Special Articles

The engineers of human souls & academia

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SUMMARY. **Aims** – There has been recent concern about interactions between academia and the pharmaceutical industry. This article seeks to explore the basis for the current sense of crisis. **Methods** – The approach taken is a historical one, outlining the origins of the crisis. **Results** – The analysis outlines the roles that brands, patents, and the control of the scientific literature play in the current marketing of psychotropic drugs, and describes the processes of guideline capture and brand fascism. **Conclusions** – The analysis makes it difficult to see current interactions between industry and academia as anything but bad for academia. One option that might restore some balance would be to restrict scientific meetings and journals to communications that made all relevant scientific data available, excluding exercises that restrict access to data.

Declaration of Interest: In recent years I have had consultancies with, or been a chairman or speaker at symposia for, or received support to attend meetings from Astra-Zeneca, and Lundbeck. I have been expert witness for the plaintiff in the past decade in 15 legal actions involving antidepressants and on patent case, and have been consulted on a much greater number of attempted suicide, suicide, and suicide-homicide cases linked to treatment, in which I have offered the view that the treatment was not involved or have declined to give a view.

BACKGROUND

The psychopharmacological era brought a wealth of new drugs to psychiatry. These, it was hoped, would treat patients and also be tools to dissect psychiatric disorders at their joints, thereby furthering the science of psychopathology (Delay *et al.*, 1955). In addition, the 1950s saw the emergence of controlled trials, and many thought these methods would help curb the excesses of the pharmaceutical industry. Finally the new drugs were made available on prescription-only by doctors who it was thought were less likely to be influenced by industry than non-professionals, and better able to understand research and its implications.

Consider then what happened in 1964, when Frank Fish reported the outcomes of neuroleptic treatment for 474 patients classified according to Leonhard's criteria for systematized or unsystematized schizophrenia (Fish, 1964). Of those with unsystematized schizophrenia, 75% responded to neuroleptics, while only 23% of systematized schizophrenics responded. Within the unsystematized group, 84% of the affect-laden paraphrenias responded, while only 1% of systematic catatonias responded. This finding appeared to bear out the hope that the new psychotropic drugs would help carve our traditional disorders at their joints. But Fish's findings and Leonhard's classification vanished from sight, with the advent of DSM-III, as did distinctions between neurotic depression and endogenous or melancholic depression, which were based on responsiveness to treatments like ECT.

Meanwhile, bipolar depression is now widely discussed, even though the treatment differences between unipolar and bipolar depression are much less than those among the schizophrenias reported by Fish, or between neurotic and melancholic depression. In addition, new disorders like social phobia and panic disorder flourish even though all apparently respond to the same interventions.

Why the eclipse of Fish's findings and the disappearance of melancholia, given that potential differences in treatment responsiveness were the reason to classify in the first instance? Few academics, however, have noticed the increasing gap between the former hope that new psychotropic drugs would help carve nature at its joints and the reality of psychiatric practice, which is that the neuroleptics became antipsychotics that it was impossible not to give to all psychotic patients despite good evidence that many would not benefit (Ban, 1987).

One reason for the mismatch between rhetoric and reality stemmed from the very methods put in place to control the industry. Strapped into a supposed clinical trial straitjacket, pharmaceutical companies found that the new methods meant that barely beating placebo would get a license for all affective disorders or all psychoses (Ban,

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2006). There was no incentive for companies to find treatments that had big effects on particular syndromes and they aimed instead for blockbuster drugs that worked across a broad spectrum of psychotic or affective disorders. Clinical trials, which began as a means to contain therapeutic claims, had been transformed by company marketing departments into a means to fuel new therapeutic bandwagons. If the drugs "work", surely it would be unethical for clinicians not to use them?

This is but one example of a marketing process that has developed since the 1970s that has stood the science of psychopharmacology on its head. Rather than drugs being used to carve nature at its joints, nature instead is being used to differentiate drug brands whose differences are trivial.

THE LEVERS OF POWER

The new marketing has availed of the use of brands, a weakening of patent laws, an industrialization of the clinical trial process, the willingness of physicians to be sold diseases and their inability to manage uncertainty. But above all it has been aided by physician ignorance of marketing.

Pharmaceutical brands stem from the late 19th century when the German company, Kalle, took out a copyright on the trade name Antifebrin for a new antipyretic agent that they could not patent. The power of brands can be seen from the success of Aspirin and Heroin a few years later that continue to have much greater recognition than their generic compounds (Healy, 1997).

Companies brand more than the name of drugs. For instance, although only shown to have effects on mania, the adverts for Depakote referred to it as a mood-stabilizer. Had Abbott referred to Depakote as prophylactic for bipolar disorder, the FDA would have declared the adverts illegal. The term mood-stabilizer, while connoting prophylaxis, was essentially meaningless and as such not subject to legal action (Healy, 2006a). Since the launch of Depakote in 1995, over a hundred articles a year have had the term mood-stabilizer in their titles or abstracts; textbooks carry chapters on the group of mood-stabilizers, and physicians include mood-stabilizers along with antidepressants and antipsychotics as a major psychotropic group. There seems almost no recognition that the term is little more than an advertising rubric that did not exist before 1995.

In a similar fashion, academic clinicians and others refer to SNRIs, as though this term has a clinical or pharmacological meaning, unaware of the extensive market testing that weeded out alternative acronyms and settled on this brand.

Two developments in the patent system made an increased focus on brands possible. First in the 1960s, older laws enabling companies to take out process patents were phased out, so that only one company could have a fluoxetine, making a blockbuster Prozac possible. As a consequence companies have a much greater incentive to aggressively defend and conceal the hazards of their compounds than before (Healy, 2004).

Second, where the patent system once aimed at rewarding substantial novelty that clearly contributed to public utility, the system has moved toward rewarding even trivial novelty with diminishing regard for evidence of benefit. Thus Abbott gained a patent on semisodium valproate for mania even though sodium valproate had already been demonstrated to be useful for mania (United States Patent, 1991; 1993). Lilly were enabled to get a patent on olanzapine on the basis that it was less likely to produce elevations of cholesterol and triglycerides in dogs compared to ethyl-flumepazine (United States Patent, 1992); a finding that is dramatically at odds with its effects in man (Lieberman *et al.*, 2005).

A third factor has been that companies gained control of clinical trials in the 1980s, when clinical research organisations (CROs) took over from academic physicians as the organisers of trials. As of 2000, CROs ran more than two thirds of clinical trials undertaken by industry, worth $30 billion (Davies, 2001; Getz & De Bruin, 2000). Privatized research of this sort is profoundly different to previous clinical research. CROs have transformed human subjects research, restructured controls of disclosure and confidentiality, and managed intellectual property in an entirely new way. RCT data collected by CROs is more clearly proprietary than when a federation of academic centers conducted trials.

CROs provide a privatized IRB system (ethics review) that grants ethical approval to company studies, when university centers might not (Lemmens & Freedman, 2000). CROs have made it possible to move trials on drugs for Western markets into Asia or Africa, in a way that university departments could not have done (Petryna, 2006). Whether this move has been prompted by concerns to avoid regulatory oversight, or cost considerations is less clear. Even in trials done in Western settings, it is now clear that CRO run psychotropic trials have included bogus patients (Healy, 2004).

But of perhaps even greater importance is a fourth factor, namely that companies now control the production of the scientific literature. In the case of drugs on patent, a significant proportion of the trials undertaken that do not

return the right result now remain unpublished, while a majority of those published are in all probability ghost-written, and bear an ambiguous relationship with their underlying data (Healy & Cattell, 2003).

The changing authorship of trials was first noticed in the mid-1990s. In response journals tightened up their authorship criteria. At this point there was little hint that the great majority of company trials appearing in major journals might be ghost-written. But by 2000, 75% of the RCTs appearing in major journals like JAMA, NEJM and the Lancet were sponsored by pharmaceutical companies, and it now seems unlikely that companies would have been prepared to leave the preparation of any sizeable proportion of these key marketing tools in academic hands. The picture that emerges is of an academic medicine transformed from what it had been during the 1960s.

The difficulties are best symbolised by the paediatric SSRI trials, where we have the greatest known divide in medicine between the raw data on an issue on the one side and the published accounts purporting to represent those data on the other. The data can now be seen to indicate that the drugs do not convincingly work and are hazardous, but prior to the release of the data the scientific literature universally portrayed these agents as safe and effective (Healy, 2006b).

One of these trials, study 329 on paroxetine, offers a landmark for the point at which science turned into marketing. An internal company assessment of this trial in 1998 had concluded that this and another study had shown paroxetine did not work for children but that it would not be commercially acceptable to publicize this finding. Instead the positive findings from the study would be published; they were in an article whose authorship line contains some of the best known names in psychopharmacology (Keller *et al.*, 2001).

There has been a recent sense of crisis about the clinical trial literature. But this has not led us to address the processes that gave rise to the divide outlined above, which must be assumed to be ongoing and producing comparable divides elsewhere in psychiatry and medicine. Instead, the focus has been on whether authors declare their conflicting interests (Fava, 2007). This focus must look good to marketing departments who would prefer the field to think that our problems stem from a few corrupt academics rather than from company practices that restrict access to data while still claiming the moral high ground of science.

The irrelevance of conflicting interests can be seen from a consideration of the process of guideline creation. Recent guidelines for schizophrenia and for bipolar disorder that have been drawn up by experts funded by industry do not differ from independent guidelines (Healy, 2006b; submitted for publication). The process by which industry has captured guidelines lies not in payments to experts but rather in ensuring the published clinical trial evidence on which they are based can only permit one conclusion. Even independent guidelines for schizophrenia and bipolar disorder now advocate using on patent agents rather than older generic agents, although FDA and other regulators, who have seen the raw data, have made it clear it would be illegal for companies to make claims of superiority for newer over older agents.

But as companies have realized for some time, the regulators do not regulate academics. And guidelines drawn up by independent academics are now among the most powerful marketing tools that pharmaceutical companies have.

Part of the power in guidelines appears to stem from clinical discomfort with uncertainty, and psychiatry's perennial concerns about its status as a science. Trials in which drugs barely beat placebo on rating scale measures are read as evidence that drugs "work", when philosophically it would be more accurate to state that in fact these trials offer evidence that it is simply not possible to say the drug does nothing and that most of whatever benefit there is stems from non-specific factors (Healy, submitted for publication). The emergence of trial results indicating that drugs do something but it is uncertain just what those benefits are should, almost by definition, have marked the point at which scientific investigation of the drugs began, not the point at which independent scrutiny of the drugs in fact has finished. Is there a population within the clinical trial cohort that shows a more substantial response to this specific agent? Given that these drugs are clearly not nosolytic, what functional changes do these agents bring about that may be beneficial for some and what light do any functional changes there may be shed on the constitution of psychosyndromes?

But uncomfortable it would seem with how little we know, and unable to force companies to undertake the research clearly called for, clinicians are vulnerable to the apparent certainties offered by guidelines. Although regulators have refused to endorse claims that newer agents are superior to older agents, clinicians inhabit a world in which the academics involved in guidelines dispel any qualms they might have about using their favourite brands in preference to less expensive and possibly more effective agents.

Control of the scientific literature and the clinical trial process has enabled companies to monger diseases (Moynihan & Cassels, 2005). Disorders such as social phobia, panic disorder, and depression have been sold in the expectation that sales would follow (Healy, 1997).

Epidemiological research that establishes how many people might potentially meet criteria for particular conditions provides some of the most valuable data for this disease mongering, as Michael Shepherd, the founder of psychiatric epidemiology, has noted ruefully (Shepherd, 1998).

This selling of disorders has gone hand in hand with a marketing of risk and fear. Early hints of depression must be detected and treated in order to reduce the risks of suicide, alcoholism, divorce, and career failure and treatment must continue to reduce the risk of relapse. Where treatment of a disease might mandate treating one person per hundred, with treatment stopping once the condition responds, treatment of those at risk of a disease or its consequences mandates the treatment of one in ten, and has no natural stopping point (Heath, 2006).

But there is more to disease mongering than this. Physicians have always been able to prescribe antidepressants for minors. The significance of company efforts to seek licenses for SSRIs for paediatric depression did not therefore lie in the opportunities such licensing might have opened up for the recognition and treatment of neglected disorders. Licenses to market SSRIs for adolescent depression would have marked the point at which companies were enabled to convert the vicissitudes of childhood and adolescence into disorders to be treated rather than any enabling of physicians.

Company marketing is less and less about spreading recognition of established disorders and increasingly about pathologizing vicissitudes. A license for Viagra, for instance, became a means for companies to question young men with normal sex lives as to whether things couldn't be better. Any of life's vicissitudes are now grist to the marketing mill, and companies with a license do not baulk at changing our understanding of what it means to be human, if it captures a niche for the product. There are no academics drawing this to wider attention, perhaps because physicians in general fail to understand where disease mongering comes from.

BRAND FASCISM[1]

The opportunities to focus on brands linked to changes in patent law, a greater ease in getting patents, and an increasing control of the means of knowledge production from the 1970s onwards, set against psychiatry's internal uncertainties, have enabled pharmaceutical companies to refashion psychiatry (and much of medicine). Where once scientists and clinicians, including those linked to companies, thought about medicine and molecules in scientific and clinical terms, they have been edged out by marketers who see molecules as pawns in a game of capturing market niches. The shift has been subtle and all but imperceptible from the outside, but it has become the driving force in all that companies now do (Applbaum, 2004).

At the heart of events is the failure of physicians to understand modern marketing. Despite regular surveys from marketing companies about the properties of a desirable antidepressant or antipsychotic, and despite the participation of clinical academics in opinion leader (focus) groups, clinicians confuse marketing with the trinkets, free lunches, lecture fees, and trips to conferences, sponsored by company sales departments. They fail to see that they are the source of the knowledge that goes into creating brands and fail to see their role in virally transmitting new brands. The actual differences between modern antidepressants and modern antipsychotics are minimal; the perceived differences come almost entirely from sophisticated consumer research aimed at understanding what physicians might swallow.

In this process, academics have three roles. First, as repositories of psychiatric knowledge their role is to help companies understand what the average clinician might perceive as a development. Second as opinion leaders they help deliver the company message to non-academic clinicians. Third, they lend their names to ornament the authorship lines of journal articles and programmes of academic meetings reporting the results of the most recent company studies.

These academic meetings have come to resemble political rallies, where the faithful assemble to hear about the evils to be vanquished and the new methods to do this. It has been some time since a trace of uncertainty entered into any of our major meetings, even though we are living through a profound medical crisis in that the health of our patients is worsening (Colton & Manderscheid, 2006) and there is open debate about the corruption of our science by companies (Angell, 2005; Kassirer, 2005). The adverse effects of psychotropic agents are only aired if it suits the marketing interests of some company. Meanwhile companies have commandeered most of our platforms and journal space to present their products under the banner of science, while flouting the basic norms of science - to make data publicly available.

In the past Stalin earned the epithet of The Engineer of Human Souls on the basis of his ability to shape the way people thought, now the market leads patients to queue

[1] The term brand fascism was coined by Kal Applbaum, author of The Marketing Era.

up to confess their bipolarity or whatever is au courant. Nothing is inconceivable - not even the diagnosis of bipolar disorder in utero (Healy, 2006a).

The market arranges for the formerly independent voices of physicians to be silenced by the una duce, una voce process of guidelines. Of course guidelines state that they are not law, but any commentary on whether one must adhere to them makes it clear that any deviations without justification dramatically increase the medico-legal risks of practice (Healy, submitted for publication). And the element of coercion may soon increase with payments being linked to guideline adherence.

The market arranges for critics of current products to be marginalized or silenced in a manner that fits well with other fascist traditions. Anyone who criticizes a brand is likely to have "friends" planted in the audience to monitor what they say and if need be challenge it; is likely to have their utterances or writings scrutinized for possible legal actions; is likely to have "friends" and colleagues interrogated about their personal lives; is likely to find "friends" complain them to whatever body monitors their registration as a physician; and is at distinct risk of losing their job (Thompson *et al.*, 2001; Blumsohn, 2006a, b; Healy, 2006c). Companies are adept at manipulating the sibling rivalries inherent in academia to their own ends, making very acute the question of what is the good academic to do in such circumstances.

Aside from specific career threatening moves, some of the most powerful public relations companies on earth will take on the more general task of discrediting the critic and reversing their influence. The methods include canceling meetings where the critic has been invited to speak (Fugh-Berman, 2006), planting hostile reviews of any books they might write, and spreading the word that this person is trouble (Healy, 2004). Added to this are difficulties with even major journals that might be thought impervious to company influence. Fearful of industry, even the most distinguished journals in the field faced with articles accepted by the peer review process may hold these articles up in their legal departments for years. Alternately, where links to companies give the perception of conflict of interest that can be managed by a declaration of interests, links to a legal action on behalf of an injured plaintiff give actual conflicts of interest that require a rejection of the article.

Just as everything was crumbling behind the rhetoric of Stalinism, so also there is good evidence that outcomes within mental health are deteriorating. While the absolute numbers of patients occupying beds in asylums began to fall in the 1950s, the numbers of both voluntary and involuntary admissions per annum has been rising steadily since then. In North Wales, for instance, there has been a 15-fold rise in mental health admissions since the 1940s; compulsory detentions into mental illness units have risen three-fold; admissions for serious mental illness have risen 7-fold (Healy *et al.*, 2001; 2005). Rates of suicide for patients with schizophrenia have increased over 10-fold (Healy *et al.*, 2006), and general mortality for serious mental illness has increased (Healy *et al.*, 2005). Evidence from elsewhere suggests this mortality is likely to correlate with the numbers of psychotropic drugs given (Joukamaa *et al.*, 2006). The picture in North Wales is mirrored widely. Uniquely, among major illnesses in the Western world, the life expectancy for patients with serious mental illness appears to be declining (Colton & Manderscheid, 2006).

While changing social expectations and other social factors play some role in these deteriorating outcomes, nevertheless this profile is inconceivable against the background of current rhetoric that endorses the practice of evidence based medicine with the latest and the best treatments. The physical treatments we use and the way services are organised around those treatments cannot but play some part in these outcomes. What we are seeing now is not what happens when treatments work; it is not what happened to the dementia paralytica services after the discovery of penicillin.

REVOLUTION OR REFORMATION?

I have outlined here and elsewhere (Healy 2004) aspects of the current set-up that enables a handful of shrewd advisors and marketers, to take advantage of the immense marketing power of pharmaceutical companies, to infect academia and health care with an academic immune-deficiency virus (AIV). The defense reactions that might have been expected from prestigious journals and professional bodies in response to the virus seem to be paralyzed. Quite the contrary the virus seems to have been able to subvert normal defenses to its own purposes. These defenses have reacted almost as though it was their programmed duty to shield a few fragile companies from the malignant attentions of a pharmacovigilante.

Our professional organisations as clinicians, scientists and academics need to take stock of the current situation and engage with the new corporate campus. Our major journals and academic meetings need to do more or they risk losing brand value.

Given an increasing company focus on lifestyle markets rather than on treatments for serious diseases either in the West or elsewhere, one option might be to attempt

to separate a more traditional medical market from an enhancement market, with a variety of physicians, but perhaps psychiatrists in particular, having to choose between being doctors or lifestyle engineers.

Another way forward lies in the recognition that drugs are not made in company laboratories - chemicals are. In order for a drug to come into being, two things have to happen. First, healthy volunteers and later patients in clinical trials agree to take these chemicals to see what happens. Willingness to participate in these studies was borne out of the global calamity of World War, when conditions of scarcity mandated the development of the first controlled trials. We participated on the basis that taking risks might injure us but would benefit a community that included our friends, relatives and children. We did so for free. At first this worked and extended the compass of human freedom from the epidemics and other scourges to which our ancestors had been subject for millennia.

But now this data freely given is sequestered by corporations who market selected parts of it back to us under the banner of science. This business model has made these corporations the most profitable on the planet. This model however, at least within psychiatry, is one that demonstrably jeopardizes the health and well being of our friends, relatives and children.

Second, companies take the inner aspirations and fears of both patients and psychiatrists to transform a chemical into a drug and also to mould a strategy designed to get patients to consume drugs more faithfully than they would do if they were living in a totalitarian regime and were ordered to consume. This is what branding and patenting is about. It yields the biggest profit margins in history, significant amounts of which go to ensuring a continuing hold on academic minds, and through academics the public mind.

There are both ethical and scientific grounds to object. It is not clear that companies own the data of clinical trials other than by force majeure. Whether they do or not, it is time for clinicians to consider whether it is ethical to enter their patients into such "exercises". The consent form should at the very least contain an explicit statement that the company may sequester any data from the trial, rendering it unavailable for scientific use. It is unlikely that patients currently entering trials know this, or would accept involvement in trials on this basis.

The scientific grounds to object lie in the fact that current academic practices breach the norms of science by not making data available. If we are to be scientific we must object. This can only be good for both psychiatry and companies in that a psychopharmacology of the sort we now have will inevitably be sterile and is only capable of rescue by the serendipitous discovery of new agents.

In objecting, it may be possible to ally with scientists and clinicians working within pharmaceutical companies who for the last two decades have been even more aware than clinicians about how marketing has changed the character of their roles. Many of them would wish to see these developments undone.

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