered by the tobacco companies in the 1960s.

What you need to know is that we are now systematically training doctors these days to make exactly that kind of mistake the whole time. They are being trained to say that if the results are not statistically significant you don't pay any heed to them. Our problems are going to get worse – not better.

While data like this exists for all major drugs pointing to increased risks, companies regulators and academics at the same time bury thousands of convincing treatment induced injury cases and continue to claim in public there is no issue.

There are two further factors linked to trials. One relates to the meaning of a trial. Trials are undertaken when there is a doubt about whether a drug works – but instead they have been transmuted into evidence it does work. The more patients recruited the greater the doubt there should be about the efficacy and safety of a treatment, but in fact this vulnerability is sold as even better evidence the drug is proven by science to work.

A second point relates to the measurement technologies linked to trials, from rating scales in mental health to blood tests of scans in general medicine, on which the drugs produce a benefit. Good marketing is able to take the fact of a minor benefit on some rating scale or blood test and conjure blockbuster sales out of this even though more lives are lost on active treatment than placebo. These technologies have escaped from the laboratory to infect medical care in general so that it has become almost impossible for any of us to take our concerns to a doctor and be seen or heard any more.

**Final Acts of the Tragedy**

We are facing a true tragedy – a system put in place with the best of intentions to prevent injuries from drugs in general but symbolized in particular by injuries to babies in utero is now leading to just the outcomes it sought to avoid.

In the case of the SSRIs as the evidence mounts that these drugs cause birth defects, doubling the rate of major malformations, doubling the rate of miscarriage, increasing rates of voluntary terminations and possibly leading to learning disabilities/autism in a significant number of children born to mothers on these treatments, we have nevertheless a mounting use of these drugs. Where antidepressants were once used rarely in pregnancy they are now among the most commonly used drugs – up to 15% of pregnant women.

This use has been actively promoted by medical academics on company sponsored platforms, by a series of ghost-written publications, and by threats against journals that might consider publishing articles warning of the hazards of treatment. This is a compelling symbol of how academic freedom has been lost.

A fuller account of these less obvious threats to academic freedom can be found in Healy D Pharmageddon University of California Press, March 2012.