Department of Psychological Medicine
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

Tel : (01248) 384452
Fax : (01248) 371397

16th April 2003

Dr Russell Joffe
Co-Editor-in-Chief
Journal of Psychiatry & Neuroscience
Canadian Medical Association
Publications Directorate
1867, prom Alta Vista Drive
Ottawa ON KIG 3Y6
CANADA

Dear Dr Joffe

Re. Antidepressant Use and Suicide: Risk-Benefit Conundrums
(Point-Counterpoint feature: manuscript A)

In early 2001 Wyeth organised a meeting at Laguna Beach, California centred on an analysis of their drug undertaken by Michael Thase. This subsequently appeared as an article in the British Journal of Psychiatry. It led thereafter to an editorial in The Lancet: “How tainted has medicine become”.

As part of the same meeting, Wyeth Canada organised Canadian input through an agency based in Toronto called CMED. When CMED put considerable pressure on myself and a colleague Dr Tranter to get involved in this meeting, we considered the possibilities and agreed. CMED were offering to write an article for us. An article duly arrived in the post with a covering letter stating that we could change whatever we wished.

We made two changes. One was to mention data from a competitor compound Mirtazapine that were inconsistent with the message that Wyeth wanted to

deliver. The other was to insert a brief reference to the fact that particular antidepressants can suit certain individuals and be very helpful for them but the same drugs can be unhelpful and perhaps harmful to other individuals. Within 24 hours or thereabouts we were told that we could not make these changes - in particular we could not make the references to Mirtazapine.

The next I got to see of this manuscript was after a final copy had been sent to your Journal without me having seen the final copy beforehand. It turned out that it was completely re-written. While Dr Tranter had considerable input into this draft, as I understand it he did not attempt to remove and would not have removed the reference to the notion that the wrong antidepressant for the wrong individual can make them suicidal but this was now missing. Also inserted was a section about further research being needed but in the meantime it would be best to prescribe everybody Venlafaxine, something that neither he nor I would ever have inserted into this manuscript.

At this point I contacted you and made it clear that I was not happy with the manuscript as it stood. This provoked something of a crisis that led you to ask authors to sign an authorship declaration. I felt it was not possible for me to sign one. At that stage I had no idea where certain key sections of this article had come from and nobody seemed interested to enlighten me.

As part of a compromise, which enabled things to move forward I offered a brief commentary on the article that incorporated some of the points that I had made in the first instance. This was reviewed and the Journal suggested that the piece as it stood was not publishable but might be considered if developed at this part of a point counterpoint piece. I readily agreed to this. It took close to a year to get the counterpoint piece in place.

I was then informed by e-mail by Megan Sproule-Jones that these would be published at the latest in the July issue of the Journal but quite possibly in the May issue. I then heard that the piece was to be reviewed again. I agreed to this.

We end up out of this with the reviews that you have forwarded to me with a comment that “while we hope that you will revise your paper taking into account the suggestions and concerns, we recognise that such revisions may be extensive and perhaps indeed prohibitive”. This I would note in passing seems to pre-judge the issue.

The first review talks about my biases although does so by saying that it’s careful not to use the word bias and ends up with the intriguing comment “you can always have an accompanying guest editorial or letter probably simultaneously that will express any remaining differences of opinion between Dr Healy, the reviewers and perhaps the editor”.

The second review offers a series of points that I respond to in the accompanying response to reviewers. This outlines my position on the issues raised.

I think in the light of these responses, it is up to you to make a decision about what you and the Journal choose to do from here rather than being up me to make a decision as to whether the extensive work that needs to be done might be prohibitive or not.

I look forward to hearing from you.

David Healy

Response to reviewers

Reviewer 1

The main point as regards to comments made by reviewer 1 is the following:

My position is that the case as to whether SSRIs can cause suicidality had in fact been established through the series of controlled case studies involving challenge, de-challenge, re-challenge designs and dose response relationships in the early 1990s. The issue that remained after that then was rather a public health issue as to whether antidepressants should have explicit warnings.

Conceivably, if this problem was extremely infrequent, warnings about suicide induction might deter patients who might otherwise benefit from treatment and although in one sense it might be correct to have warnings a greater number of people might die as a consequence. But clearly there can also come a point at which the problem happens with sufficient frequency that on balance warnings are warranted.

This is the main thrust of my article - and the word conundrum in the title picks up on this point. Reviewer 1 appears to miss that what I'm doing is not attempting to prove through the scrutiny of randomised controlled trial data or epidemiological studies that SSRIs cause suicide but rather attempting to establish what can be said about the rate at which this is happening with a view to deciding whether warnings are appropriate or not. On balance I come down in favour of warnings.

I suspect that this is a position that most secondary care or academic clinicians would favour in that when I hear them talk about this issue in lectures, even clinicians who deny the possibility that SSRIs cause the problem with any significant frequency typically state that it is good clinical practice to warn patients of developing hazards and that they may feel worse in one way or another. The main difference between me and these other clinicians lies in the fact that I think the data is sufficient to warrant explicit warnings.

Response to reviewer 2

The first point to make in response to reviewer 2 is a point that also applies to reviewer 1 which is that I suspect it's quite possible that neither reviewer knows that I was operating under a space constraint. When developing this piece I had been informed that there was a relatively strict word limit upon it – one that quite obviously made it difficult to develop the argument in full.

Let me ask you whether the reviewers were aware of this?

The first point made by reviewer 2 has to do with the Kahn paper and the removal of placebo washout suicides and suicidal acts, and suggests that this may not be problematic.

I can tell you as editor and this reviewer that when asked to justify this procedure regulators from the FDA testifying under oath as well as FDA documents on the issue state explicitly that it is not warranted to include placebo washout suicides and suicidal acts within the body of suicides and suicidal acts that result from the remaining randomised phase of a study. I can provide documents to this effect.

On the second point, I can provide a statistical significance rate for the differences between antidepressants and placebo as requested.

Third, the reviewer picks up the Storosum and Laughren references but in fact doesn't deal with the Laughren reference. The Storosum reference is one that the reviewer fails to appreciate is compromised by almost precisely the same issues that affect the Kahn analysis – namely that it's difficult to have confidence in company trials submitted to regulators when it comes to claims about the rates of suicide and suicidal acts occurring on placebo.

As regards the issue of long-term studies, then raised by the reviewer, this point seems to miss the most important methodological point made in my argument, which we can term for the present the Space Shuttle Fallacy. Somewhere in the mid 1980s SSRI producing companies learnt that analysing their data by patient exposure years minimised the apparent problems linked to the drug. However, analysing the data in this fashion breaches the randomisation in these clinical trials because it selects out a group of patients who are not responding adversely to the drug. This then enables the companies to prove something equivalent to the notion that travelling on a space shuttle is actually safer than walking around your own house. A space shuttle covers millions of miles and the numbers of deaths per million miles is almost certainly lower than the number of death per million miles walking around one's house. However, what this fails to take into account is the hazards of exiting the earth's atmosphere in order to get into orbit and equally the hazard of re-entry. The problem with SSRIs, as outlined in my article, lies in the hazards of exit and re-entry. The typical problems are not ones

that apply to patients who are orbiting successfully on treatment. Selecting long-term studies in order to look at this issue is entirely inappropriate because it explicitly selects “orbiting patients”.

The next point raised by the reviewer is the criticism I offer of the analysis undertaken by Lilly of their database. The reviewer suggests my arguments are less than cogent. I have developed these points more fully and more cogently elsewhere and these other sources are referenced. Because of constraints on word count did not develop them as fully as I might have done in this article but this could easily be done.

The problems in Lilly’s analysis are far more profound than will be apparent from what I’ve said in this section of the paper and I invite you and your reviewer to consider the following.

In their Beasley paper in 1991, Lilly analysed a total of 3000 odd patients. But at the end of 1985 they had 8000 patients and data on these 8000 patients were submitted to the German regulators as follows – see Table 1.

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. Comparator here includes all patients randomised to either other antidepressants or placebo.

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	6903	63	0.054	0.91%
Comparator	2310	7	0.02	0.3%
Washout/Run In		4		
Other		4		

The figures on which Table 2 is based comes from Exhibit 1 in the Deposition of Gregory Brickler in Fentress v Eli Lilly in 1994. I would be happy to provide this to you and your reviewer on request. I would be fascinated to hear what you or your reviewer make of Tables 1 and 2. In the light of these Tables, I wonder whether the reviewer still thinks the points being made about my criticism of the analysis done by Lilly hold.

The next point made by reviewer 2 can be handled readily. I am happy to concede that the analysis offered by Beasley et al in 1991 and Montgomery et al in 1995 for Paroxetine demonstrate that SSRIs can reduce suicidality in some patients. This is not damning with faint praise but rather is a key point in the argument. If this is the case then the resulting figures, which demonstrate an excess of dead bodies and suicidal acts on SSRIs compared to placebo, becomes even more problematic.

The reviewer then turns attention to an apparently gross omission, which is not mentioning that some suicidal patients may have been bipolar – this appears to indirectly concede drug causation. Owing to word count constraints I did not go into the mechanisms by which SSRIs can trigger problems. Where I have done so elsewhere, the reviewer could quite readily find I have noted that the precipitation of manic or psychotic episodes is one of the likely mechanisms whereby suicidality is engendered in some patients. It seems that the reviewer and I can agree on this point.

The reviewer then moves on to a claim that the epidemiological evidence is far from convincing. A number of confounding factors are noted. I readily conceded that there may be confounding factors. The point behind randomised controlled trials I thought was to control for such confounding factors. The appearance of exactly the same result from the randomised controlled trials as from the epidemiological studies seems to me to be reassuring on this point. What is less reassuring is that the reviewer does not seem to have taken this into account.

It may well be as the reviewer says that clinicians in real life have restricted these compounds to patients who appeared at greater risk. It could also be that these compounds cause a problem and the patients who are at greater risk and who end up on these compounds in actual fact are being put on compounds having had the problem caused by this group of compounds in the first instance. It would be nice if the reviewer had the grace to concede both possibilities. At the end of day, the data seem to indicate that at the very least these drugs are not minimising the problem in people who may be at greater risk.

The final point made by the reviewer refers to the Leon study. Again, there certain possibilities seem to have been overlooked here. One is that this was a study conceived 20 years before Prozac had been first brought on the market and begun 10 years before Prozac had first appeared on the market. Over 300 patients had dropped out by the time Prozac came on the market. Many of these will have been treated at one point or another with drugs that are serotonin reuptake inhibitors such as the older tricyclic agents. In this fashion there is enormous scope for the particular study in question to have weeded out patients likely to have problems with drugs that are serotonin reuptake inhibitors. The fact that Prozac did not do particularly well against this background really doesn't offer any grounds for a lack of concern regarding this drug.

The Leon study was not a prospective naturalistic study designed to look at suicidality and Prozac as the reviewer implies but rather a post-hoc analysis and as most methodological texts say such post-hoc analysis are fraught with problems. Given that only 185 patients go on Prozac compared with more than 50,000 who go on an SSRI of one sort or the other in the prospective naturalistic studies I make reference to and the approximate 16,000 patients who go on SSRIs in clinical trials I refer to, I find myself less than impressed by this particular point.

Finally, as I understand it, it is not the job of a reviewer and perhaps not even the job of an editor to agree with the overall conclusions arrived at in an article. The job of the reviewer is to comment on methodological issues. It is not clear to me that this reviewer has done this despite the appearances of commenting on methodological issues.

Where the points raised do concern methodological points such as the appropriateness of including long-term studies, it appears that the reviewer and I have quite different understandings of the methodological point at stake. I agree with the first reviewer at this point, which is that perhaps one of the ways to handle such differences is in a point and counterpoint fashion until such time as these methodological issues – quite aside from any conclusions that they may lead to - are resolved.