The Antidepressant-Suicide Controversy: A Study of the Scientific Rhetoric of Risk

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Abstract: This paper extends inquiry into pseudo-controversy through investigation of a case that discounts evidence in the interest of maintaining risky state of the art practice. The controversial relationship between antidepressant medication and suicidality is examined. When imipramine, the first tricyclic antidepressant, was first described in the scientific literature in 1958 by Roland Kuhn, an increased risk of suicide was documented as a side-effect. Since then, there has been increasing evidence that a wide range of psychiatric medications can cause reactions in certain patients—particularly children—that if left unchecked can lead to suicidal ideation and, sometimes, successful suicide attempts. When Prozac became a household name in the early 1990s and the market for antidepressants expanded to an ever-widening range of stakeholders, many of whom were not severely depressed, what was initially a scientific/clinical issue acquired financial and public relations implications, systematically distorting scientific discourse in a way that prolonged and intensified the ensuing public controversy. In May 2007, this culminated in the FDA requirement that antidepressant medications carry a ‘black-box warning’ describing the risk, which remains controversial. We catalog the public arguments on both sides of the issue, and explore the use of statistical arguments by agents of pharmaceutical companies in their efforts to deny a link between their product and suicide, and the various transformations these arguments undergo as they move into the public sphere.
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Leah Ceccarelli (2011) has turned attention toward the realm of pseudo controversy in specific cases where dissensus has been falsely extended in the public sphere. This case mirrors the problem in reverse. The inquiry takes up risk and the politics of the supplement; that is, the justifications for benefits and risks to the individual seeking to modify the material conditions of the body with health enhancing drugs. The symbolic regulation of risk on the industry is matched to the information given to the consumer. Safety is a matter of research determination, matching theories of effect with cases defining outcome. In this case, we find an instance where strategic institutional discounting of arguable effects has produced state-of-the-art rationales for needed research and to stigmatize publically criticism and its engagement. An anecdote starts us off.

In 1999, the University of Toronto’s Department of Psychiatry recruited Dr. David Healy for the position of Clinical Director of their Mood and Anxiety Disorders Program. On November 30 of the following year, Healy, who had accepted a formal job offer, was invited to give a lecture entitled “Psychopharmacology and the Government of Self.” In this lecture, Healy presented several pointed criticisms of the pharmaceutical industry and its research practices, challenging the adequacy of randomized controlled clinical trials, the ethics of ghost-written scientific literature, and the scientific validity of meta-analyses given the widespread suppression of data from unsuccessful trials on the one hand and the multiple reporting of data from successful trials on the other. These practices, Healy contended, enabled dangerous side effects to go unnoticed, specifically citing the relationship between the selective serotonin reuptake inhibitor [SSRI] class of antidepressants and suicide. Comparing the pharmaceutical industry to the tobacco industry, Healy (2000b) argued:
In the case of tobacco industry, it now seems clear that the legal advice in the face of the problems of smoking was not to research the hazards of smoking, as to do so would increase the legal liabilities of the corporations involved… And the same lawyers who advise the pharmaceutical corporations are the lawyers for the tobacco corporations… Advice like this would convert prescription-only arrangements into a vehicle to deliver adverse medical consequences with legal impunity. Prozac and other SSRIs can lead to suicide. These drugs may have been responsible for 1 death for every day that Prozac has been on the market in North America. In all likelihood many of you will not agree with me on this – you haven’t seen the information that I have seen. However we can all agree that there has been a controversy about whether there may be a problem or not. What I believe you will also have to agree with is the fact since the controversy blew up, there has not been a single piece of research carried out to answer the questions of whether Prozac does cause suicide or not. Designed yes, carried out – no. (para. 53–54)

In the week following the talk, Dr. Healy was notified by e-mail that his job offer had been rescinded, as David Goldbloom, Professor of Psychiatry and Physician-in-Chief at Toronto’s psychiatric hospital, had come to believe that Healy’s “approach is [not] compatible with the goals for development of the academic and clinical resource that we have,” a view that was “solidified by your recent… academic lecture” (Goldbloom, 2000).

The University of Toronto had just emerged from a high profile international battle involving Nancy Olivieri, a hematologist at the university’s Hospital for Sick Children, who fought for three years to keep her job after she, following the instructions of the institutional review board, informed patients involved in a trial of deferiprone (a treatment for the blood disorder thalassaemia) of emerging data suggesting a risk of liver toxicity, which lead Apotex, the maker of deferiprone, to prematurely end the study and to threaten legal action against her for violating a confidentiality agreement (Olivieri, 2003).¹ Eli Lilly, the manufacturer of Prozac, provided more than half of the funding for the Mood and Anxiety Disorders Program, and had recently donated $1.5 million to fund the ‘Eli Lilly Education Centre’ at the university’s

¹ The controversy surrounding Olivieri took a bizarre turn when, after the discovery of DNA evidence, two of her senior colleagues (who did not have to fight for their jobs) were linked to the volumes of hate mail (including lines like: “You cannot overestimate the amount of contempt, appaul [sic], and mistrust we have towards you”) she began receiving subsequent to her disclosure of the possible risks of deferiprone (Birmingham, 2000).
psychiatric hospital. Only a few months earlier, Lilly revoked funding from an unrelated clinic that published an article suggesting a link between Prozac and suicide. Against this background, Robert Birgeneau, then-president of the University of Toronto, insisted that the decision to revoke Dr. Healy’s job offer was “not influenced in any way by Eli Lilly or by any other pharmaceutical manufacturer” (Booth & Turk, 2001; Swiatek, 2001). Dr. Healy subsequently sued the University of Toronto for $9.4 million; the lawsuit was later settled for an undisclosed amount.

This blatant assault on academic freedom illustrates the extent to which the pharmaceutical industry influences and systematically distorts the scientific process of knowledge production in the field of psychopharmacology. In this case, a scientist was disciplined for the crime of asserting the existence of a controversy and identifying as suspicious the field’s failure to conduct research that could answer the basic question motivating the controversy. In public scientific controversies, which have epistemic, juridical, and ethical dimensions and which “embed epistemological disputes over knowledge-claims within pragmatic contexts of public opinion formation in order to achieve intersubjective consensus on broad-based policies that are legitimated through the shared understanding of complex problems,” the problem of systematically distorted communication is ever present (Crick & Gabriel, 2010). Technical systems operate according to their own unique instrumental logics, imperatives, and levels of tolerance for uncertainty and risk, and the discourses that circulate throughout can become systematically distorted through the exploitation of deficient integration between systems (Habermas, 1985). When the effects of this process become publicly salient in the “life-historical background of violated interests and threatened identities,” a public controversy can arise that may provoke legitimation crises for the institutions involved at the
intersection of the relevant technical systems (Habermas, 1996, p. 351).

Institutions set standards for normal and exceptional practice, and tend to resist critique most severely from within. David Healy is not an outsider associated with the anti-psychiatry movement, but a practicing clinical psychiatrist, author or co-author of 20 books and over 150 refereed scientific articles. In his inaugural lecture, Healy deliberately defied a social taboo against the public discussion of the ethically and scientifically dubious practices of a corporate sponsor. This can be understood as the opening breach of a social drama, a “public [episode] of tensional irruption,” with the potential to “widen and extend until it becomes coextensive with some dominant cleavage in the widest set of relative social relations to which the conflicting or antagonistic parties belong” (Turner, 1978, pp. 35, 38; 1988). The crisis phase of a social drama is “a stage of turning points full of moments of danger and suspense, where people start to speak the truth about the real state of affairs and where it is no longer possible to wear masks and pretend that nothing is wrong” (Nell, 2011, para. 11). Healy’s lawsuit against the University of Toronto marks the third redressive phase, which is followed by an attempt to “reintegrate opposing forces into a new status quo” (Gross, 2005, p. 43). In this way, David Healy’s Toronto affair is synechdochic of the larger social drama that began shortly after Eli Lilly won FDA approval for Prozac in 1987 and was still ongoing 20 years later in 2007 when the FDA instituted a mandatory ‘black box warning’ for antidepressant medications describing the increased risk of suicidality in children and adolescent patients.

The controversy concerns the material relation of state-of-the-art practices to adverse outcomes, and how authorities (regulatory, with the public; scientific, with other scientists; and clinical, with patients) should communicate about the associated risks and benefits. Adverse

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2 This is not counting articles ghost-written for him in his writing style that he declined to attach his name to and were subsequently ‘authored’ by others (Healy, 2004; Healy & Thase, 2003).
outcomes can be contextualized as either a) expected and bad, but understood relative to the outcome of inaction; or b) as self-serving risks in which costs are born by one group while profits are enjoyed by another. The contested framing of state-of-the-art risks occurs at “a crucial nexus between the scientific and public spheres [which] exists precisely at those points where scientific theories and research programs have implications for prevalent world views, ideologies, and practical social policies” (Czubaroff, 1997, p. 52). Though the manifest concern is the safety of a consumer product, the controversy involves larger latent issues—the nature of depression as a discrete disease entity and the antidepressant as a medical treatment (and not a lifestyle-enhancing supplement), the rhetoric of the body and the application of categories to describe changing conditions of affect (defined as mood disorder), and the direction of presumption and stasis regarding uncertainty and violence in our contemporary risk society.

*Early Antidepressants*

Before outlining the contours of the controversy, it is worth asking what was known about the putative link between antidepressants and suicidality before the advent of the SSRIs, and how long the issue has been on the horizon of psychopharmacological research. Though the biological effects of antidepressant therapy are more or less the same as they were a half-century ago when the first antidepressants were developed, the socio-cultural-institutional environment was such that what was controversial in the 1990s was not so in late 1950s – early 1960s. The therapeutic effects of imipramine (better known by the trade name Tofranil), the first tricyclic antidepressant [TCA], were first described by Roland Kuhn in 1958, who had used the compound to treat over 500 cases of depression over a two year period. Kuhn identified several “relatively slight” side effects that he had observed clinically: dry mouth, tachycardia, sweating, and other anticholinergic effects; hypotension; agitation; mania; and psychosis (Kuhn, 1958, p.
460). Of greater concern to Kuhn was

…whether, and to what extent, imipramine hydrochloride influences healthy impulses of conscience, consciousness of guilt and resistance against criminal or immoral actions… [If] a medicament such as imipramine hydrochloride exerts an effect on mood and possibly provokes manic-like reactions, then it must be expected that in certain persons their moral structure may be imperiled. The inhibition against committing suicide must also be seen in this light; just as in the spontaneous course of a depression, phases occur in which resistance against suicide is lessened, during the course of imipramine hydrochloride treatment there may be an increased risk of suicide. It is essential to take this into account, and in spite of the possibilities which imipramine hydrochloride offers, to commit to an institution patients who are endangered in this way.³ (pp. 463-464; our emphasis)

Indeed, in other discussions of antidepressant therapy in the scientific literature over the subsequent few years, the importance of considering the possibility that the drug could increase the risk of suicide, particularly given the possibility that a patient could use the drug to commit suicide by taking a large overdose, was almost taken for granted. The phenomenon, and a possible explanation, was widely documented; five years after Kuhn’s initial report, Kristiansen (1963) described the case of a patient “in whom no change was observed, but 3 days after the commencement of the treatment he attempted suicide, and this may, as has so often been maintained, be expressive of a decrease in the inhibition at the same time as the depressive mood remains unchanged” (p. 237; our emphasis).

One could argue that the link between antidepressants and suicide was identified before their identity as antidepressants was established. The serendipitous discovery of the monoamine-oxidase inhibitor (MAOI) class of antidepressants occurred after it was observed that

³ Kuhn was pleased to note, however, that he did not observe “any particularly striking signs of interference with ethical or moral standards,” a point he illustrated with an example of a depressed patient who had committed “homosexual offenses” – his depression remitted within three days of treatment, but there remained “a perfectly adequate sense of his own moral failure and to a natural reaction of repentance,” and indeed “[the] homosexual desires became strikingly less prominent during treatment… [Substances] such as imipramine hydrochloride need not necessarily seriously impair a patient’s moral attitude and sense of judgment” (p. 464). As this study suggests, antidepressants do in fact have the tendency to disrupt healthy feelings of guilt concerning moral failure – but this side effect afflicts the agents of pharmaceutical companies that sell the antidepressants rather than the patients who are treated with them.
tuberculosis patients receiving isoniazid became strangely happy despite their illness; as reported on the front page of the *New York Times*, the patients adopted “a normally optimistic instead of a depressed attitude… [suggesting] the use of the chemical in conditions other than tuberculosis” (Laurence, 1952). A closely related compound, iproniazid, was developed by the pharmaceutical company Roche in order to compete with isoniazid as a treatment for tuberculosis. Around the same time, a psychiatrist named Nathan Kline had been studying the tranquilizing effects of reserpine, a compound that had been identified in 1953 as the active component of a root used in traditional Indian ayurvedic medicine. A small percentage of patients given high doses of reserpine for hypertension became sad and anxious, exhibiting crying spells and having suicidal thoughts (Lemieux, Davignon, & Genest, 1956). Though the same could be said of all antidepressants, and though reserpine was actually the first compound ever shown in a randomized controlled trial to be an effective antidepressant (Davies & Shepherd, 1955), this side effect was interpreted as drug-induced depression. It was then discovered that reserpine did not have a tranquilizing effect on animals pretreated with iproniazid, apparently due to the inhibition of the enzyme monoamine oxidase (Chessin, Dubnick, Kramer, & Scott, 1956). On the basis of this finding Nathan Kline approached Roche in 1956 with a proposal to administer iproniazid to depressed patients, leading to its later marketing as a ‘psychic energizer,’ a term fiercely advocated by Kline, though it never caught on and was eventually eclipsed by the term ‘antidepressant’ (Healy, 1997; Loomer, Saunders, & Kline, 1957).

Two years before that, however, a report was published describing a tuberculosis patient who became suicidal very shortly after receiving isoniazid: “Always considered a quiet, cooperative, well-behaved patient… on Feb. 5, 1952, she was placed on isoniazid and on May 9, 1952, she suddenly tried to commit suicide by jumping out of the window and was found to be
acutely disturbed, dazed, apprehensive, and complaining of auditory hallucinations” (Pleasure, 1954, p. 316). This case is particularly noteworthy because it is impossible to blame the suicide on an underlying depressive disorder, the preferred strategy adopted in the 1990s by pharmaceutical companies attempting to raise doubt about the side effect. The side effect was uncommon, but when it occurred, there was “unequivocal evidence” that the drug was the cause, “including a fairly sudden onset after a period of drug therapy, with clouded sensorium, agitation, and auditory and visual hallucinations… [The side effects] rather quickly cleared up as soon as the drug was discontinued” (pp. 315-316).

Prozac

In December 1987, about thirty years after the first antidepressants were discovered, Eli Lilly received approval from the Food and Drug Administration [FDA] to market the compound fluoxetine, better known by the trade name Prozac. Fluoxetine belonged to a new class of antidepressants, the SSRIs, which operate primarily on the serotonin [5-HT] system. Though not more effective than older antidepressants in the treatment of depression (with the possible exception of depression presenting with high anxiety), the SSRIs have less toxic side effects and are less capable of facilitating suicide by overdose. Their introduction was heralded as a revolutionary advancement in the treatment of depression. Prozac became a media event, appearing on the front covers of Newsweek, Time, and New Yorker, in the play Prozac sisters, the video game Virtual Prozac, and in psychiatrist Peter Kramer’s (1993) best-selling Listening to Prozac: A psychiatrist explores antidepressant drugs and the remaking of the self, helping Prozac sales reach a record $1.2 billion that year (Montagne, 2001). 4 The next year, Elizabeth Wurtzel’s memoir Prozac nation was published and was later made into an independent film.

4 To put this number in perspective, consider the fact that in 1987, the year Prozac was introduced, the entire market for all antidepressants combined added up to just over $300 million. By the time the patent expired in 2001, Lilly had made more than $21 billion in Prozac sales (McLean, 2011).
Routinely described in the popular press as a ‘happy pill,’ a ‘wonder drug,’ and the ‘feel-good pill,’ Prozac became the most well-known brand name in psychiatric medicine, fully saturating the everyday lifeworld consciousness of the public (Montagne, 2001). Unlike previous psychiatric media events like Valium and Miltown (the ‘penicillin for anxiety’) or electroconvulsive therapy (as depicted in cultural artifacts like One flew over the cuckoo’s nest) in which the treatments were almost exclusively framed negatively, the coverage of Prozac was largely positive during this period (Healy, 1997). The notion that we had entered a new era of ‘cosmetic pharmacology’ (in which psychiatric medication could be used to change patients “not just away from illness but toward some desirable psychological state”) lead to suggestions that all sorts of people who might not self-identify as ‘depressed’ might benefit from trying Prozac as a ‘personality enhancer’ (Cowley & Springen, 1990, p. 38).

One topic that was not featured prominently in the initial popular coverage of Prozac was the possible side effect of suicidal (or homicidal) ideation. In 1987, the year Prozac received regulatory approval, two patients (one of whom had no history of depression) involved in a trial of fluoxetine for panic disorder developed suicidal thoughts (Gorman, Liebowitz, & Fyer, 1987).
In February 1990, a collection of case reports was published describing patients that developed “intense, violent suicidal preoccupation after 2-7 weeks of fluoxetine treatment… [which] persisted for as little as 3 days to as long as 3 months after discontinuation of fluoxetine” (Teicher, Glod, & Cole, 1990, p. 207). While previous accounts of antidepressant-related suicidal behavior situated the side effect as a product of the removal of inhibitions, enhancement of drive, and counteracting of psychomotor retardation among patients who were suicidal to begin with, these case reports were unique in that fluoxetine seemed to provoke severe and intense thoughts of suicide in patients who never had such thoughts before treatment:

In no case was there evidence that strong preexisting self-destructive urges were activated and energized by fluoxetine. No patient was actively suicidal at the time fluoxetine treatment began. Rather, all were hopeful and optimistic, and the strong obsessive suicidal thoughts apparently emerged de novo after weeks or months of treatment. In four patients… these thoughts were accompanied by abject acceptance and detachment. Two patients… tried to conceal their suicidal feelings and impulses and to continue fluoxetine treatment, believing that the drug would eventually enable them to successfully kill themselves! …[We] were especially surprised to witness the emergence of intense, obsessive, and violent suicidal thoughts in these patients. Their suicidal thoughts appear to have been obsessive, as they were recurrent, persistent, and intrusive. They emerged without reason but were the patients’ own thoughts. It was also remarkable how violent these thoughts were. Two patients fantasized, for the first time, about killing themselves with a gun… and one patient… actually placed a loaded gun to her head. One patient needed to be physically restrained to prevent self-mutilation. [Another patient], who had no prior suicidal thoughts, fantasized about killing himself in a gas explosion or a car crash… In our own experience, this side effect occurred in 3.5% of patients receiving fluoxetine. (pp. 209–210)

A similar study involving children (aged 10-17) undergoing fluoxetine treatment for obsessive-compulsive disorder who developed suicidal thoughts and self-injurious behavior was published the following year (King et al., 1991).

These reports were surprising both for their intensity and because they ran counter to theoretical expectations. The mechanism by which the older antidepressant drugs were thought to promote suicidal tendencies was the inhibition of the reuptake of noradrenaline, a
neurotransmitter which scientists believed to “regulate the impetus or drive, whereas serotonin (5-HT), the other monoamine of the ‘serotonin-noradrenaline link hypothesis of affective disorders,’ …seems to be more involved in mood regulation,” which lead to the prediction that “selective inhibitors of 5-HT… should be preferable in patients with high suicide risk” (Feuerstein & Jackisch, 1986, p. 422). The existing neuro-biological theories of depression could not explain why a serotonergic drug with no direct effect on noradrenaline neurotransmission would cause some patients to develop violent suicidal thoughts and behaviors. Psychopharmacologists were further nonplussed by the phenomenon due to the prevailing belief that central serotonin hypofunction is the primary biological factor in suicide (Bourgeois, 1991).

These early reports of suicidality as an adverse effect of fluoxetine were met immediately with intense, obsessive, and persistent criticism. When mentioned in popular media, the risks were discounted. For example, a *Time* magazine story in July 1990 quoted Paul Leber, director of the FDA’s neuropharmacology division, arguing that “[even] if we got several hundred reports involving suicide and Prozac, we wouldn't be alarmed, given how many people use the drug and the nature of the disease… Depressed people commit suicide;” the article’s conclusion was that people should not be “scared away” from this “wonder drug,” as “the evidence linking Prozac to suicidal behavior is tenuous and relies mostly on anecdotal histories” (Toufexis & Purvis, 1990, p. 54). A large meta-analysis of data involving thousands of patients was conducted that suggested that there was no link between fluoxetine and suicide (Beasley et al., 1991). Further, several defenders of fluoxetine argued that by effectively treating depression, fluoxetine lowered the overall risk of suicide; in response to this argument, in a review article published in 1994 by David Healy, then a consultant for Lilly, Healy remarked that “the fact that pertussis vaccines reduce the overall likelihood of brain damage from the pertussis virus does not prevent legal
action in the event of vaccine-induced brain damage” (Healy, 1994, p. 225). Healy also questioned the utility of database analysis over and against case report evidence given that the database evidence was “collected as part of the clinical trial programme for fluoxetine in the early 1980s [and] did not specifically focus on the question of suicidal ideation” (p. 227). He further suggested that the problem might be obscured by biases in the scales used, social desirability bias, the infrequent and unpredictable nature of the putative side effect, the unwillingness of patients (as well as their doctors) who had previously had a negative reaction to fluoxetine to agree to a re-administration validity check, and a wide range of other potentially confounding variables. Healy pointed to evidence that propranolol, a beta-blocking drug that antagonizes one potentially relevant serotonin receptor (5-HT1a, an autoreceptor), can “relieve the akathisia/suicidal ideation precipitated by re-exposure to fluoxetine,” suggesting a possible neuro-biological mechanism by which serotonin enhancing drugs might produce suicidal reactions in some patients (p. 229). While concluding that the “volume of case reports and other studies is sufficient to demonstrate that antidepressants… may induce suicidal ideation in certain individuals under certain conditions,” he suggested that the side effect was uncommon and easy to manage, and noted that he continues to prescribe fluoxetine in his own clinical practice (ibid.). Healy’s review was immediately criticized by researchers employed by Lilly as both misleading and dangerous (Nakielny, 1994).

The following year, Jick et al. (1995) published a large scale epidemiological study of over 172,000 patients that found that there were more than twice as many suicides associated with fluoxetine than the next highest antidepressant. The difference became even more significant once patient risk-level was controlled for—the older antidepressants that were thought to be stronger but more potentially dangerous were disproportionally prescribed to
higher risk patients more likely to be suicidal to begin with. The study used multivariate regression to control for a wide array of variables, so much so that the more than doubled risk associated with fluoxetine was characterized as not statistically significant. The retrospective use of significance testing, in this case on data assembled from several studies, “may be the single most common ‘tool’ used by companies to hide adverse effects” (Healy, 2011, p. 11).

One problem with this study, and other similar studies that have been conducted over the years, is that the best source of data on adverse effects comes from randomized controlled trials, which often have samples just large enough to detect therapeutic efficacy, but not large enough to provide evidence about relatively rare side effects (Hall & Lucke, 2006). Another more serious sampling problem is that suicidal patients are always excluded (Reeves & Ladner, 2010). The official position of Lilly is that it would be “neither safe nor ethical” to include suicidal patients in a study in which they might be assigned to the placebo condition (Langreth & Ruiz, 2010, p. 32). Consequently, there is scant data concerning how suicidal patients respond to antidepressants. This allows statistical arguments to be made comparing the frequency of suicides and suicidal thoughts in treatment groups to overall levels in untreated patients, which is skewed from the beginning since the groups are non-equivalent. At the same time, though ostensibly it should undermine the industry argument that patients treated with antidepressants who become suicidal were suicidal to begin with, in practice those two arguments are almost always paired together in Pharma’s apologetic rhetoric.

**Proving causality.** Debates about causation have a long history in modern medicine. In 1884, when the germ theory of disease was still young and controversial, two German physicians named Robert Koch and Friedrich Loeffler developed a series of postulates (‘Koch’s postulates’) about causality that helped establish the bacterial aetiology of anthrax and tuberculosis and have
remained influential in biomedicine over the last century (Inglis, 2007). According to Koch’s first postulate, in order to establish that a given microorganism is responsible for a disease, it must be found in all individuals suffering from the disease, and also not be found in healthy individuals. In other words, the microorganism in question must be both necessary and sufficient to cause the illness attributed to it. Further postulates stipulate that when the microorganism is eliminated from the individuals suffering from the disease, the disease should resolve, and if the microorganism is subsequently reintroduced, the disease should return.

Richard Doll (2002), the foremost epidemiologist of the 20th century, has argued that Koch’s postulates have at times obscured the production of epidemiological knowledge. As a medical student, Doll was taught that “smoking could not cause Buerger’s disease because my teacher had seen a case in a non-smoker, and the same objection was occasionally raised some 15 years later to the idea that smoking might cause lung cancer” (p. 500). The tobacco industry challenged epidemiological studies along these lines, arguing that not everyone with lung cancer was a smoker, nor did everyone who smoke get lung cancer, so therefore whatever it was that the epidemiological studies of tobacco and lung cancer had uncovered, it was not a causal relationship.

The pharmaceutical industry has made similar arguments about antidepressants and suicide. In some ways, their arguments mirror the arguments made by the tobacco industry, except in reverse, as Healy notes:

The SSRI companies argue, for instance, that the evidence I have been putting forward regarding SSRI-induced suicidality is not evidence of cause and effect. They argue that clinical studies in which the problem appears in individuals on treatment, disappears when the treatment is discontinued, and reappears on the reinstitution of treatment—along with evidence for a dose-response relationship between SSRIs and agitation and, indeed, evidence of agitation and suicidality emerging in healthy volunteers—does not provide evidence for a causal link. These companies argue that cause and effect can only be demonstrated in randomized controlled trials and epidemiological studies…. [This]
argument is intriguingly the mirror image of the tobacco company position… that epidemiological studies do not provide evidence of cause and effect, and that what is required is challenge, de-challenge, and re-challenge relationships, as well as dose-response relationships showing the emergence of tumors in human lungs under the influence of smoke. (Healy, 2002, pp. 258–259)

Healy goes on to note the curious irony that “these mirror-image arguments of the SSRI and tobacco companies are sometimes delivered by representatives from the same legal firms” (p. 259).

The tobacco industry introduced the dialectical terms ‘junk science’ and ‘sound science’ into medico-legal discourse, and argued for ‘good epidemiological practices’ that “would make it impossible to conclude that secondhand smoke—and thus other environmental toxins—caused diseases” (Ong & Glantz, 2001, p. 1749). These terms were redeployed by the pharmaceutical industry once the question of legal responsibility was introduced. Describing the situation as a “junk science epidemic,” Huber (1991) describes the evidence in favor of a link as “tentative” and “cautiously phrased” and attributes the existence of the controversy to “trial lawyers, in a bizarre alliance with the Church of Scientology, [who] have launched a huge campaign to smear Prozac and its manufacturer, Eli Lilly” (p. 70).

**Legal challenges.** In 1989, a little more than a year after Prozac had been introduced to the market, Joseph Wesbecker, who had been taking Prozac for a little over four weeks, shot 20 people (killing eight) with an AK-47 at his place of employment in Kentucky before killing himself. The specific array of psychotic symptoms Wesbecker displayed immediately prior to his death had been reported in Lilly’s trials though not disclosed to the public (Glenmullen, 2000). The families of the victims later sued Eli Lilly, and the terms of the 1994 settlement included the publication of internal documents about the side effects of Prozac. These documents, many of which were only ultimately disclosed after the patent for Prozac expired in
2001, revealed that Lilly was aware of the suicide risk as early as 1978 and discussed the risk in more than a dozen internal memos and reports before the Teicher et al. report was published in 1990 (“What did Eli Lilly know about Prozac induced violence & suicidality?,” 2006).

The Wesbecker case almost was stopped before it began, as the attorneys for the plaintiff initially had a great deal of difficulty finding an expert witness, as virtually every psychopharmacologist they interviewed was either a consultant for Lilly or was kept on retainer (Healy, 2004). The jury eventually voted 9-3 in favor of Lilly, leading Randall Tobias, CEO of Lilly, to assert that “The members of the jury, after hearing the scientific and medical facts… came to the only logical conclusion—that Prozac had nothing to do with Joseph Wesbecker’s actions” (Cornwall, 1996, pp. 286–287). Not mentioned was the fact that Lilly settled with the plaintiffs for almost $100 million in advance of the verdict on the condition that they not contest certain legal questions concerning jury instructions (p. 299).

This trial was not an isolated incident – by 1990, two years after Prozac had been approved, there were 54 pending lawsuits, and hundreds more were filed in the following years (Healy, 2004). In the trials that followed, the statistical shenanigans of Lilly-affiliated expert witnesses became clear. One strategy, which had its roots in the first meta-analysis by Beasley et al. (1991) was to claim that suicide was not reported as an adverse event after first reclassifying mentions of suicide as a symptom of a depressive episode. In a deposition for the Wesbecker trial, John Heiligenstein, one of the co-authors of the meta-analysis, gave the following testimony:

A: Suicidal ideation is not an adverse event.
Q: Why not?
A: It’s a component of the illness.
Q: Doctor, is it your testimony that nobody has ever become suicidal because of the use of fluoxetine?
A: In my estimation, to the best of my knowledge, no. (Deposition of John Heiligenstein,
Even more telling, from the same deposition:

**Q**: Can you conceive as a clinical research physician and scientist, anything that would change your opinion on whether or not Prozac has a causal relationship between it and suicidality?

**A**: I doubt if there is any study that could be done that could possibly demonstrate a relationship between fluoxetine and suicidality. (*Deposition of John Heiligenstein, 1994*)

One reason for this difficulty, according to Leigh Thompson, another expert witness for Lilly in the Wesbecker trial, is that it is incredibly difficult to separate suicidality caused by depression from suicidality caused by fluoxetine: “Now, in terms of whether we specifically designed a study to address the issue of suicidality separate from all of the other issues of efficacy and safety, the answer is no… we’ve spent an awfully [sic] lot of time and money trying to figure how to do [it]… Millions of dollars” (*Deposition of Leigh Thompson, 1994*). That money may not have been well spent; a few years later, David Healy conducted a study costing $15,000 with sertraline (better known by the trade name Zoloft), another SSRI, on healthy volunteers, two of which became suicidal within two weeks, statistically significant at the level of $p = 0.0000005$ (Healy, 2000a).

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5 Lest one think that Healy was engaging in a crusade against sertraline, it should be noted that he remained a strong advocate of the drug, “ensuring that it was listed as the SSRI of choice in the hospital formulary [in Wales]. The problems of possible suicide induction as I saw them were ones that could be handled with appropriate warnings and monitoring” (Healy, 2002, p. 253).
adolescents being treated with SSRIs. As evidence mounted that made it difficult for industry scientists to maintain that all cases of suicidality in patients treated with antidepressants could be attributed to the pre-existing mental illness rather than to an iatrogenic adverse effect of treatment, new arguments were sought. The suggestion was made that

…the widespread use of antidepressants in the new ‘SSRI-era’ [appears] to have actually led to [a] highly significant decline in suicide rates in most countries with traditionally high baseline suicide rates… We conclude that rather than being a threat, the judicious clinical use of antidepressants actually does serve to effectively treat and indeed protect depressed patients from suicidal outcome. (Rihmer & Akiskal, 2006, p. 3)

This rather dubious argument suffers from several problems, not the least of which is the fact that suicide rates in Western countries began declining before Prozac came on the market and do not seem to co-vary with prescription rates (Reseland, Le Noury, Aldred, & Healy, 2008). As for the accumulating data that suggest a link between antidepressants and suicidality, we are told that research protocols are complicated and that this “is an instance where clinical wisdom surpasses evidence-based medicine” (Rihmer & Akiskal, 2006, p. 10). What about ‘smoking gun’ evidence that data was withheld from the FDA and the public?

The issue of not disclosing relevant data by FDA or other data protecting agencies which could have warned the prescribers of nine antidepressants in children and adolescents with depression and emerging suicidal communication among them is debatable. The disclosure of such data is justified only if it is not premature and at the same time enhances public safety. (Qureshi, 2004, p. 307)

So basically, not a big deal; there is nothing incriminating here, and in fact it would have been unethical if they had prematurely disclosed the risks to the public. This rhetorical strategy was unsustainable.

In 2007, the agency completed a comprehensive meta-analysis of data from trials conducted from 1988 to 2006 and concluded that the benefits of SSRI therapy in children and adolescents suffering from depression and anxiety disorders most likely outweigh the risks, but
also noted that recipients of SSRIs were twice as likely to exhibit suicidality as those receiving placebo. On May 2, 2007, the FDA required that prescribing and patient information sheets for all antidepressant medications carry an expanded ‘black-box warning’ disclosing information about an increased risk of suicidal symptoms in young adults aged 18 to 24 (Food and Drug Administration, 2010). This is the strongest type of warning in prescription drug labeling required by the FDA, indicating the existence of comprehensive evidence for serious (often potentially life-threatening or permanently disabling) adverse effects (Food and Drug Administration, 2011).

Of course, the move was immediately criticized by industry affiliated psychiatrists, though there was little more they could do. Friedman and Leon (2007) offered in the New England Journal of Medicine the following criticism:

The new black-box warning is clearly an attempt to balance the small risk posed by antidepressants against their well-documented benefits. But this new label has the potential to confuse both patients and physicians. After all, if depression and other psychiatric illnesses are “associated with increases in the risk of suicide,” as the warning states, and antidepressants are known to be effective treatments for such disorders, why not just state the obvious: that untreated depression and psychiatric illness carry a significant risk? Because such a statement would too closely resemble a treatment recommendation, which is outside the purview of the FDA… There may be controversy about the risk posed by antidepressants, but there is none about the risk associated with
untreated depression: estimates of the lifetime risk of suicide in depressed persons range from 2.2 to 15%, depending on the population under study — not to mention the considerable suffering and functional impairment caused by this illness. In contrast, the FDA meta-analyses reveal an absolute risk of suicide in patients taking investigational antidepressants of 0.01%. Granted, this rate reflects risk during the short duration of a randomized trial, typically 4 to 12 weeks, but suicide is clearly an extremely rare treatment-emergent phenomenon… The real killer in this story is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease..

(p. 2343-2346, our emphasis)

By this point, the existence of the risk was impossible to deny (though the continued existence of controversy was asserted), so the grounds of the criticism shifted to relative risk and institutional responsibility. A recent review article describes the increased risk as “an uncommon occurrence but also a legitimate phenomenon” (Reeves & Ladner, 2010, p. 227).

Demanufactured Controversy

Prior research about scientific controversies has explored controversies that are ‘manufactured’ in the public sphere “about a matter for which there is actually overwhelming scientific consensus” in the technical sphere (Ceccarelli, 2011, p. 196). In these cases, the manufacturers of the controversy use an array of tactics to produce uncertainty while undermining the appearance of a consensus among experts (Corbett & Durfee, 2004; Dunwoody, 1999; Michaels, 2005, 2008a, 2008b; Miller, 1992; Oreskes & Conway, 2010; Smithson, 1980; Stocking & Holstein, 2009; Zehr, 2000). In the case of the Prozac controversy, however, we have the reverse situation: what starts as a controversy in the technical sphere is characterized as a non-controversy. This process similarly involves the manufacture of uncertainty—so much uncertainty that no serious scientist takes the claim seriously—while at the same time maintaining certainty about the value and safety of the drug. Shortly after the first reports of suicidality began to appear in the popular media, Eli Lilly made headlines by offering to pay the legal costs of doctors who prescribed Prozac and were subsequently sued for malpractice. In an
explicit attempt to rhetorically reframe the nature of the emerging controversy, Lilly spokesman Edward West claimed that the matter was “a public relations controversy, not a medical controversy. Doctors need to understand that we stand squarely behind the drug and their use of it” (Gehorsam, 1991, p. C3).

In manufactured controversies, the lack of an apparent controversy in the technical sphere is often explained by framing the mainstream scientists as representing an orthodoxy that is both close-minded and driven by questionable motives (Ceccarelli, 2011). In the Prozac controversy, the presence of an apparent controversy in the technical sphere is explained by framing the dissenters as non-scientific extremists. In this they were aided by the Church of Scientology, whose opposition’s to psychiatry lead them to immediately seize on the controversy and run daily full page advertisements in USA Today. Though distinct from the actual scientists and clinicians raising the issue in the medical literature, industry apologists metonymically invoked Scientology when referring to their opponents, while explicitly (though vaguely) questioning their real motives. After the FDA first examined the issue and failed to find convincing direct evidence of a link between Prozac and suicidality, Lilly’s public relations department wrote a letter to the editor of the St. Petersburg Times in which they insisted:

For nearly two years, the Church of Scientology has focused its longstanding vendetta against psychiatry and psychotropic drugs on the antidepressant Prozac…This fringe group has repeatedly misrepresented scientific studies of Prozac during its… propaganda onslaught… Initially, the nation's news media featured the Scientologists’ groundless assertions without investigating either their motives or the factual accuracy of their charges. Consequently, many patients suffering from major depressive disorders have chosen to forgo treatment with the antidepressant that would have been their physician's first choice. Moreover, it appears that many depressed patients have simply chosen not to seek any treatment for this life-threatening disorder that has long been the subject of social ridicule. The Scientologists seemed to be realizing their goal of restigmatizing a disease that affects millions of Americans. That was the case until… the FDA emphatically rejected the… petition… Several major organizations including the American Psychiatric Association and the National Mental Health Association vigorously endorsed the agency's decision. The FDA's response represents an important milestone in
a sordid controversy that has exposed many depressed patients to unnecessary risk. We hope that you will help your readers better understand what the Scientologists' frightening, confusing publicity campaign is all about. (West, 1991; our emphasis)

This is not a scientific controversy, but rather an attempt by a fringe cult—which is not only outside the scientific institution but directly opposed to it—to gain publicity, Lilly claimed. At the same time, just as controversy manufacturers invoke academic practices to explain why there seems to be a false consensus, Lilly, in their attempt to demanufacture this controversy, argued that there seemed to be a false dissensus only because of journalistic norms that value reporting ‘both sides’ of the issue.

Postmodern Personality Disorder

Unlike the scientologists, or even fringe psychiatrists associated with the antipsychiatry movement like Thomas Szasz (The myth of mental illness) or Peter Breggin (Toxic psychiatry), David Healy was a more problematic interlocutor. His psychopharmacological credentials were unimpeachable. However, his character as a scientist was still a viable target, and continued attempts were made to undermine his ethos. In one case, his efforts to raise awareness of the adverse effects of another SSRI, paroxetine (better known by the trade name Paxil), were compared to the claim by “postmodern media critic Jean Baudrillard… that the Gulf war did not happen” (Cowen, 2002, p. 910). In an interview with Christopher Lane, Healy attempted to turn this kind of attack back at the pharmaceutical industry:

Many clinicians, scientists, and patients have heard about postmodernism. They might have heard company criticism of someone like me along such lines as “Pay no heed to him, he’s just a postmodernist.” The implication is that postmodernism is all-but a psychiatric disorder in its own right, in which academics like me refuse to concede that there’s any reality to human behaviors—or the physical underpinnings of disorders of human behavior. By contrast, the story goes, there are the hard scientists who work in or with drug companies who deal only with facts and hard data, and the proof is that they bring new and helpful drugs to the market… [Pharmaceutical] marketing departments are actually the postmodernists par excellence. They treat the human body (including its disorders and complaints) as texts to be interpreted one way this year and in just the
opposite way a year or two later. In contrast, when it comes to the hazards of these
drugs—just like the tobacco companies before them—the motto of Pharma has become
“doubt is our product”—they simply refuse to concede that their drugs are linked to any
hazard at all . . . until the drug goes off patent. You cannot get a better definition of
postmodernism than “doubt is our product.” (Lane, 2009)

If Prozac were a lifestyle-enhancing supplement that provoked suicidality in a small percentage
of its users, it would be fairly easy to notice, as it was in the tuberculosis patients who had
psychotic reactions to isoniazid and iproniazid. But what if instead it is a treatment for a disease
that is defined (in part) by an elevated risk of suicide and suicidal ideation? By packaging
depression as a risk disorder and marketing Prozac as its remedy, the terms of the debate made it
difficult to discuss the increased risk of suicidality as an adverse effect of Prozac without a high
degree of uncertainty. In this way, Lilly’s product was so infused with doubt that it took nearly
two decades to untangle the risks that had actually been well established decades before Prozac
even came on the market.

The politics of the supplement addresses rhetoric, the body and materiality. All state-of-
the-art institutional practices involve a balance of risk and uncertainty. The state regulates
institutions in relation to safety. Safety is a judgment based upon known research and the range
of outcomes in trial test and actual cases. Experiences grow with new theories, new
developments, and accumulating cases. The result is a politics where legitimacy of state-of-the
art comes into question. This study reveals the techniques of institutional self-protection and
advance through discounting standing research and associating criticism with radical, non-
scientific research. The politics are largely structured around and played out in the forensic
realm which does not so much settle the issue as it does fix individual complaints and provide in
principle a deterrent. The linguistic turn in this kind of politics thwarts the transparent practice
of science through subordinating uncertainty to the interests of money and power.
References


Birmingham, K. (2000). No dismissal for hate-mail author. *Nature Medicine, 6*(6), 609–610. doi:10.1038/76146


223. doi:10.1080/02773941003614464


Kramer, P. (1993). *Listening to Prozac: A psychiatrist explores antidepressant drugs and the*
remaking of the self. Bloomington, IN: Indiana University Press.


Antidepressant – Suicide Controversy

Archives of Neurology and Psychiatry, 72(3), 313–320.
doi:10.1001/archneurpsyc.1954.02330030047004


