

## Guest editorial

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# A failure to warn

### 1. A problem

In January 1988, a selective serotonin reuptake inhibiting (SSRI) antidepressant, Prozac, was launched in America. During the 1990s, this brand name had all the prominence Valium once had. The main problem with earlier antidepressants was their toxicity in overdose. The Prozac marketing drive was sustainable because compared to the benzodiazepines, it was non-addictive and, compared with older antidepressants, it was safe in overdose [1].

In February 1990, Teicher and colleagues [2] reported an emergence of suicidality on Prozac. This report was followed by others [3–9] many involving challenge-dechallenge-rechallenge cases, a widely accepted means of establishing a strong causal link between drug and effect [10]. The investigators were senior figures and included authorities on akathisia, which by then was seen as the mechanism, whereby Prozac induced treatment-emergent suicidality.

Eli Lilly, the makers of Prozac, responded by “meta-analysing” their RCT database, indicating that Prozac reduced suicidal ideation [11]. This analysis covering 3,065 patients, was festooned with eponymous statistical tests and had the appearances of scientific rigour. It later became clear that most Prozac trials had been omitted from the meta-analysis, so that the 3,065 patients had been drawn from a clinical trial database of approximately 27,000 patients, that within those trials analysed, up to 5% of patients had dropped out for akathisia-like symptoms and had been omitted and no mention was made of approximately 198 US and 94 non-US Prozac-associated suicides [12,13]. No mention was made of the benzodiazepines co-prescribed with fluoxetine to minimise drug-induced agitation [13].

The Lilly response to criticisms that the methods used in the meta-analysis were flawed [14] was dismissive [15] but it has since become apparent that they recognised that the meta-analysis did not answer the issues. As of September 1990, Lilly scientists wrote (these) “trials were not intended to address issue of suicidality” [16]. Aspects of the problem were debated in mainstream journals, generally supporting the possibility of treatment-emergent suicidality [17,18] but the meta-analysis appeared to settle the question within academic circles. Whenever, the issues were raised thereafter [19,20], they drew a swift response from Lilly [21,22]. Subsequent silence may say more about the need for sponsorship of a viewpoint than it says about how satisfactorily the issues had been addressed.

Akathisia emerged early as a problematic side-effect of psychotropics leading to suicide [23]. It is pernicious as the main complaints may be of strange feelings or impulses, which may be regarded as evidence of the underlying problem unless clinicians are suitably suspicious [24,25]. Until the advent of Prozac, akathisia was only associated with antipsychotics, where it was linked to suicide [26] and suicide-homicide [27] precipitation. But patients at risk were largely inpatients, being given regimens that degraded any capacity to act.

Akathisia appeared in the first studies with Prozac at a 25% rate [28] and led to clinical decompensation so that concomitant benzodiazepines were introduced in Prozac trials to minimise the problem.

Nevertheless, throughout the 1990s, Lilly's published view was that "any association between this symptom (akathisia) and suicide is not proven", that there was no evidence that Prozac was more likely to lead to akathisia "any more than other antidepressants" and that "clinical trial data has failed to confirm the hypothesis that some patients treated with an antidepressant who develop akathisia experience treatment emergent suicidality" [21]. Given these denials, there must be doubts about how prepared primary care prescribers, many of whom would have had no education on or experience of akathisia, could have been to use a drug causing this problem.

## 2. Cause and effect?

By 1994, over 160 American Prozac lawsuits had been filed, a number of which led to substantial settlements [29]. Without a guilty verdict, however, there was no unavoidable onus on Lilly to ensure that patients were warned of any hazards even though FDA statutes require companies "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. . . Special problems, particularly those that may lead to death or serious injury, may be required by the FDA to be placed in a prominently displayed box" [30].

As of October 1997, more than 1,630 American Prozac-associated suicides were recorded on the FDA's ADR system, which is thought to capture 1–10% of serious adverse events; of these over 450 had clear indicators of akathisia and in this sample there is an equivalent male–female suicide ratio unlike the normal 4 males to 1 female ratio [31]. One might have thought Lilly should have had to warn of possible causation, unless it could prove that all suicides were caused by an underlying depression. In fact, although company monitors had from 1990 "assigned Yes, reasonably related on several reports", Lilly turned the burden of proof upside down by adopting a strategy of blaming the "patient's disorder and not a causal relationship to Prozac" [32]; "its in the disease not the drug" [33].

The academic community appeared not to recognise a problem here, perhaps because during this period, RCTs had supposedly become a "gold standard" as regards cause and effect linkage and Lilly's meta-analysis had apparently demonstrated that there was no linkage between Prozac and treatment-emergent suicidality.

Epidemiological studies may also contribute on issues of drug-induced injury. As it transpired, another antidepressant, Prothiaden, which was widely prescribed but dangerous in overdose, led to an epidemiological study looking at suicides associated with antidepressant use in British primary care [34]. In this study, the relative risk of Prozac was 2.1 times the Prothiaden risk, with no overlap of confidence intervals at a 95% significance level. Controlling for selected confounding factors reduced the risk of all antidepressants except Prozac but the sample size was dramatically reduced in the process, saving Prozac from a damning conclusion.

The first point is what did not happen after publication of this worrying study. It was easily replicable with a larger dataset but no other studies appeared. New drugs come to the marketplace in groups; one gets a set of SSRIs, rather than a set of diverse antidepressants. Conceivably therefore no competing company would have had an incentive to pursue the issue, in case the problem were class based, for which there was in fact some evidence [35].

Pharmaceutical companies have considerable resources to "pad the record", if they so choose. Just as the Beasley meta-analysis could be undertaken, so also they can "produce" supportive *de novo* "epidemiological" studies. Lilly cite three. The first [36] in fact was a prescription-event-monitoring rather than an epidemiological study, whose results re-analysed indicate that Prozac is 3 times more likely than placebo

to induce suicidality [37]. The second [38] was a naturalistic prospective study of anxious patients (only 654), in which the only suicide occurred on Prozac, undercutting claims that depression was the cause of the problem. The third study [39] another prospective naturalistic study, was instituted a decade before Prozac's launch in which only 185 patients got Prozac. It was not designed to detect this problem and its designers were mostly deceased at the time of this "reanalysis". All three studies, however, have been used as of 1999 to support claims that Prozac does not cause suicide.

The emphasis on RCTs, meta-analyses and epidemiological studies obscures the fact that neither RCTs nor epidemiological studies were required to prove cause and effect in this case. This had already been proven by the initial controlled clinical studies. RCTs and epidemiological studies, however, require enormous resources and the goodwill of academic investigators, thereby putting the potential to contest the issues out of reach for most people. This also, in practice, pushes into the background any liabilities from not warning patients of potential treatment risks.

RCTs have never been used legally to establish causation for drug-induced adverse effects for good reason. Adverse effects of psychotropic agents may be elicited by spontaneous reports, systematic checklists or detailed interviewing by senior clinicians. Lilly have supported a study which demonstrates that spontaneous reports underestimate side-effects by a six-fold factor [40]. Systematic checklists are the best that could be expected from current clinical trials, which while run under the aegis of senior investigators in some settings are run by junior medical or untrained non-medical personnel [41]. Spontaneous reporting is, in fact, the method employed. But akathisia is in principle not codable under current spontaneous reporting systems. As a result, the most authoritative compendium on psychotropics [42] can state that "fluoxetine's propensity to cause akathisia is widely recognised" yet Lilly's published database of 42 side effects of Prozac does not mention akathisia [43].

To call this data scientific or to think that it might help resolve scientific issues is misleading. Unfortunately participation in clinical trials using these methods potentially puts all patients in legal jeopardy, as the absence of data produced by current methods is taken in practice as evidence that the agent does not cause effects consistent with injuries to a patient.

Concerns about the Jick study could be set aside, if its Prozac suicide figures (187/100,000 patient years) were set against conventional figures that depression produces suicide rates of 200–600/100,000 patient years. However these figures for depression were derived from hospitalised patients. In fact as of 1995, no one knew what the suicide risk for primary care depressions was. There was reason to suspect that it had to be considerably lower than 187/100,000 patient years or else British annual suicide figures would not add up. It has since become clear from various sources, including an analysis of a database of half a million patients (2,500,000 patient years), that the suicide risk for primary care depressions in the United Kingdom cannot exceed 40/100,000 patient years [44], increasing concerns about Prozac-induced suicidality.

Lilly [45] cite a Swedish study as indicating a 79-fold increased suicide risk in depression (790/100,000 patient years). The figure from the same study, however, for suicide risk in non-hospitalised depressions was 0/100,000 patient years [46]. Lilly have portrayed the benefits of detecting and treating depressions, in great part, based on the possibility of lowering suicide figures of 200–600/100,000 patient years. If, the figure for primary care depressions does not differ substantially from the general population figure, the Jick study suggests a real risk that unmonitored treatment will increase rather than reduce suicide risk. But the impact of treatment cannot be monitored properly if physicians are not adequately warned about potential hazards. Could Prozac-induced suicidality pass undetected? If the same treatment reduces risk in some, it could. Many more people take antidepressants now than a decade ago, yet suicide rates remain the same.

### 3. Prescriptions, patents and solutions

Since the early 1980s pharmaceutical corporations have grown greatly. They are now managed by managers, who rotate in from non health-care corporations, whose personal wealth increases with the company share price – when sales increase. It is clear that some corporations, such as tobacco corporations, have avoided research on the advice of their lawyers that to engage in such research would increase their legal liability [47]. Pharmaceutical corporations are advised, in some instances, by the same law firms offering this advice to tobacco corporations. If the advice is the same, it risks striking at the heart of prescription-only arrangements.

Prescription-only arrangements were aimed at protecting consumers by having medical practitioners as their advocates. The general understanding is that companies will provide appropriate information in good faith to doctors. Because of this arrangement, there are no strong consumer groups in the health care arena. Elsewhere corporations, such as Nintendo, post warnings of possible convulsions on computer game systems. In medicine, the Prozac story indicates companies could evade the need to post a warning by invoking the duty of the physician to outline the risks of treatment. In such an instance, prescription-only arrangements would have become a vehicle to deliver adverse medical consequences with near legal impunity.

Prozac is patented under a system, which gives companies several years to promote a brand name version of the drug, thereby recouping development costs. This system, it is hoped, will foster innovative developments rather than copies of an original idea. Despite this, new drugs emerge as classes; fluoxetine was the 5th of 7 SSRIs. The patenting of Prozac, however, gave Lilly considerable incentive to promote its brand name and to defend the product. It produces a situation where companies may go for “block-busters” rather than a portfolio of compounds. A situation where in 1990 a senior executive in Lilly wrote “Lilly can go down the tubes if we lose Prozac and just one event in the UK can cost us that” [48]. Surely not a comfortable position for either companies or the consumers of their products.

A possible reform would be to advise patients against participation in clinical trials unless side-effect data were collected properly. Ethical committees could require companies to state in consent forms that side-effect data could not be used in academic or legal debate unless collected in certain ways. Many companies would be happy to adopt such arrangements. The knock-on effect internationally would be immediate, in that few trials of significance are conducted today that are not multinational and all must adhere to the same protocol.

Alternatively an inability to get a guilty verdict in the circumstances outlined here would leave lawyers with little recourse but to include prescribing physicians in future actions on any drug. The strategy would be to probe exactly how educated the doctor thought they were on this issue. Did small print on a datasheet amount to sufficient warning?

Prescription only arrangements were established at a time, when it was unthinkable to question the proposition that a doctor in all cases would put the interests of their patients above all others. Since then a bio-ethical movement has developed based on a recognition that in cases involving patients on respirators, in transplant programmes or in research, this assumption is no longer tenable or at least needs monitoring [49]. The Prozac story may yet mark a significant milestone in the evolution of bioethics.

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