

Methodological mimesis and the value of pharmaceutical failures

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Recent controversies over the safety of drugs such as Vioxx, a painkiller manufactured by Merck, and Seroxat, an SSRI antidepressant manufactured by GlaxoSmithKline, have led to a consequence that at first seems entirely positive: they have attracted more attention to the suppression of negative clinical trial data by industry and academic researchers, helping to establish clinical trial registries where randomized controlled trials (RCTs) must be registered at their outset.

In this paper, through a focus on debates over the safety of selective serotonin reuptake inhibitor (SSRI) antidepressants such as Seroxat, I examine recent efforts to provide more public access to clinical trial data, documenting how, despite declarations of their commitments to openness, pharmaceutical companies have found ways to evade the need to publicly disclose trials. Secondly, I suggest the emphasis on securing more access has fostered the adverse effect of deflecting attention from methodological limitations within studies that are widely available. Drawing analogies to work by Bourdieu, I argue that a paradoxical consequence of the demand for more access is the tendency to solidify faith in the moral authority of RCTs, something that inadvertently

strengthens the authority of those, such as regulators and industry groups, which withheld RCT data to begin with.

I suggest it is the very limitations of RCTs – their inadequacies in producing reliable evidence of clinical effects – that help to strengthen popular and scientific assumptions of their superiority as methodological tools. This point sheds light on the question of why systems widely recognized to be ineffective often assume greater authority at the very moment when people speak of their dysfunction.

GlaxoSmithKline, Seroxat and access to data

Although researchers such as Iain Chalmers, a co-founder of the UK Cochrane Collaboration, have argued for over two decades of the need for more access to RCTs (Chalmers 2006, 1990; Roberts et al. 1998), there was little political impetus to insist companies disclose data until cases such as GlaxoSmithKline (GSK)'s suppression of Seroxat data, its bestselling antidepressant, drew public scrutiny to the pharmaceutical industry's tendency to disclose only favourable clinical trials.

Suspicious that GSK suppressed clinical trial data led to legal actions in the UK, where the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK equivalent to the US Food and Drug Administration (FDA) launched a criminal investigation in 2003 to ascertain whether GSK had withheld information on the drug's effect, and in the United States, where the former New York Attorney General Eliot Spitzer launched a lawsuit in August 2004 accusing GSK of consumer fraud by depriving consumers and doctors of information necessary to make informed decisions (Lancet 2004). GSK later settled out-of-court with Spitzer, refusing an admission of wrongdoing,

but agreeing to pay a fine of \$2.5 million. In the UK, after a nearly four-year investigation, the MHRA announced that although GSK had acted, in the view of regulators, *unethically* by internationally withholding clinical trial data on the efficacy and safety of Seroxat, the agency did not have the legal means to prosecute the company, because of previously undetected loopholes in the UK's 1968 Medicines Act (MHRA 2008).¹

The case of Seroxat reinforced calls for more equitable access to clinical trial data, calls that at first seemed answered by the pharmaceutical industry's insistence that it would voluntarily post details of trials on databases managed by industry, as well as by the UK Labour Party's insistence, in its 2005 election manifesto, that it would pass laws to ensure industry complied with the need to register trials.

In recent years, it has been apparent these initiatives have failed to produce many practical changes. As Tim Kendall, co-director of the UK National Collaborating Centre for Mental Health said to me during an interview in December 2006:

TK: The Labour government stated in their manifesto for the last election that they would make it mandatory for drug companies to publish their trials. It has not become mandatory in any meaningful way. Indeed, although the ABPI [Association of the British Pharmaceutical Industry] asserts that drug companies do publish all completed trials, it is impossible to prove whether or not this is happening. Eli Lilly do list large numbers of trials on their website, many of which have not been published... However, there are a growing number of trials referred to as 'ongoing' and some of these have been 'ongoing' since 2000. Perhaps 'ongoing' has now replaced 'unpublished.'

A separate but related barrier facing access to data is that, as the UK health minister noted in February 2008, EU legislation prevents the UK government from

¹ For details of the legal ramifications of GSK's suppression of data for Seroxat (manufactured as Paxil in the United States), see McGoe, L. and Jackson, E.'s (2009) "Seroxat and the suppression of clinical trial data: regulatory failure and the uses of legal ambiguity." *Journal of Medical Ethics* 36(2): 107-112.

delivering on the Labour party's 2005 election promise and forcing companies to publicly disclose all clinical trial data (Rose 2008).

Frustrated with the ineffectiveness of current systems of disclosure, public health scholars in the United States have called for a "Sarbanes Oxley for Science," a reference to US securities legislation passed in the wake of the Enron and Worldcom scandals in the early 2000s. The fraud committed at Enron, Worldcom and other companies led to creation of the 2002 Sarbanes Oxley Act, the largest overhaul of corporate governance securities legislation since the Securities Exchange Act of 1934 (Paredes 2003; Heminway 2003). Sarbanes Oxley enforces a number of new regulations, such as the need for the Chief Executive Officer and Chief Financial Officer of publicly listed companies to verify the truthfulness of a company's financial certificates, risking criminal penalties if found guilty of fraud. Scholars such as David Michaels have suggested that developing parallel legislation – a "Sarbanes Oxley for Science" – would help tackle the problem of the underreporting of clinical trials at places such as GlaxoSmithKline (Michaels 2006):

When the Enron and WorldCom scandals were revealed, the executives of those firms claimed that they were unaware of the accounting misrepresentations in which their companies were engaged...At present, there is virtually no oversight or independent review of corporate decisionmaking as it relates to the sequestration of scientific data. An important lesson of the accounting scandals is that responsibility must be linked with accountability; this should apply to scientific as well as financial data (Michaels 2006: 16).

Michaels suggests a Sarbanes Oxley for Science "would require corporations to designate a person responsible for reporting the results of studies undertaken by the firm" (Michaels 2006: 16), as well as ensure more access to the raw data – anonymized data on

patients participating in trials – in both industry-sponsored and publicly funded clinical trials.

Although his proposal has some merits, it also raises a number of problems with calls in general for more access to clinical trials data. The first problem is Michaels' implication that mere access will foster the ability of regulators to act on data that *is* disclosed. In the case of the SSRI controversy, access to data alone was not sufficient to ensure prompt regulatory action. Institutional factors, such as the UK regulator's 100 per cent funding reliance on industry for the service of licensing medicines, seem to have compounded the inability of the MHRA to access swiftly in publicly disclosing data which it did receive from industry (McGoey 2007).

The case of SSRIs is similar to Enron, where some suggest that problems emerged not simply from Enron's refusal to disclose accurate financial statements, but also from the inability of financial analysts and other financial actors to effectively interpret data that was available, something perversely compounded by an *excess*, rather than a lack, of information (Macey 2003; Gladwell 2007):

In the case of Enron, it was well known to many, especially to insiders, that the company and its reported growth were problematic and the collapse in retrospect was perhaps predictable, just as the fact of the September 11 attack on the US (if not the timing) is being reported in hindsight as predictable. But for the institutional actors at the time (financial analysts, accountants, FBI, CIA) it is necessary to understand the conditions under which such predictions and warnings could not be uttered, or if they were, could not be heard and processed (Hutter and Power 2005: 12).

There are numerous parallels between Enron and the SSRI case. For example, from the early 1990s onwards, as a result of anecdotal evidence from physicians that suggested SSRIs were contributing to suicidal reactions in some users, the MHRA conducted more than six internal inquiries in order to determine the safety and efficacy of

SSRIs. During a 2003-4 investigation into the safety of SSRIs, the MHRA discovered that daily doses of SSRIs of more than 20 milligrams were no more effective at treating depression, regardless of its severity, than doses of 20mgs or less. At the time 17,000 individuals in Britain were receiving daily doses of SSRIs at 30, 40 or 60 mgs, therefore increasing their risk of suffering adverse effects, without any improvement in efficacy. This newfound understanding about the ineffectiveness of higher dosing levels was not prompted by newly submitted information, but from a *reanalysis* of clinical trial data which had been in the MHRA's possession for over ten years, and which the MHRA had either not detected, or been unable to act on publicly, at an earlier time (McGoey and Jackson 2009).

Difficulties in interpreting data are compounded by numerous methodological limitations of RCTs for psychiatric drugs, such as the limitations of rating scales in measuring responses to medication, and biases stemming from patient recruitment criteria, that make it difficult to determine the safety and efficacy of drugs such as Seroxat when distributed among a clinical population, even when clinical trial data is widely available. In the next section, I briefly examine such methodological limitations, before discussing why such limitations have the adverse effect of solidifying, rather than indicting, the value of RCTs in determining a treatment's efficacy.²

The limits of RCTs in psychiatry

In order obtain a product license for a new pharmaceutical, or to extend the use of an existent product to a new indication, manufacturers must submit a certain number of

² The following description of methodological limitations is a cursory one, touching on just recruitment bias and problem with ratings scales. Numerous other factors, such as endpoint recording; placebo response (For an overview of some of the politics and implications of placebo use in trials see Wahlberg 2008); and discrepancies between statistical significance and clinical efficacy, have a bearing on the value of the evidence derived from RCTs.

positive RCTs to regulators. The need to test products via the methodology of RCTs raises specific challenges, as Andrew Lakoff notes, for the field of psychiatry, where the process of diagnosing patients often varies between different clinical observers, making it difficult to find a standardized group of subjects eligible for enrolment in a clinical trial.

In response to this, researchers developed rating scales, such as the Hamilton Rating Scale for Depression, where behaviour and mood is codified and categorized according to standardized checklists. Patients receive a score for responses to questions about mood, insomnia and so on – and the final score is used to help determine the severity of a patient’s illness. By translating “subjective experience into quantitative cut-off points and outcome measures, [rating scales] make it possible to assemble and compare groups of patients across sites and between evaluators” (Lakoff 2007: 58). Even though manufacturers “are quite sceptical about the capacity of the standard rating scales to produce a consistent patient population for testing... and also that the scales are applied inconsistently by raters,” they must adhere to regulatory demands to demonstrate a consistent drug response (Lakoff 2007: 65).

Often, as psychiatrists have described to me during interviews, standardized scales are imported to a trial without adequate consideration of whether the measurements are appropriate for the age of the subjects in a trial. One psychiatrist I spoke with in March 2005 suggested that in examining SSRI trials in children, the MHRA did not take into account whether the measurement tools used in some of the studies were appropriate for a paediatric population. In some cases, three-year-old toddlers were given written questionnaires to read and respond to:

I did try and question the MHRA about the assessment tools they used in these trials, where they’ve got very young children. Because with very young

children, you do not give them questionnaires. You give them picture questionnaires. Because, you cannot assess a fifteen year old in the same way as you would assess – if you can believe it, some kids as young as three had [written questionnaires]...But [the MHRA] were not won over to tell me what the assessment methods were.

When designing an RCT to test a new antidepressant, the demands of selected a standardized group of patients are complicated by the requirements of ethical review boards in North America and Europe, which often stipulate that the more severe a person's disorder, the greater the ethical duty to avoid placing such a patient in a randomized trial (Miller and Brody 2002; Miller and Silverman 2004). In recent years, ethical review boards in the US and UK have sought to adhere to statutes such as Helsinki by demanding that researchers curtail the use of placebo in clinical trials, as well as avoid recruiting subjects at the severe end of a disorder.

A result of the stipulation against placebo use, as a psychiatrist based at the University of Oxford described during an interview in February 2005, is that much of the available RCT data for antidepressants is “necessarily skewed towards the relatively mild, trouble-free end. Because they're the only people that it's actually ethical to put in.”

Another psychiatrist, who holds a senior position at the UK's Royal College of Psychiatrists, mentioned the same problem: “you almost have to be well in the States to get on a trial. Because if you've got anything wrong with you, you get excluded.”

An epidemiologist I spoke with said he found it unsurprising that antidepressant trials had not shown the suicidal risk later suspected by practicing clinicians because “they select out all the suicide people. That's what you do in clinical trials. There's nothing underhand about that.” There may be nothing underhand about that tendency, but

it does raise the question of the usefulness of RCTs in determining clinical effects among patients routinely excluded from trials for ethical reasons.

To researchers and clinicians, these points are not surprising. If anything, the opposite is true: what is surprising is how mundane such methodological obstacles appear to those conducting and implementing RCTs. The question, though, is why such mundane difficulties are difficult to challenge except with recourse to the very methodological tools found wanting to begin with.

RCTs and the complicity of failure in cementing authority

During controversies over the safety of pharmaceuticals, individual criticisms of RCTs, in order to be viewed as legitimate challenges, often have to be corroborated with reference to RCT data that contests earlier studies, something that inadvertently the strengthens the authority of the methodological tools which failed to produce reliable evidence in the first place. This point helps to address the question of why controversies from seemingly antithetical parties – such as those who insist on the need for more access to data, and those who insist on the commercial imperative to withhold trials – tend to strengthen the rhetorical and practical authority of a particular methodology or system at the very moment when that system is subject to escalating public scrutiny and attack.

An analogy can be drawn to work by Bourdieu, who suggests, in the essay “Rethinking the State: genesis and structure of the bureaucratic field,” that state injunctions owe their obviousness, and thus their potency, to the fact that the state has sought to impose the very cognitive structures through which it is perceived. He suggests that people respond doxically, or pre-reflexively, to a social world riddled with “calls to

order,” and argues this pre-reflexive submission helps to explain the ease with which the state maintains its monopoly over physical and symbolic violence (Bourdieu 1999: 69).

From this insight, I draw a simple but useful point. It is within the nature of any authoritative power to influence and prescribe even the forms of resistance which that authority has engendered in the first place. An invulnerability of method emerges, something I term “methodological mimesis.” A reason for this is that the personal illusion of individuals, or their shared sense of investment in the rules of a game and its outcome, tends to structure resistance to the game itself according to certain tacit assumptions (Bourdieu 1992: 66). An example appears in Bourdieu’s analysis of the Barthes-Picard Affair in France, where he analyzes the debates between Roland Barthes and Raymond Picard, two literary critics who differed in their interpretation of Racinian tragedy. For Bourdieu, despite their apparent conflict, a shared faith of both scholars was their belief in the value of studying classical French thinkers such as Racine. Thus “behind their apparent dispute lay a certainty ‘complicity,’ ‘the *consensus* in *dissensus* which forms the unity of the intellectual field” (Lane 2000: 73; see also McGoey 2009).

The mimetic power of dominant methodologies is comparable to what Michael Power, a theorist of risk and accounting, describes as the opacity of auditing processes. “Audits,” Power argues, have a “remarkable capacity of being invulnerable to their own failure.” When attention turns to isolated audit failures, individuals are typically blamed instead of the circumstances in which they worked.

Rightly or wrongly, corporate collapse is always accompanied by scrutiny of the role of the auditors and, in some cases, litigation on the grounds that they have performed their task negligently. One of the surprising features of these experiences is that they tend not to call into question the role of the audit itself. Instead, where audit has failed, the common response has been to call for more of it. Indeed, the

great puzzle of financial audit is that it has never been a more powerful and influential model of administrative control than now, when many commentators talk of an auditing crisis (Power 1994: 7).

Financial or pharmaceutical failures are useful, in other words, for the authorities which preside over those failures. What has rendered RCTs for psychotropic drugs so invulnerable to the widespread recognition of their inadequacies? Why is the authority of RCTs augmented, rather than diminished, the more people point out the deficiencies within individual studies? One answer lies in the influence of methodological mimesis. The solution to failed audit is more audit. The solution to failed RCTs is more RCTs, their shortcomings magnified through techniques such as meta-analyses which aggregate individual studies, strengthening the authority of methodologies that led to failure in the first place.

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