SUICIDE AND THE REGULATORS

The First Regulatory Submissions

The story begins circa 1985/1986, when Eli Lilly had trouble getting fluoxetine licensed in Germany. One of the hazards flagged up by German regulators was an association between fluoxetine intake and suicidal acts. The German regulators have had prior experience of two SSRIs, zimelidine and fluvoxamine, both of which seemed to be associated with increased rates of suicidal acts. In the case of both zimelidine and fluvoxamine, experts have briefed regulators that this might be simply a coincidental finding as when the data sets were analysed further it seemed that those who were most suicidal to begin with did best with the SSRI.

After considerable internal company assessment of the issues, Lilly resubmitted a portfolio of data to the German regulators and comparable data to other regulators in the US and the UK. The German regulatory submission in 1986 gave the data on suicide as in Table 1 below.

Table 1

Drug	Patients	Suicidal Acts	Acts/PEY	% Suicides & Suicidal Acts
Fluoxetine	6903	63	0.054	0.91%
Comparator	2310	15	0.043	0.65%

From Table 1 it can be seen that there is an excess of suicidal acts on fluoxetine whether these data are calculated in terms of the absolute numbers of patients or in terms of patient exposure years. Through to the mid 1980s the preferred method of data submission to regulatory authorities was in terms of absolute patient numbers.

Table 1 however is misleading. Of the 15 patients described here as committing suicidal acts and falling in the non-fluoxetine group, scrutiny of the clinical trial records reveals that 4 of these occurred during the placebo run in (placebo washout) phase of various clinical trials. A further 4 appeared to have occurred at some point after the trials were over. These patients were recruited by following patients up over the course of a year and if any engaged in a suicidal act at some point during that year, even if they had been on fluoxetine beforehand, provided they had been discontinued from fluoxetine for 6 weeks beforehand, these were classified under comparator.

Removing these two patient groups leads to the figures in Table 2, which gives much clearer evidence of an increased rate of suicidal acts on fluoxetine

compared to other whether the data are calculated in terms of either patient exposure years or absolute numbers of patients.

Table 2				
Drug	**Patients**	**Suicidal Acts**	**Acts/PEY**	**% Suicides & Suicidal Acts**
Fluoxetine Comparator Washout/Run In Other	6903 2310	63 7 4 4	0.054 0.02	0.91% 0.3%

There are further possibilities here. One is to accept Lilly's approach and include these extra patients in the comparator group but to analyse the resulting data appropriately. In this case, the patient number denominator needs to change so that it includes all patients who have entered the study as all go through a washout stage and all effectively survive through to a year's follow-up. If this is done we end up with the figures in Table 3.

Table 3				
Drug	**Patients**	**Suicidal Acts**	**Acts/PEY**	**% Suicides & Suicidal Acts**
Fluoxetine Comparator	6903 9213	63 15	0.054 0.002	0.91% 0.16%

If we accept that suicidal acts occurring up to a year after the trial begins are to be included in the analysis and that there have only been 4 such acts, this leads to the figures for PEY recorded in Table 3. In this case all patients who entered the study must be assumed to have been followed up for an entire year, and the denominator becomes the total number of patients in years minus the duration of exposure to fluoxetine.

Methodological Issues

From the mid to late 1980s, data on aspects of treatment also began to be presented in terms of patient exposure years. The calculation of an outcome in terms of patient exposure years or in terms of survival curves makes sense in the

case of an illness such as breast cancer where one looks at the length of time to recurrence. In these circumstances there is no particular reason not to use patient exposure years given the clear cut nature of the endpoint and in particular if the treatment protocols are not being used to demonstrate dose response effects to treatment.

However, if the issue at stake is a drug induced adverse effect, in which dose response relationships would clearly be involved if, in fact, there is a causal relationship between the drug and the adverse effect, and if the full details of variations in dose during the course of the treatment protocol are not known, then calculating the incidence of adverse effects in terms of patient exposure years is inappropriate.

It is also inappropriate to use patient exposure years where the end point is not clear-cut, or is one that characteristically appears early in treatment, or is one that can be avoided by remedial measures.

In contrast to the appearance of breast cancer, which cannot be avoided, the evolution of a clinical picture to a suicidal act in patients taking a psychotropic drug is open to outside influence. Patients commonly first get agitated. Patients who are agitated can be recoded as failures to respond to treatment rather than as patients suffering from an adverse effect of treatment. Whether the origin of the agitation is linked to treatment or a failure to respond to treatment, the patient can be discontinued from the treatment protocol.

In the case of SSRI agents and possible suicidality, the only reasonable end point that would justify the use of patient exposure years or a survival analysis is the appearance of agitation. However, agitation itself can be a feature of the illness and hence even this is not unambiguous in terms of how it might be coded by companies. In the case of trials on sertraline, whatever the origin of the agitation, trials that I have complete details on show a drop-out rate for agitation of 4.75% on sertraline versus 0.65% on placebo. These data have not been analysed in terms of patient exposure years.

A further possibility is the adoption of the use in clinical trials of a rating scale sensitive to the emergence of suicidal ideation. Such a scale was prepared by Lilly in 1990 but appears not to have been adopted in any of their clinical trials.

There is a further difficulty in terms of patient exposure years calculations in this series of antidepressant trials, which is that many of the trial protocols have involved patients who are crossed over to drugs like fluoxetine and it will not be clear in many instances just when the calculation of exposure time starts. It should ideally start after commencement on fluoxetine rather than after commencement in the trial. The relation between any dose escalation of treatment and suicidal effects in such protocols is also uncertain.

Against this methodological background, given that many of the patients who drop out are likely to be the ones sensitive to the drug induced problem, the use of patient exposure year protocols and calculations will breach randomisation by leading to the artificial selection of a group of patients who are good responders to the drugs.

1988

In the mid to late 1980s, regulators in the United Kingdom in particular, but the US also to a lesser extent, faced a crisis regarding the benzodiazepine group of drugs. These drugs, the minor tranquillisers, had been the dominant drugs on the psychotropic market up till then. But in the early 1980s, dependence on benzodiazepines was described and the benzodiazepine group of drugs fell under a cloud.

In 1988, the British regulators, the MCA, issued a position paper indicating that the benzodiazepines can make people suicidal and can also make them dependent. As regards making patients suicidal the basis for this statement comes from classic challenge dechallenge and rechallenge (CDR) reports, as well as evidence of dose response effects, and temporal relations between drug intake and outcome. These are the standard methods of demonstrating causality in this clinical domain.

The Emergence of a Public Controversy

In February 1990, a paper appeared (Teicher et al 1990) demonstrating on a CDR basis, with some evidence of dose response effects that Prozac can lead to the emergence of suicidal ideation in patients being treated with it. A series of other studies followed providing further evidence of this type.

Similar reports were filed with all companies producing SSRIs in the succeeding years, either spontaneously or in the course of clinical trials. In the course of following-up of these reports, company monitors indicated a causal relationship between each of the major SSRIs and suicidal acts based on CDR, dose-response indicators, and temporal relationships.

In some cases company monitors over-rode the assessments of treating physicians to indicated that the SSRI had caused the problem, even when the treating physician had indicated a belief that the adverse effect was not drug related.

The Licensing of Sertraline & Paroxetine

By 1991, Pfizer had applied to get sertraline licensed for the treatment of depression, and SmithKline had applied to get paroxetine licensed for the treatment of depression. The data from the clinical trials undertaken by these companies had been lodged with the regulators. These data show the following frequencies of suicides and suicidal acts for sertraline – Table 4.

TABLE 4				
Drug	**Patients**	**Suicides**	**Suicidal Acts**	**% Suicides & Suicidal Acts**
Sertraline	2,053	2	7	0.44%
Comparator	595	0	1	0.17%
Placebo	786	0	5	0.64%

And for paroxetine – see Table 5

Table 5				
Drug	**Patients**	**Suicides**	**Suicidal Acts**	**% Suicides & Suicidal Acts**
Paroxetine	2,963	5	40	1.52%
Comparator	1151	3	12	1.30%
Placebo	554	2	6	1.44%

However again as with fluoxetine there are discrepancies between these tables and the underlying raw data. In the case of both sertraline and paroxetine, placebo run in / washout suicides and suicidal acts have been coded as placebo suicidal events. Retabulating the data in a manner that separates run in from true placebo yields the data in table 6.

TABLE 6				
Drug	**Patients**	**Suicides**	**Suicidal Acts**	**% Suicides & Suicidal Acts**
Sertraline Comparator Placebo Washout/Run In	2,053 595 786	2 0 0 0	7 1 2 3	0.44% 0.17% 0.25%
Paroxetine Comparator Placebo Washout/Run In	2,963 1151 554	5 3 0 2	40 12 1 2	1.52% 1.30% 0.20%

The FDA and other regulators were in possession of these data at the time that the psychopharmacological drug advisory committee (PDAC) meeting on fluoxetine took place in 1991 to consider whether there was any evidence that fluoxetine could trigger suicidality. These regulatory hearings did not hear about any evidence on sertraline or paroxetine. The hearing came to the conclusion that the case against fluoxetine had not been proven.

One factor invoked in the fluoxetine PDAC hearings was a public health argument, according to which it might be possible to warn that fluoxetine can cause problems for some but those warnings might deter others who would benefit from fluoxetine from seeking treatment such that the overall effect of a warning might be an increased rate of suicide and suicidal acts.

This raises intriguing questions about whether in effect in the SSRI story there has been a process of covert vaccination. Some patients who will be harmed by the drug have been deliberately kept uninformed so that others might benefit.

Whatever about the ethical aspects of such an approach, a lot hinges on demonstrations that overall fluoxetine and other SSRIs reduce rates of suicide and suicidal acts in patients. The above figures make it impossible to argue that in the main SSRIs reduce suicidal events.

In fact, the original problem thrown up by Teicher et al suggested that perhaps only a small subset of patients would be adversely affected by SSRI induced akathisia/suicidality. This led to a methodological problem, namely was it possible to detect any signal from an adverse effect of this type against the

background of a larger number of patients benefiting from Prozac and other SSRIs. This problem appeared to necessitate a CDR placebo controlled randomised trial design. Such a design was drawn up by Lilly in collaboration with the FDA but was never instituted.

The figures in Tables 1 – 6, however, demonstrate that these methodological difficulties do not in fact arise. This is because while the SSRIs as a group may make some patients less suicidal, they do not appear to have a protective effect in the main but actually pose a risk in the main. This risk comes through in an absolute increase in the number of suicidal acts on drugs compared to placebo. This absolute increase holds true for all SSRIs on which data have been submitted to regulators. Data for citalopram and venlafaxine are included below in Table 7. (There are no details on whether all of the suicidal acts coded for placebo actually occurred on placebo). Comparable problems had been noted with zimelidine and fluvoxamine.

Table 7

Drug	Patients	Suicides	Suicidal Acts	% Suicides & Suicidal Acts
Citalopram	4,168	8	91	2.38%
Placebo	691	1	10	1.59%
Venlafaxine	3082	7	36	1.40%
Placebo	739	1	2	0.41%

Background Factors

First the advice from the MCA regarding the benzodiazepines and the propensity to trigger suicides would appear to be based on classic determinations of causality in the clinical domain - that is by appeals to CDR responses rather than on RCT data. The evidence on the propensity of SSRIs to trigger suicidality both from CDR reports and RCT sources is considerably more compelling than any data on the benzodiazepines.

Second, if it were argued that the data on SSRIs from clinical trials simply does not establish conclusively that there is a problem with SSRIs triggering suicidality, at the very least this data does establish conclusively that SSRIs do not in the main reduce rates of suicidality. These drugs however have been actively promoted and continue to be promoted on the basis that they should be given because they will reduce rates of suicides and suicidal acts.

This is particularly the case in the treatment of children, where in fact the data on SSRI induced problems appears most problematic – see Table 8

Table 8: SSRIs in CHILDREN				
Drug	**No**	**Suicidal Act**	**%**	**Suicidal/ Behavioural**
Sertraline: depression	44	4	9	7
Sertraline: total	197	6	3	9
Placebo	85	1	1	1
Paroxetine: depression	93	5	5	10
Imipramine	95	1	1	2
Placebo	87	1	1	1

In the course of an interview on Panorama recently, Alaistair Benbow of Glaxo SmithKline made the following statements at separate points in his interview.

"There are a number of allegations that you made there, none of which are correct and in terms of whether we think Seroxat should be made available to children? Absolutely. 2% of children, 4% of adolescents will develop depression. The adolescents are at particular risk of suicide.

"We have an obligation to make our medicines available to those patients at need. Adolescents are some of the patients who are most at need of anti-depressants. Suicide in adolescents is the third leading cause of death. ... We have a strong obligation to study our medicine in these patients to see if we can help them.

"The vast majority of these patients did not have side effects significantly enough to withdraw from the treatment. The reality is that in this population depression is an extremely serious condition and in many cases leads to suicide".

In fact, in the case say of all 13 year olds in the United Kingdom in any year between 1995 and 2002, there have in fact been at most 5 suicides. There may be valid reasons to get children on treatment with SSRIs, but suicide is not one of them. However these drugs will be promoted for use in children and adolescents on that basis, just as they have been for adults. The figures provided here, and there appear to be no other clinical trial figures that are relevant, provide no justification for such claims.

There is in fact no justification from the trial figures provided above to warrant promoting these drugs for adults on the basis of a reduction of suicidal risk either.

There might be a rationale for so doing if there were appropriate warnings to the effect that the SSRIs are the right drugs for some people but not for others, and that once we have determined that these drugs in actual fact do suit you, then ongoing treatment might have some potential to lower your suicide risk. Even this however is far from proven.

In so far as there is evidence that SSRIs may lower suicide risk in some patients to the same extent the figures from clinical trials of actually completed suicides and suicidal acts reflect an underestimate of the potential of these drugs to cause problems.

Other Data
As of 1999, when asked to investigate the effect of sertraline and suicidality by the Irish Medicine's Board, Pfizer had 252 suicidal events in its clinical trials programme, with a number of actual suicidal acts in triple figures. In a double-figure percent of cases, the investigator had linked the suicidal event to sertraline intake. In an even larger number of cases, Pfizer reviewers had linked the suicidal event to intake of sertraline. These linkages in the case of Pfizer reviewers can only have been made on the basis of assessing classic determinants of causality viz. CDR, dose-response and temporal relationships between drug intake and the adverse event.

Based on these figures, there is every reason to believe that all companies have sufficient clinical trial data on file to analyse the linkage between their drug and suicidality, taking into account the range of underlying conditions treated, the dose of drug used, and the duration of exposure. Such data however remain unavailable to the academic community.

SPC/PIL
The current SPc and PIL ambiguously refer to suicide risk increasing in the early phase of treatment. These statements are made against of background where the majority treatment of depressive disorders is in patients with milder conditions, likely to benefit little from treatment, but more importantly in a patient group treated in the community unsupervised and unwarned.

Again and again the story from patients in response to programmes like Panorama is that when they encounter problems during the early phase of treatment and consult their GP they are likely to be told that this is their illness and they are commonly encouraged not just to adhere to treatment, but to increase the dose. This response can be justified by GPs on the basis of an appeal to the current SPc and regulatory figures and others have portrayed the current UK wording as meaning just this.

For patients similar factors apply. When they get worse in the course of treatment, they often do not make the connection to treatment and failing to do

so suffer an injury to their self-esteem and self-confidence that can in my experience be very long-lasting.

If patients have engaged in actual suicidal acts as a result of treatment and the connection to treatment is not made, given that prior suicide attempts appear to increase the risk of future successful suicides, it can be said that the risk of a future successful suicide has been increased accordingly.