



Review

Clinical trials and legal jeopardy

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*This month's **REVIEW** begins with a paper that examines the way in which information about a serious side-effect of Prozac - suicide - has been handled by the manufacturer and by academics. It then prints two questionnaires used by the Tayside LREC to audit both how approved research projects are carried out and the experiences of research subjects who take part. The section ends with some book reviews.*

On neither side of the Atlantic have research ethics committees found a satisfactory way of ensuring that all serious side-effects of new treatments being studied are noted and reported to them, without being deluged in reports of minor adverse events. The author of the following paper is probably the leading historian of psychopharmacology: he discusses the issue, and its implications for RECs, in the light of the serious side-effects of the new generation of SSRI antidepressants.

Background

This paper explores the implications for research ethics committees of efforts to determine whether the antidepressant Prozac causes significant adverse problems for a proportion of patients, and their efforts to seek redress.

In January 1988, a selective serotonin reuptake inhibiting (SSRI) antidepressant, Prozac, was launched in America. During the 1990s, this brand name has had all the prominence Valium once had. Prozac was marketed as non-addictive compared to the benzodiazepines and as safer in overdose than older antidepressants.¹

In February 1990, Teicher and colleagues reported an emergence of suicidality on Prozac. This report was followed by others^{2,4,6,7,8,9} many involving challenge-dechallenge-rechallenge

cases, a widely accepted means of establishing strong causal links between drug and effect¹⁰. The investigators were senior figures, including the leading authorities on akathisia, which by then was seen as the primary mechanism whereby Prozac induced suicidality.

Eli Lilly, the makers of Prozac, responded by "meta-analysing" their RCT (randomised controlled trials) database, indicating that Prozac reduced suicidal ideation¹¹. This analysis, covering 3,065 patients, had the appearances of scientific rigour. No mention was made of the fact that the 3,065 patients had been drawn from a trial database of over 26,000 patients, nor that within those trials analysed up to 5% of patients had dropped out for akathisia-like symptoms, nor that benzodiazepines were co-prescribed with fluoxetine (Prozac) to minimise drug-induced agitation, just what was at issue, nor that some of the trials analysed had been rejected by the FDA for registration purposes^{12,13}.

The Lilly response to criticisms that the methods used in the meta-analysis were flawed¹⁴ was dismissive¹⁵ but it has since become apparent that internally they had previously recognised just this. 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 suicide²³. 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 suicide²⁶ and suicide-homicide²⁷ precipitation. But in these cases the patients at risk were largely inpatients, being given regimens that degraded any capacity to act.

Akathisia appeared in early studies with Prozac at a rate of 25%²⁸. 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.

Cause and effect?

By 1994, over 160 American Prozac lawsuits had been filed, a number of which led to substantial settlements²⁹. As of October 1999, more than 2,000 Prozac-associated suicides were recorded on the FDA's Adverse Drug Reaction system, which is thought to capture 1-10% of serious adverse events; of these over 500 had clear indicators of akathisia, and in this sample there is an equal male:female suicide ratio, unlike the normal ratio of four males to one female³⁰. 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"³¹; "it's in the disease not the drug"³².

The academic community appeared not to recognise a problem here, even though some of the earliest clinical studies reporting problems had involved children being given Prozac for obsessive-compulsive disorder, i.e. who were not depressed⁴. This scotoma may have arisen because during this period, RCTs were actively portrayed by Lilly as 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.

RCTs are not the gold standard for determining cause and effect for adverse effects, for reasons outlined below. But as a further point, germane RCT evidence on the issue was not published. As of 1986, Lilly's clinical trial database was showing rates of 12.5/1000 patients attempting suicide on fluoxetine versus 2.5/1000 patients

on placebo and 3.8/1000 patients on reference antidepressants³³. This data remained unpublished and unreported to the FDA. There are other unpublished studies consistent with this finding, in addition to one published set of figures³⁴.

Epidemiological studies

Epidemiological studies may contribute on issues of drug-induced injury, primarily to estimates of frequency and risk. As it transpired, another antidepressant, dothiepin, which was widely prescribed but dangerous in overdose, led to a study looking at suicides associated with over 172,000 antidepressant prescriptions in British primary care³⁵. In this study, the relative risk of Prozac was 2.1 times the dothiepin risk, with no overlap of confidence intervals at a 95% significance level. Controlling for selected confounding factors reduced the risk of all other 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 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. If the problem were class based, for which there was in fact evidence³⁶, no competing company would have any incentive to pursue the issue.

Pharmaceutical companies have considerable resources to "pad the record". Just as the Beasley meta-analysis could be undertaken,²² so also they can "produce" supportive de novo "epidemiological" studies. Lilly cite three. The first³⁷ was a prescription-event-monitoring rather than an epidemiological study, whose results re-analysed indicate that Prozac is three times more likely than placebo to induce suicidality³⁸. The second³⁹ was a naturalistic prospective study of 654 anxious patients, in which the only suicide occurred on Prozac, undercutting claims that depression was the cause of the problem. The third was another prospective naturalistic study, instituted a decade before Prozac's launch, in which only 185 patients were prescribed Prozac⁴⁰. 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.

In fact, despite company claims that Prozac was the most researched psychotropic drug in history, since Teicher's first reports, no new research to answer the questions raised by the early clinical studies has been published.

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 years⁴¹, increasing concerns about Prozac-induced suicidality.

Lilly⁴² 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 years⁴³. 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.

From the Jick, Kasper and unpublished Lilly data outlined above,^{34,35} it can be estimated that 1/1000 patients suicide on Prozac and 1/100 attempt suicide. Given that there have been in excess of 1 million individuals who have taken Prozac in the UK since its launch, this gives figures of one patient per week suiciding since its launch and one per day attempting suicide. Could a problem on this scale pass undetected? At these rates few general practitioners, hospital consultants or coroners (150 in England and Wales) would see more than one case every few years. Overall national suicide rates remain the same, despite the great increase in antidepressant prescribing that might otherwise have been expected to reduce them⁴⁴.

RCTs and legal jeopardy

The emphasis on randomised controlled trials, 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, in practice, minimising 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 reasons. 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 factor⁴⁵. 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 personnel⁴⁶. 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 psychotropics⁴⁷ can state that "fluoxetine's propensity to cause akathisia is widely recognised", the physiological mechanisms by which this happens are relatively well understood⁴⁸, yet Lilly's published database of 42 side effects of Prozac does not mention akathisia⁴⁹, even though, prior to its launch, it had been associated with akathisia and agitation, occurring with sufficient frequency and intensity to lead to recommendations that benzodiazepines be co-prescribed with it in clinical trials.

Consider also emotional flatness or blunting. This side-effect, reported frequently by patients on Prozac, is arguably all but intrinsic to the mode of action of the drug, which generally reduces emotional reactivity⁵⁰. It has been reported in observational studies, where it has been linked to other potentially harmful behaviours⁵¹. But nothing resembling emotional blunting appears in the clinical trials side-effect database for Prozac.

Whether or not the reader believes that an antidepressant could induce suicidal ideation, as a matter of fact, along with emotional blunting and

akathisia, treatment-emergent suicidal ideation is not recognised by any code in current clinical trial systems. It is not recorded as a side effect of Prozac in the Lilly database.

There are, therefore, a number of problems with current side effect data. If RCT-based side-effect profiles were used just for marketing purposes, there might be little problem with this state of affairs. These profiles have, however, also been used in academic debate and for legal purposes to deny that claimed adverse effects are happening^{21,22}. Because of this, the participation of patients in clinical trials using these methods potentially puts the entire national community 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.

This is a problem that could be readily remedied. If UK ethics committees were to insist that consent forms for trials included a statement that side-effects collected by current methods could be used for marketing but for no other purposes, the present poor arrangements could continue without posing a threat of legal jeopardy to all of us. Alternatively ethics committees could request better side-effect collection methods, which would both enhance the scientific information provided by clinical trials and minimise the risks of jeopardy. As many important trials are now multinational and must adhere to the same protocols, these simple manoeuvres would have an immediate international effect. Many companies would be happy to adopt such arrangements.

An ethical crisis?

Ethics committees came into existence, in part, because the process of recruitment of patients to clinical studies was not transparent⁵². Beecher's review of practices in 1966 indicated a situation where some abuses were happening or could happen⁵³. A similar situation applies today to the use of data emerging from clinical trials.

Since the early 1980s pharmaceutical corporations have grown greatly. They are now managed by managers, who rotate in from non health-care corporations. 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 liability⁵⁴. 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. They were established at a time when it was unthinkable to question the proposition that a doctor would put the interests of his patients above all others. The general understanding is that companies will provide appropriate information in good faith to doctors. This information comes largely from clinical trials. 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 can evade the need to post a warning by invoking the duty of the physician to outline the risks of treatment. How physicians can adequately outline such risks if the systems in place do not collect the pertinent data is unclear. In such an instance, prescription-only arrangements risk becoming a vehicle to deliver adverse medical consequences with near-impunity legally. The Prozac story may yet mark a significant milestone in the evolution of bioethics.

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