

Our Ref: DH/JT

31 May 2000

Richard Horton
Editor
The Lancet
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Dear Dr Horton

Please find enclosed a short piece as a possible commentary for the Lancet.

I realise that commentaries are ordinarily invited. This piece therefore needs some introducing. Along with colleagues I recently conducted a double blind randomised healthy volunteer study here in North Wales which has generated a large amount of data that I and my colleagues are currently working on. One of the very clear outcomes however was that two of our healthy volunteers, medical and nursing colleagues became suicidal. The study hadn't been planned to detect this eventuality. The level of suicidality was disturbing. I enclose a peer reviewed copy of the article where we've reported on this aspect of the study.

I am also involved in a small number of legal cases involving SSRIs and suicidality. In the course of this I've become aware that there are a number of other healthy volunteer studies dating back many years which have found similar results. Indeed the rate of development of the kind of complications we saw has in some other studies been much higher than we found. Owing to confidentiality agreements I am under some constraints as regards communicating to you exactly what has happened in these other studies which remain unpublished. However as you will see in reference 2 in the enclosed piece I refer to a deposition that I recently gave in the United States where many of the details of one of the studies in question were laid out. In brief in one placebo controlled study all volunteers randomised to Sertraline dropped out within days with severe agitation. The entire deposition can be forwarded if need be. I am aware of other similar studies with Paroxetine.

Continued/..

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The situation therefore I believe is, as I've reported it in the commentary, that it would be extremely problematic for ethical committees in this country or the insurers of research to let studies with SSRIs in healthy volunteers go ahead without appropriate warnings and monitoring. There are a number of centres both here and elsewhere conducting such studies. More to the point however are the implications for all other subjects taking these drugs.

One reason for seeking a publication in the Lancet is in order to communicate this situation to as large a number of prescribers as effectively as possible. The issues are clearly very sensitive. I may well not have phrased the important points as clearly as possible. Further elaboration in certain areas may be called for. If you have any interest in this piece or some piece in this area I would be very happy to travel to London to meet you and discuss how best to craft something that would have the best risk/benefit ratio.

Brief though this piece is, I have as you will see attempted to bring a few other issues into the frame at the same time. The points I'm making are very clear to me but I've lived with these issues for so long now that there is a real risk that what appears straight forward to me may not appear so straight forward to others. The connection between all the points may not be obvious to others. I enclose a further piece on Clinical Trials and Legal Jeopardy which lays out some of the issues in slightly greater detail.

It would not surprise me if you felt that these are issues that are not appropriately addressed in this form in the Lancet at this point in time. I would be very grateful, however, if your hunch from the start is that this is likely to be the case that you would perhaps let me know early on in the process so that I can begin thinking about what else I should do to move some of these issues forward.

Any thoughts or advice you have on some of the points I've raised would be very welcome.

Yours sincerely

David Healy
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Encs.

SSRIs & SUICIDE: A Situation Without Precedent.

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We recently reported the results of a double-blind cross-over study in twenty healthy volunteers comparing the effects of sertraline, a selective serotonin reuptake inhibitor (SSRI) and reboxetine, an agent with no effects on the serotonin system. One of the outcomes of this study was that two volunteers became agitated and suicidal (1). Other studies of healthy volunteers reporting much higher rates of marked agitation and probable suicidality, within days of starting an SSRI, exist (2). They remain unpublished. Accordingly, this information was not known to us, at the point of application for ethical permission for the above study.

In the light of these healthy volunteer studies, ethical committees in this country would have significant problems sanctioning studies with SSRIs in healthy volunteers without well-thought out arrangements for warning volunteers and monitoring their progress. The agencies, which insure such studies for university departments, might have even greater problems.

In 1993, in the course of pharmacokinetic studies with sertraline in children, an 8-year old boy with obsessive-compulsive features developed suicidality and mutilated himself severely. The clinical investigator attributed this to the sertraline the child was taking (3). Pfizer, when reporting this to the Food and Drug Administration in May of 1996, noted that “[drug]- induced activation is a plausible explanation for the emergence of suicidal behavior in our patient” (4). They invoked earlier reports of similar findings on fluoxetine (5).

Despite the difficulties ethical committees or insurers might have letting medical or nursing personnel take an SSRI, and despite frank admissions of causality filed with regulatory authorities, these drugs remain available without warnings in this country. They are in fact being prescribed to an ever-larger number of people, who are more accurately seen as suffering from stress reactions or adjustment disorders rather than depression. In addition, they are being prescribed for an ever-larger number of children. Among primary care physicians, who are the largest prescribers of these drugs, some recognise the hazard and monitor appropriately but many, perhaps a majority, do not. Enquiries from companies will lead to a denial of the problem. The situation is extraordinary, perhaps unparalleled in therapeutics.

There are a number of other extraordinary features to this situation. The initial reports of drug induced agitation or akathisia came 45 years ago; they were notable because this reaction led to suicides in individuals who had no history of mental illness, taking reserpine for hypertension (6). Despite this and despite acknowledgment by senior figures in the field that akathisia is probably the greatest hazard of psychotropic agents, there has never in the past 45 years been a single symposium at any major meeting in either the English speaking world dedicated to this problem.

A second point is as follows. When the SSRIs emerged, fluoxetine was associated in independent clinical studies with a rate of akathisia in up 25% of those taking it (7). Authoritative manuals on psychotropic drugs state that the propensity of fluoxetine to

induce akathisia is well known (8). In the clinical trials programme associated with its commercial development, however, neither akathisia nor suicidal ideation appear as hazards of treatment. These events were not recorded. The results of these latter trials, and comparable trials for other SSRIs, are at present being used in legal contexts to deny that fluoxetine could have induced akathisia or suicidality in subjects who have committed suicide. If this defense is successful, one consequence would appear to be that participation in any clinical trials that are part of the development programme for any drug risks putting the entire national community in a state of legal jeopardy (9).

Finally, it has recently emerged that Lilly have purchased the marketing rights on a patent of an isomer of fluoxetine, R- fluoxetine. This has been patented on the basis that it may, but is less likely to, induce akathisia and suicidality than the parent compound (Prozac) (10). Given the basis of the patent, this compound if marketed in several years time will presumably have to come complete with warnings. It is not clear how regulators and companies could tolerate a situation in which such an agent would come with warnings while older more hazardous agents do not have a warning. But neither is it clear given legal actions currently in train, how such an inconsistency can be avoided. If not unprecedented, the situation would appear at least to be extra-ordinary.

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20th July 2000

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Dear David

Many thanks for your letter of May 31 and apologies for not getting back to you sooner. My hunch is that this is the sort of subject that should be raised in the pages of *The Lancet* but I think the best approach would be for you to write a slightly fuller viewpoint article of say 1500 words. I see you already have had several publications that relate to this subject, and it would be important that you try to say something new and original in a piece for us. Would you like to try and put that together? What we would then do is to seek a response from the drug company and perhaps even a regulator within the Medicines Control Agency or Food and Drug Administration. Let me know if this is an idea that appeals.

Kind regards

Yours sincerely

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30th November 2000

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Dear David

Many thanks for submitting a draft of your piece on SSRIs and suicidality. I think your arguments are very cogent and I welcome the piece very much. As far as referencing is concerned, we would send your piece out for peer review when it is in a final form and so you should write it and reference it thinking about the sort of criticism that might be levelled against you regarding your interpretation of the available data. The arguments and supporting evidence should be designed to neutralise these criticisms. When you are comfortable with a final version do please send it to me and I can get on with the process of reviews.

Kind regards

Yours sincerely

Richard Horton
Editor

Our Ref: DH/JT

18 December 2000

Dr Richard Horton
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Dear Richard

Enclosed is a reviewable draft of the SSRIs and Suicide article. I have been to see the MCA and had a very cordial meeting. Clearly while they may not be prepared to fully endorse in public the article you have here, there was no hint from anything in the meeting that they would disagree with anything you find here. I was rather hoping that there was some evidence somewhere in the system that I've overlooked that would cause me to stop and think further.

There is some background to this article that it might be helpful for you to be aware of. In brief healthy volunteer studies with all types of psychotropic drugs were conducted from the 1950s onwards. There was a clear recognition in the field that in contrast, for example, to studies with minor tranquillisers in healthy volunteers that even single doses of antidepressants could give quite odd and strange reactions. (I can provide references to this.) People who were depressed in the 60s and 70s, however, looked very different to normal individuals. This led to a reasonable assumption that there indeed was something clearly wrong with the brains of such depressives and that this might underpin the discrepancy between the apparent deterioration in the level of wellbeing of healthy volunteers on antidepressants and the improvement in people who were depressed on the same drugs. This rationalisation sat beside evidence from the very first clinical trials in the late 1950s that people who were depressed given antidepressants might have exactly the same odd and strange reactions as healthy volunteers leading some of the early clinical trialists to implicate antidepressants very clearly in the production of suicidality.

The major problem for this rationalisation has been the swing during the 1980s from anxiety, anxiolytics and tranquillisers to depression and antidepressants. Put bluntly cases of Valium have become cases of Prozac. Whereas in the 1960s and 1970s it was only relatively severe forms of depression that were treated – very often under supervision in hospital settings - now by far the commonest mode of treatment is the primary care treatment of what many might judge to be stress reactions in otherwise normal individuals. These individuals do not look very different to normal volunteers and the expectation therefore that antidepressants will not produce the kinds of effects that they were widely recognised to produce during the 1970s and 80s no longer seems a safe assumption – particularly as the healthy volunteer studies with SSRIs probably show an increased frequency of such reactions in normal volunteers. It is this background that underpins the opening construction of this piece. I mention it partly to shed light on some of the dynamics involved but also because you may well feel that opening up the article making these historical connections more explicit might be more helpful. I am open to revising any points such as this or others you feel might be handled more constructively.

I've tried to retune the piece so that you'll have a minimal amount of unpublished material. For the Eli Lilly RCT data from 1986 (reference 10), I enclose the referenced memorandum, which is public domain material and can be forwarded to any referee. There are however a number of points that need to be borne in mind about this document. First as regards the suicide and suicide attempts listed under Placebo in the document, it is clear that two of these occurred in the placebo washout period of the clinical trials in question with the patients randomised to go into active treatment rather than the placebo arm of the studies. There are therefore a number of options for handling these data. Clearly Lilly have picked the option most convenient for them – to count these in the placebo treatment arm. Another option would be to subtract these two subjects from the placebo group and allocate them to the fluoxetine figures. A third option would be to add a figure of approximately 6000 suicide-episode-free patients to the placebo arm on the basis that all of these were on placebo at some time during which no suicidal episodes occurred other than the two in question. A fourth option would be to discard these two subjects completely. Using any of the latter three options, you get the figures I cite in the paper.

In managing these data Lilly undertook another interesting methodological step. In the case of all patients who had been on fluoxetine at some point who made any suicide attempt during the year following their clinical trial participation, these attempts were allocated to the comparator group. This would appear to many perfectly reasonable – when they committed their suicide attempt they were of course not on Prozac and were on another antidepressant. However the situation methodologically works out as follows. If in 100 patients taking fluoxetine there are 10 suicidal attempts while in 100 patients taking comparator antidepressants there are only 5, following up the 100 patients taking fluoxetine over the course of the following year and detecting anyone who has any suicide attempt and allocating these to the “other” group very rapidly produces a situation where if there are 5 suicide attempts during the following year there will then have been 10 suicide attempts from 100 patients on fluoxetine and 10 suicide attempts from 105

patients taking comparators. I cannot quantify for you the extent to which this may have influenced the figures you have here but it is part of public domain trial testimony that it happened. I have not however factored this into my calculations. The true figures for suicide attempts on comparators should be lower than the figures I have used.

The final methodological issue although it's not relevant for these figures is that Lilly introduced the notion for controlling for exposure time and expressing the figures in terms of patient years. This favours them in that the problems on fluoxetine occur in the first month of treatment and the patients who then go on to extended treatment for a year or so clearly introduce a dilution effect.

In the case of my own analysis of Pfizer's clinical trial database, I am not at liberty to reference any material. However going into print with this claim does offer the manufacturers the opportunity to publish their own data in order to rebut the point that I'm making. And in fact I believe I'm being somewhat generous to them in this area by looking only at figures for suicide and suicide attempts and not including figures for people who have become suicidal or who discontinue treatment because of suicidality. Were that included the relative risk for Sertraline would be greater than the figure I cite here.

In the references you'll see in some instances I've included up to three references under the one note. I'm not clear on how you would wish to handle this. As regards, other public domain documents mentioned in this piece, I can forward any or all if need be.

Yours sincerely

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SSRIs & SUICIDE:

A Situation Without Precedent.

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We recently reported the results of a double-blind cross-over study in twenty healthy volunteers comparing the effects of sertraline, a selective serotonin reuptake inhibitor (SSRI) and reboxetine, an agent with no effects on the serotonin system, one of the outcomes of which was that two of the volunteers taking sertraline became agitated and suicidal (1). There are other studies of healthy volunteers reporting even higher rates of dose-dependent agitation and probable suicidality, within days of starting sertraline, published (2) and unpublished (3).

The traditional defence of SSRI-producing companies to the argument that these agents can induce suicide has been that any suicidality stems from underlying depression and not the drug. These healthy volunteer studies breach that defence, as do unpublished reports that eight year old boys with obsessive compulsive disorder have become agitated and suicidal on sertraline with company assessments that the suicidality has been caused by the drug (4), along with reports to Lilly of patients with eating disorders becoming suicidal on fluoxetine (5) and extensive testimony to the Food and Drug Administration from individuals without affective disorders, prescribed SSRIs for obesity and smoking cessation, becoming suicidal shortly after starting fluoxetine (6).

The original studies linking fluoxetine to suicide came from senior psychopharmacologists in a number of eminent centres and included evidence of dose-response relationships between fluoxetine and suicidality, challenge, de-challenge and re-challenge relationships, and a clearly outlined mechanism, sufficient understanding of which was available to permit demonstrations that certain agents minimised the problem

(7). By the end of 1991 according to standard canons of causality for the assessment of drug induced adverse events, there was a conclusive relationship between fluoxetine and suicidality. All that remained to be done was to establish the frequency at which the phenomenon was happening.

In response, the makers of fluoxetine, Eli Lilly, in 1991, meta-analysed a series of studies, none of which were designed to test whether fluoxetine could be associated with the emergence of suicidality. They claimed that the meta-analysis showed that fluoxetine was as good as other agents and better than placebo for patients who were suicidal (8). In fact only 3,067 patients of the approximately 26,000 patients entered into clinical trials by the company were included in the meta-analysis. No mention was made that benzodiazepines had been co-prescribed in the clinical trial programme in order to minimise the agitation that Lilly themselves recognised fluoxetine could cause. No reference was made to the 5% of patients who dropped out for anxiety and agitation, the very problem that was at the heart of the argument. No mention was made that some of the trials and investigators whose work was being reported had had their work questioned by the FDA. Despite these manoeuvres, the scrutiny of the data by FDA officials, by statistical reviewers with the British Medical Journal, as well as by Lilly's own consultants made it clear that the core problem had not been addressed and that even from these data there was an excess risk of suicidality on fluoxetine (9).

In contrast to the results from selected studies in 1991 the entire depression clinical trial database for fluoxetine as of 1986, comprising approximately 8000 patients, indicated a

three-fold increase in the relative risk of suicidality for fluoxetine over placebo, and a 5-fold risk over comparator antidepressants (10). These data remain unpublished. My analysis of the unpublished sertraline depression trials database as of 1991, indicates a similar excess risk for sertraline over placebo of approximately 2-fold and a greater relative risk for sertraline versus comparator antidepressants. These data are consistent with published data from Pierre Fabre's clinical trial database showing a three-fold excess risk of suicidality for SSRIs over milnacipran or tricyclic antidepressants (11). They are also consistent with data recently published indicating a relative risk for newer antidepressants over placebo of 1.4 (12).

There are two points of note in these figures. One is that these same studies show a differential relative risk of inducing suicidality between new and older antidepressants, although a proper analysis of the relative risk of older antidepressants versus placebo has still not been undertaken. In academic and medico-legal debate at present, following the breast implant litigation controversy (13), pharmaceutical companies argue that the fact that there is no evidence that the relative risk of inducing suicidality for SSRIs versus placebo is not greater than 2.0, there is no evidence that these agents cause a problem. There are considerable difficulties in establishing an appropriate relative risk for an agent that both causes and cures a particular problem, as in the case of pertussis vaccines for instance. Based both on the preliminary evidence for older antidepressants from SSRI trials and a common sense analysis, it is possible however to suggest that the relative risk of inducing suicidality for an antidepressant in clinical trials versus placebo probably

should not exceed 0.5. In situations where it does, there are grounds to suggest that warnings of a specific drug-induced problem may be appropriate.

In reply to concerns based on the above patient and volunteer data, the Medicines Control Agency (MCA) have stated that a relationship between suicidality and SSRIs is not supported by the epidemiological evidence on fluoxetine (14). The epidemiological evidence cited by the MCA consists of six studies. The first is a one column letter, which even Lilly have not used in their defence (15). The second was a selective retrospective post-marketing chart review (16), which analysed by the American College of Neuropsychopharmacology, the FDA and others shows a 3-fold increased relative risk for fluoxetine versus other antidepressants (17).

A third study was conducted by Warshaw and Keller (18) on anxious patients. In this the only suicide occurred in someone taking fluoxetine, undercutting the standard disease and not the drug argument. More importantly however this study was a study of 654 patients of whom 192 only got fluoxetine. It was neither a study designed to test fluoxetine's capacity to induce suicidality, nor an epidemiological study.

The fourth study, by Leon et al (19), was conceived 20 years before fluoxetine was launched and instituted 10 years before launch. This was clearly not a study designed to answer the question of whether fluoxetine could induce suicidality. Nor was it an epidemiological study. There were only 632 patients of whom only 182 at any point got fluoxetine.

The fifth study by Mackay et al (20) was a post-marketing surveillance study. While containing a large number of patients, it only compared SSRI antidepressants to each other and hence cannot answer the question of whether the risk of suicide is raised compared with non-SSRI antidepressants or non-treatment. It was furthermore conducted against a background of Lilly representatives advising that a “serotonin pickup syndrome” can occur during the first weeks of treatment and that this is a sign that the drug is working and that patients should not be discontinued from treatment. It is far from clear that physicians are likely to report evidence that a drug is working, or events they are told stem from the disease they are treating, through an adverse event reporting system. The MCA omit from their list another set of post-marketing surveillance studies which have compared SSRIs with non-SSRIs and found a clear differential in the rate of suicide induction (21)

Finally the MCA refer to a study by Jick and colleagues (22). This study of 172,000 scripts for antidepressants in primary care in the UK is the only epidemiological study in the field. This gave a doubling of the relative risk of suicide on fluoxetine compared with the reference antidepressant dothiepin. Controlling for all confounding factors left the relative risk at 2.1 times greater for fluoxetine compared to dothiepin and greater than for any other antidepressant studied. The suicide rate for fluoxetine was 187 per 100,000 patient years. This needs to be set against the figure for the probable annual suicide rate for primary care depression in the UK or elsewhere. The traditional rates of a 15% lifetime risk for suicide for affective disorders are derived from hospitalised samples of

melancholic depressives in the pre-antidepressant era. The only figures available for primary care depression are from Sweden (23), which gives a figure of zero per 100,000 patient years, and from Holland, which gives a figure of 33 per 100,000 patient years (24). Set against these figures, the Jick study points to a possible 6-fold increase in the relative risk of suicide on fluoxetine.

There have been recent regulatory moves to highlight the risk of suicide in the treatment of depression but the current wording nevertheless stresses the patient and their condition as the origin of any problems. Against the background outlined above however it is difficult to see how regulators can maintain a position of failing to warn that drug treatment may carry an independent risk of provoking suicidality. It is highly unlikely that Ethics Committees aware of this data or insurers aware of similar data would sanction a study in healthy volunteers using an SSRI in which those volunteers were unwarmed and unmonitored. This however remains the case for the many patients with nervousness in primary care who are given Prozac and other SSRIs and for the increasing number of adolescents and children being put on these drugs. The gravity of the situation makes the regulatory recourse to the “epidemiological” studies listed above extraordinary.

Finally it has recently emerged that Lilly purchased the marketing rights for R-fluoxetine, an isomer of the parent compound. This was patented on the basis that it was less likely to induce suicidality than the parent compound (25). Owing to a technicality, this compound is not now going to be developed by Lilly. The situation is nevertheless

extraordinary in that the new compound would presumably have had to come complete with warnings indicating the hazards the agent itself posed, on the basis that its patent states that it may induce suicidality although it is less likely to do so than fluoxetine. At the same time the original and a growing number of generic versions of fluoxetine would presumably have remained without warnings. The situation is without precedent.

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Dear Dr Healy

The reception of your paper at the hands of referees has been almost as lively as the article itself, as you can see from the enclosed comments. To put it simply, you are charged with bias. A totally balanced viewpoint is, arguably, no longer a viewpoint but the strength of the criticisms of your draft do suggest that more care is needed. For example I have had the opportunity to read re. 22 in your paper which clearly does not reflect the authors own interpretation of their findings. An uncited paper by Jick and colleagues published in *Pharmacotherapy*, 1992; 12: 451 concludes that "These data indicate that fluoxetine does not directly cause suicidal behaviour at a substantially higher frequency than do lofepramine, mianserin, and trazodone". I know you have appeared as a witness for plaintiffs in litigation in this area and I do feel that involvement should be declared.

The Lancet is willing to look again at your paper once you've had a chance to digest the enclosed comments and to revise the paper in the light of them. However, I cannot really make many firm promises as to what the final outcome might be.

Yours sincerely

David Sharp MA
Deputy Editor

EncSSRIs and Suicide: A situation without precedent.

Referee A

Re: DS/lal – 00/12340

As you say this is an immensely important issue: indeed the effectiveness/risk profile of the SSRIs is an issue which has concerned me for some time. One of the reasons for my not tackling it is that it seems too big to deal with in almost every dimension. There is such widespread use, for such different indications; there are so many of such a variety of serious and curious putative ADRs; and there are such entrenched attitudes in different sectors of society.

I say the above because Dr. Healy touches on one major issue in his letter, but not in the article, namely the change in diagnostic criteria and the management of depression, and other psychiatric illness, which has taken place concomitantly with, or because of, the use of SSRIs. Charles Medawer has tried to capture some of this in an overview article ‘The antidepressant web’ and links to previous work (refs. Enclosed).

I, perhaps out of my own inferiority or just awe at the amount of effort needed to deal with this drug phenomenon effectively, have difficulty in seeing how to tackle the problem either piecemeal or broadly.

The issue of suicide is a continuing saga. Dr Healy, in this paper, does not refer to the early hypothesis that the SSRIs improve the depressed patients poverty of positive ideation, sluggishness and immobility, before they elevate the mood, so that the depressed patient may be more able to take action based on any suicidal thoughts they may have. This explanation, albeit speculative, is very widespread and is somewhat, and critically, different from the dichotomous view Dr Healy expresses, that the depression is said to blameworthy (how he sees the relevant companies' view) and that the drug is to blame (his hypothesis). I think this is why there has not been more concern over the issue; this latter explanation really blames an interaction between the drugs and the disease, and has allowed both the for and against SSRI lobbies to claim some measure of success. It has also resulted in a strategy to alleviate the early symptoms of SSRI use in depression (eg. Smith WT et al. Encl).

Dr Healy has re-focussed us on the drug itself as cause for suicide by arguing that suicidal ideation occurs in volunteers, and by giving us his critical analysis of key evidence. Unfortunately, this is not a complete survey of all the evidence, and I have enclosed the result of a Medline search done simply on ‘SSRI and suicide’. This has come up with several papers (encl.) for and against Dr. Healy’s view. This illustrates the importance of the controversy, and the need for a complete analysis of the evidence. Dr Healy has not always indicated when there is discussion, on key references which he uses such as Jick (ref.22), which refers to possible selection bias, also proposed by the authors themselves.

I made the point earlier about the vast use of SSRIs and the changing face of psychiatric treatment. That SSRIs may now be used in patients with minor psychological and even non-psychological illness should be of crucial importance to this paper. It is this which justifies a fresh consideration of the issue, and must be taken out of the letter and into the

paper. I must now return to the broader issues. There are many suspected adverse reactions reported to these drugs in the WHO database, in the order of 100 000. Moreover, they are from many body systems and of different types. Many of the events reported may be unrelated to the drugs, but mood changes of various sorts, endocrine, and sexual dysfunctions stand out from the background. As I have said before I have felt the urge to try to analyse the information into some logic, but the task was difficult prior to the use of data mining. For example, inappropriate ADH secretion is one outstanding effect, as is altered electrolyte balance. Clearly they may be associated , but is there a further association with suicidal ideation because of the physiological changes? How frequently and to what degree is ADH secretion altered overall in patients? Does the alteration in fluid balance link to visual disturbances and glaucoma which are also reported? What about other endocrine disturbance? All these links are patho-physiologically plausible leads to follow. In terms of effectiveness – risk balance such an analysis is vital given the use of the drugs in such a large number of patients. Socially and politically we must know the overall effect long term. One view, which is implied by Dr Healy in his letter, is that SSRIs are not the ‘opium of the people’ and that we may be using these drugs to combat psychological illness which may have roots in the way society is changing. Is this desirable?

Charles Medawar has previously drawn attention to this sort of issue in ‘Power and Dependance’, so my thinking is not new. Many have tried to ignore his warnings, even though the SSRIs, are the second most sold drugs in the US (Prozac alone is the 19th most prescribed drug in the US). Because of extensive use of these drugs in nearly normal people, we have to consider their use in a depth and breadth of context hitherto unheard of. Though benzodiazepines have also enjoyed very wide use, their impact on physiological function seems to be much more limited.

I appreciate that the above is a rather rambling response to your specific request to referee Dr Healy’s paper. I hope that you can distil from the above that I think:

- It is a topic of great importance
- Dr Healy’s review of the literature is incomplete
- The changing face of psycho-social disease and its management needs to be included as background to provide the context of the concern.
- There should be some attempt to relate this concern to the overall effectiveness/risk profile of the SSRIs, and to indicate where there may be differences between drugs in the risk of suicide.

I have taken the unusual step of enclosing some references as printouts from an interesting web searching sessions. I am happy that these and my comments and name/contact details can be give to Dr Healy. I will also help in any way I can, and wish him well with this. I feel, as I feel about genetically engineered products and environmental warming, that there is a real concern which we are neither formulating nor tackling adequately.

Referee B

SSRIs and Suicide A situation without precedent

David Healy

This extraordinary manuscript presents a fascinating case implicating SSRIs with treatment emergent suicidality. A series of reference citations is presented that purportedly support the author's position. A great deal of the information is based on unpublished data (references 3-6, 9, 10, 12, and 14) and, consequently not available for this reviewer to evaluate. Other information appears to be hearsay (e.g., pages 3 and 4 top para of page 5)

Several of the peer-reviewed manuscripts that are cited are presented in a way that either ignores or misrepresents the authors' conclusions (eg., references 12, 17, 18, and 19). For instance, the conclusion of reference #17 (page183) is that there is no evidence that SSRIs trigger emergent suicidal ideation over and above that of depression or other antidepressants. Similarly, Dr. Healy dismisses references 18 and 19 as uninformative because they were not designed to answer the question fluoxetine and suicide. I agree that the studies, which each commenced prior to the introduction of SSRIs, were not specifically designed to address the question, yet that does not preclude the use of their data for such purposes. Both references are from ongoing longitudinal, observational studies of mental disorders that allowed a look at suicidal behaviour before and after the introduction of fluoxetine, in particular. They both concluded that their respective data sets failed to lend support to the hypothesis that fluoxetine is associated with increased risk of suicidality.

Page 3/top para: this is at best hyperbole, quite likely inaccurate.

The use of the term 'relative risk' should be replaced with 'odds ratio' given the designs of several of the reference citations.

Page 4/lastpara/sentence 3:"In academic and medico-legal...." The double negative renders this important sentence incomprehensible.

Page 7/top para/last sentence: The comparison is flawed for a variety of reasons including variation in study designs, inclusion/exclusion criteria, calendar years, and even cultures where suicide rates could vary markedly.

Page8: It is unclear if the warnings are quoted from the patent.

The manuscript does not read as a scientific document, but appears to be a list of unsubstantiated claims veiled as well-accepted scientific fact.

Incidentally, it is well known that Dr Healy has testified in numerous lawsuits against the drug industry on just this topic. It is not clear whether that indicates that Dr Healy has a conflict of interest.

Referee C

RE: (ds/Ial-0012340) SSRIs and Suicide: A situation without precedent. David Healey

Thank you for asking me to review this paper. I thought because of its unusual nature I would give a quick initial response. My secretary is away so I hope this e-mail will be OK.

David's views on SSRIs and liability to suicide are well-known and this article does not attempt to take a balanced view. Really, it is like the opening speech for the prosecution which certainly makes it a good read! It is not a scientific review in the usual sense but obviously will stimulate, frighten and annoy. Clearly whether it should be published and whether there should be a commentary on it or a reply to it is an editorial decision.

I have not attempted a detailed review of the article mainly because to collect all the cited references, many of which are in rather obscure journals, would take a couple of weeks and this would have to be followed by another week reviewing them. I could do this if you wished or we could ask David for the articles. At this stage I thought it might be useful to make some more general comments. I would have no objection to you showing them to David or acknowledging me as the source if this would make the reviewing process easier.

There are a couple of general issues:

- 1). Is David implicating all SSRIs or mainly fluoxetine with a nod to sertraline?
- 2). What is meant by suicidality in this context? A number of authors have suggested that akathisia might be the mechanism by which SSRI use can, in certain people, lead rarely to suicidal ideation and behaviour (see for example Power and Cowen, Brit J Psych 161, 735-741, 1992). This is because akathisia is known to be associated with inner restlessness and occasional suicidal agitation. Is this what David is proposing or does he believe that somehow SSRIs more directly cause suicidal thinking and behaviour? In addition sometimes David talks about suicidal behaviour, sometimes suicide attempts, sometimes "suicidality", I think the article needs to be more specific.
- 3). Should contrary evidence be mentioned? For example, epidemiologically Isaacson has correlated an increase in (mainly) SSRI prescribing with a decrease in suicide in Sweden. Also, in a blind, randomised trial, Verkes et al found that paroxetine decreased suicidal behaviour in people with a history of repeated suicide attempts.

Some more specific points:

- 1). David mentions his study which describes the effect of sertraline to induce suicidal ideation in two healthy volunteers. This is obviously an important piece of work so why did David publish it in such an obscure journal? I have heard David describe this study at a lecture and therefore my memory may be at fault. My recollection, however, is that these two subjects had been abruptly withdrawn from reboxetine before being started on sertraline. I think this leads to a rather complex pharmacological situation which makes it hard to argue for a simple cause and effect. Because the original article is hard to locate I think David needs to be open about the study design and possible limitations.

- 2). The memorandum from von Keitz is obviously important in showing concern at Lilly about reports of suicide. By my reading of the memorandum, however, while the number of suicide attempts appears to be increased in patients taking fluoxetine relative to placebo (about 1% v 0.25%), the number of completed suicides is lower (0.18% v 0.63%). Interestingly similar relative figures for suicide attempts and suicides occur in the paroxetine database cited in reference 17. The same reference provide data for sertraline and suicide attempts that differ from the analysis that David has carried out himself in showing no difference in suicide attempts between sertraline-treated patients and those on placebo.
- 3) I found the paragraph on page 4 difficult to understand. I think it needs rewording.
- 4) The Jick study (reference 22) was not randomised. It is therefore difficult to avoid the not unlikely possibility that patients judged to be more at risk of suicidal behaviour might also be more likely to be placed on fluoxetine.
- 5). The study cited by David as reference 12 is an example of the problem of what to take from the published literature. David quotes a relative risk of 1.4 of newer antidepressants over placebo but it is not clear what risk he is referring to. In the paper taking all drug together there are numerically greater risks for suicide attempts (2.7% v 2.8-3.4%) and suicides (0.4% v 0.7-0.8%) in patients taking a range of new antidepressants relative to placebo. However, these differences are clearly not significant. Should we therefore treat them as though they are? Also many of the newer drugs are not regarded pharmacologically as SSRIs. In fact if one looks at the data in the paper on classic SSRIs (paroxetine and sertraline) there is not really even a numerical difference between SSRI and placebo in terms of suicidal behaviour in this particular analysis.

COVERING LETTER

1. As regards the use of articles as Jick (formerly ref 22) to support conclusions not offered by the authors, my statement as regards this article was that it gave rise for concern rather than allayed any concerns. The fact that the authors did not conclude Prozac caused people to commit suicide was inherent in their design – there was no control group. Nevertheless, there was a doubling of the relative risk on Prozac that could not be explained by selection factors. Most epidemiologists I have talked to believe this is a very disturbing study. It becomes more disturbing when juxtaposed against the only figures available for suicide rates in primary care depression – something Jick and colleagues did not do (there was no reason for them to do so).
2. I have now cited the other Jick article you refer to. I have cited it to make the following point: that epidemiology is not the way to answer the question of SSRIs and suicide. Dr Jick and colleagues say so themselves at the end of the paper. I agree with them. According to the standard ways of assessing causality, the case had already been proven at this point.

- 3. Generally the reviewers have suggested I have not analysed all the evidence or taken into account all possible confounding factors – as in the Jick reference. This misses the point of the piece (at least the piece I think I am writing which I suspect is not quite what the reviewers have seen themselves as reviewing) – which is a certain stupefaction on my part at the MCA response. The MCA lists a series of studies, none of which are epidemiological studies except the Jick study and the Jick study gives grounds for concern rather than the reverse.**
- 4. This makes more problematic the failure of companies to conduct any study designed to tackle the issues in the 10 years since the controversy first emerged. I have never claimed that the Jick study proves anything – it's the MCA who appear to rely on it. I have visited the MCA several months ago at their invitation, hoping they would be able to lay my concerns to rest, but they were able to provide no further evidence and even declined to stand by their own list of studies as settling the issues.**

Professor Stephen Evans was at the meeting and he may be able to tell you whether my reading of what transpired is mistaken.

- 5. More generally, this revised version of the paper hopefully reframes the issues in a manner that puts the burden of proof back on those who claim there is no problem. This is not a paper aimed at proving that any SSRI causes suicide. It aims to highlight the lack of research and an anomalous regulatory response.**
- 6. On the issue of the argument being one-sided, there is the simple point that over 11 years after the controversy first blew up there has not been a single study designed to test the issues. I can provide at least 5 or 6 depositions taken over the last year, including a recent one from Dr Beasley, and another from Dr Ian Hudson, recently of SmithKline and now of the MCA, agreeing that there have been no studies undertaken that were designed to test the issues. This seems to me sufficiently black and white to transcend any biases I may have.**

7. I have used relative risk rather than odds ratio throughout as this is the terminology that all the articles I refer to have used. I would be happy to convert if I don't then get accused of somehow misrepresenting the views of those I have cited.
8. I am happy to enclose a statement of competing interests.

REVIEWER A

1. This reviewer apparently enclosed a Medline search but this search has not been forwarded to me, nor has the Smith WT et al article to which reference is made. Without reading Smith WT et al, however, it is possible to immediately note that the need for a strategy to alleviate early symptoms of antidepressant treatment, which arose with the SSRIs, is implicitly conceded by this referee.
2. I have not referred to any earlier hypotheses about SSRIs producing suicidality by "improving depressed patients poverty of ideation.. because they elevate mood" because this hypothesis antedates the SSRIs – it originally applied to all antidepressants. (The European tradition was that all earlier antidepressants which appear to pose a lesser risk than the SSRIs could induce suicidality – I can provide a number of references for this). The results with SSRIs in healthy volunteers also antedated (at least for company personnel) any later clinical use of these drugs in depression. Furthermore, the dichotomous view of disease or drug is not a distinction that I have introduced. This distinction is one that was introduced by Lilly.
3. I think this referee is however correct to note the widespread use of SSRIs, touched on in my covering letter, and how this widespread use may shift risk-benefit calculations. This was implicit in the original piece but not spelt out for reasons of space. Given the interest this piece has generated, I have taken the liberty of including the point in the revision, in a greatly compressed form.

REVIEWER B

1. The first point to note here is the general thrust of this reviewer's remarks; as mentioned in your covering letter, this was a viewpoint article rather than a review of all evidence pertinent to the question.
2. I have tried to minimise the amount of unpublished material, eliminating a number of references. I enclose all exhibits referred to as well as all depositions. These are all in the public domain and can be passed on to all reviewers and others at your discretion. On the issue of hearsay, it is worth noting that these depositions are all sworn testimonies.

3. Reference 14 (now 20) is correspondence from the MCA that simply says that the following epidemiological studies suggest that there is no convincing data implicating fluoxetine. I enclose a copy of this letter.
4. As regards the information on pages 3, 4 and on the top of page 5 noted by this reviewer to be presented in “hearsay” format, I have supplied sworn testimony in the shape of the Beasley and Messner depositions and an exhibit.
5. As regards ignoring or misrepresenting the authors conclusions in references 12, 17, 18 and 19 for example I specifically use reference 17 for instance to provide support for the claim that the Fava and Rosenbaum study suggest a 3.3 times greater risk for fluoxetine compared with other antidepressants. This is found in reference 17. Reference 17 does not claim that there is no evidence that SSRIs trigger suicidal ideation. It in fact claims that the body of evidence at that point (1991) did not suggest that antidepressants as a group increase suicidality. It goes on to call for further research and for warnings.
6. As regards references 18 and 19, the critical point here is that these studies simply cannot be portrayed as epidemiological studies – a point the reviewer does not address, although s/he concedes that they were not designed to address the issues. They are however in court, in academic debate, and by the MCA being so portrayed. I can happily provide references for specific legal and academic portrayal on these lines (and attach a set of interrogatories). There are furthermore notable conflict of interest issues to do with these studies that I have not drawn attention to – the authorship line in study 19 is primarily drawn from Eli Lilly.
7. Given that these are not epidemiological studies and that they were not designed to answer the question of whether Prozac could trigger suicidality or not, my simple point is that little or no reliance can be put on these studies, particularly given the authorship lines of these particular studies.
8. Regarding the point on page 7, top paragraph last sentence, I accept fully that the comparison is problematic but as mentioned the only figures available are the figures that I have cited. In point of fact one would have expected the figures from the available period from Sweden to be considerably higher than comparable figures from the UK for the present day – in that community depression then referred to a much more clearly endogenomorph clinical picture. It is not clear therefore that the sources of variability outlined by the reviewer pose a problem for the argument being made.

Furthermore along with a colleague, Dr Boardman, I have present a model of likely suicide rates in primary care in England at a recent BAP meeting. Our estimate as a figure under 30/100,000 patient years is the most likely figure for suicidality in England and Wales. This model and its figures for England is currently under peer-review. I could reference our presentation or may be able to reference a paper in

press in due course. I provide a copy of the poster and especially of the figures we have used.

9. As regards the point made on page 8, I have now incorporated the wording of the patent.

REVIEWER C

1. I am not quite sure what this reviewer means by raising the point of an obscure journal. This piece is being addressed to the Lancet after all. The original study was offered to a major journal who didn't even want to peer review it.

I think all SSRIs are implicated to some extent but clearly there is a greater amount of data from fluoxetine. The new closing section of the revised article provides data indicating that SSRIs are a greater risk compared with tricyclics but that there may be a differential within the SSRI family (ref 31).

2. The revised version gives a definition of suicidality at the start and adheres to this throughout.
3. As regards point number 3, before Göran Isacsson's article was published I invited him to a symposium on antidepressant induced suicidality at the British Association for Psychopharmacology meeting in Cambridge last summer, that I organized and chaired. This gave him the opportunity to present the data referred to reviewer C. Clearly therefore I'm not in the business of only seeing one side of this argument. This data however does nothing to address the question of possible adverse effects of SSRIs in susceptible individuals. It is furthermore very difficult to place much weight on the data provided by Göran Isacsson in any larger risk-benefit argument. In his presentation, he suggested that his claim that increased SSRI use will reduce rates of suicide in populations would be shown to be wrong if there was a population somewhere where rates of suicide show an increase in the face of increased SSRI prescribing. There are such populations – such as teenagers in the United States.
4. Göran Isacsson's data however do provide some of the best data on which to mount a response to the viewpoint that your reviewers assume (and possibly many readers will assume) I'm putting forward – looking at cause and effect between SSRIs and suicide rather than the company and regulatory response to a problem which is what I in fact think I am addressing. He might be someone therefore that you might consider approaching for a response or an alternative point of view.
5. As regards the Verkes et al article there are some points to make clear. Following the initial controversy Stuart Montgomery undertook a study in recurrent brief depression in the course of 1990/91. The results of this were not published until 1994 when the Wesbecker trial was taking place. The article was entitled Lack of An Association Between Fluoxetine and Suicidality. In fact however the study was not designed to

test whether there could be an association. More than half of the subjects recruited dropped out and the readers of the published version of the study were not in a position to determine whether this was because of Fluoxetine induced akathisia/suicidality or what. This is a very curious article in which the response to placebo was significantly better than the response to Fluoxetine at a P=0.001 level. These data however were not presented in the published version of the article.

Sometime afterwards Dr Montgomery and colleagues undertook a further study in recurrent brief depression with Paroxetine and reported that it was as effective as Placebo. The results of suicide attempts however were not reported. These ran at a 3 times higher rate on Paroxetine than on Placebo. These data remain unpublished.

Against this background we can consider the Verkes study. This is a further study in recurrent brief depression in which it is claimed that paroxetine reduced suicidality compared with placebo. However in the course of this study 75% of the patients taking either Paroxetine or Placebo dropped out in the course of the study. From the published data it is impossible to assess whether Paroxetine may or may not in some cases have triggered suicidality in some of the patients involved.

I have no doubt that there were some residual patients left in the study who benefited from Paroxetine. At no point in this or any other article have I ever claimed that Paroxetine or indeed any other SSRI might not indeed be useful or indeed preferentially useful in some patients who are suicidal to begin with. My concern is with patients who are not suicidal to begin with. Based on my understanding of the overall picture I chose not to present you with either the Verkes data or the unpublished Montgomery et al data. I think this was and still is the correct decision but I would be happy to discuss it further.

6. As regards specific point 1), I would of course be happy to spell out the limitations of our study if need be – it is primarily the constraints of space that have stopped me from giving more detail. It is true that in our study the two volunteers who had become suicidal on sertraline had previously had reboxetine. They had not, however, been abruptly withdrawn from reboxetine. I am happy that any discontinuation from reboxetine can be ruled out as a factor in that among the unpublished studies on sertraline that I have had access to, as well as the one other published study, it is clear that in placebo controlled studies with no other antidepressant to contaminate the picture healthy volunteers given sertraline become suicidal on it.
7. As regards specific point 2), as mentioned in my covering letter it is very clear from Lilly's material that a number of the "placebo" suicides should not be attributed to placebo in that these occurred during the washout phase rather than in a placebo arm per se. My understanding is that both of these subjects should be assigned to the Prozac group of suicides.
8. Further on specific points 2) and 5), as regards the sertraline and suicide attempts in reference 17 (should be reference 12), it is important to understand the origins of this

article – which is not an article about SSRIs and suicidality but rather one about the ethics of placebo controlled trials. It was not the brief of the authors therefore to comment on the somewhat unexpected implications of their findings as regards suicidality.

Reference 12 is furthermore restricted to certain placebo controlled studies in depression filed with the FDA. I have had access to a much greater number of depression studies and draw my figures from this larger database. I believe it may be possible to give the entire set of figures to this or all reviewers if need be – I will need to check on the confidentiality status of the material if you would wish to take up this option.

But even if the argument is restricted to the figures giving an equivalent odds ratio/relative risk between paroxetine, sertraline and placebo, the finding of such a figure must be cause for concern. These drugs are sold on the back of claims that they reduce the risk of suicide. If they do so, which I am happy to accept, on the basis of an equivalent relative risk, it follows, as night follows day, that they must be increasing the risk in others. This was the point behind the section outlining the methodological problems in assessing risk with agents that may both reduce and increase a certain hazard.

9. This paragraph which two reviewers found obscure has been amended.
10. As regards specific point 4), the Jick study was not randomised but the authors did control for the effect of GPs putting patients who they felt were more at risk on antidepressants that were safer in overdose. These included mianserin, trazodone and flupenthixol as well as fluoxetine. When they did this, the relative risk for all these other agents fell but that for fluoxetine remained unchanged.

Competing Interests Statement

In recent years I have had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend foreign meetings from;

Astra, Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia and Upjohn, Pierre Fabre, Pfizer, Rhone-Poulenc, Roche, SmithKline Beecham, Solvay, Zeneca.

I have been expert witness for the plaintiff in two legal actions involving SSRIs and have been consulted on a number of other attempted suicide, suicide and suicide – homicide cases following antidepressant medication, in the majority of which I have offered the view that the treatment was not involved.

THE LANCET

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Please quote ref: VB/Dtc 00/12340

10th May 2001

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FAX: 01248 371397

Dear Dr Healy

I have taken over your manuscript, as Davis Sharp is about to retire. We have sent it for legal advice, and I will be in touch as soon as we have had a chance to see this, and discuss it.

I read with interest the article in the Guardian concerning the blocking of your move to Toronto. On a practical point, can you confirm that the address we have for you is still correct?

Yours sincerely

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21st June 2001

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FAX: 01248 371397

Dear Dr Healy

I now have the reports of both our legal advisor and our statistician. Both had substantial problems with your paper, but in the end we were swayed by that of the statistician, which I enclose. As you will understand, in the face of these criticisms, it is impossible for us, as editors, to publish your paper.

In order for you to answer these criticisms, you may want to enlist the help of a statistician in rewriting the paper. We would look at any revised manuscript, but we feel that the paper we have now is not publishable and we have rejected it.

I am sorry that the whole process has been so prolonged, but the criticisms in the end were too overwhelming.

Yours sincerely

Virginia Barbour MRCP DPhil
Senior Editor
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c.c. Richard Horton

The Lancet
Statistical Review

MS 00/12340
David Healy – Viewpoint

The article is one-side rather than providing a comprehensive and critical appraisal of the literature and the available evidence. The author neglects to discuss all studies available and selectively cites partial evidence. No attempt is made to discuss methodological issues that may underly associations observed.

Specific comments:

1. Confounding by indication: The key issue here is whether sicker patients might have received more effective drugs – such as fluoxetine. The author does not discuss this issue at all. But it might well be an explanation for any increase in risk observed.
2. Page 4, reference 15: Khan et al. did not find a significantly increased risk. The author is taking this out of context.
3. Page4, 2nd paragraph, 10th line: It is completely bizarre to suggest that a relative risk exceeding 0.5 should be interpreted as increased risk. This lacks any statistical sense and ignores variability of the estimate altogether.
4. Page 5/6: The discussion about epidemiologic studies or not is splitting hair about nothing. A clinical trial may well be considered epidemiology – this is a matter of definition.
5. Page 5/6: whether or not the studies/trials were designed to evaluate whether fluoxetine induces suicide or not is not important. It is highly unethical to design a study to test this hypothesis. Therefore, data on suicide have to be derived from clinical trials and studies deigned to test the efficacy of the drug.
6. Page 7, 2nd para: I find it hard to believe that only Sweden and Holland should provide data on expected suicide rates. Also, a comparison across countries may not be appropriate.
7. Page 7, 3rd paragraph: It is no true that the issue of suicide and SSRIs has not been studied,. The study by Khan et al. did exactly that and there are probably others.
8. Page 8, 2nd para: The fact that the patent states this does not mean it would enter the patient leaflet. We no not know what the patent for fluoxetine states.

Our Ref: DH/JT

25 June 2001

Drs Virginia Barbour/Richard Horton
The Lancet
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Dear Drs Barbour/Horton

RE: MANUSCRIPT 00/12340

I'm taking a somewhat unusual step in responding to the points made by your statistical reviewer on this manuscript in a separate letter to the revised manuscript enclosed with another letter. There are a number of reasons for doing this.

The first and most important reason perhaps is that unfortunately for all of us the issues under review in these papers are the subject of medico legal actions. This means that there is every risk that the lawyers for one of the SSRI producing companies will request the referee reports. I am therefore under somewhat of an obligation to respond to these in full and perhaps more fully than I would otherwise respond, if only as a risk management strategy.

This position however clearly carries an implication for you as well as for me. I may be wrong but I thought the tone of the statistical review that you sent me was somewhat unfortunate – given the circumstances. This may become a bit more clear as I answer the points in detail in the attached response piece.

Some of the tricky aspects of all this can perhaps be illustrated as follows. In the midst of what you described as a prolonged process with manuscript 00/12340 I received a phone call telling me that the manuscript was likely to be rejected and specifically suggesting that this would be so because of the political sensitivity of the issues at present and because the situation had got so hot.

Continued/..

Page 2.

This puts me into a very unusual position, as I'm sure you can see. It was partly for this reason that I've suggested in a number of letters calling in to meet you or potentially some of your reviewers face to face should this seem appropriate or in any way helpful. Clearly it would not be appropriate in the ordinary course of events but these articles lie somewhere outside of the ordinary course of events. I would imagine that the statistical reviewer of this manuscript might for instance have provided a slightly different commentary had they been aware that there was a risk of this material ending up in the public domain (I hasten to reiterate the point that it would be lawyers for the SSRI companies that will engineer this situation if it were to happen, not I.)

Unfortunately also it would seem that there is no easy way to go back from the current position. If you take into account what I've outlined above, I've little option but to submit a further manuscript to you. Equally it would seem that you have little option but to engage with this manuscript. Not engaging would seem almost impossible in that given the extensive review processes that have taken place to date the Lancet would seem to have potentially at least a de facto public position on these issues.

I'm truly sorry for the difficulties this may cause you and indeed cause me as well. I certainly had not appreciated the potential ramifications on getting involved in a medico legal process like the SSRI medico legal process has been. I know that you are aware from previous correspondence that this has probably cost me a job.

There is a further reason for suggesting a meeting with either yourselves or any of your reviewers who may be interested. I have spoken in public on these issues and offered to speak in public on any platform. I've visited the MCA. In all instances part of my motivation has stemmed from a willingness indeed almost a desire to be proven wrong, as the consequences of not being proven wrong are in many respects horrific. If you have a reviewer who is prepared to work through the issues with me and can point out the error of my ways I will be more than happy to have these pointed out and take any steps that might be called for in the light of any conversion.

The comments from your statistical reviewer on the last manuscript however do not as they stand provide any grounds for a conversion. I'm confident on the statistical issues in question, which really are rather simple and in the light of these am submitting the new manuscript.

Yours sincerely

David Healy MD FRCPsych
Director
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MANUSCRIPT 00/12340 – RESPONSE TO STATISTICAL REVIEW

General Comments:

The first point to make is that the article is of course rather one-sided. I thought I'd been asked to provide viewpoint article – and gave you what I considered a duly impartial polemic. The new manuscript covers all the relevant literature.

I can see why the reviewer believes I've selectively cited partial evidence. I think this criticism arises essentially from someone unsympathetic to the position I'm taking rather than someone who is keen to have the issues aired even in viewpoint form.

I accept that there was not an extensive discussion of the methodological issues in this area but there was a detailed discussion of the methodological issues underpinning the key article referred to (the Beasley article). There is no response from the reviewer to this discussion.

Specific Comments

Comment 1.

The first point made is a floating point. It is not tied down to any point in the text and I'm not quite sure how or where it applies.

The key point for this reviewer to consider as for the Editors of the journal is this. There is no indication that sicker patients have received more effective drugs such as fluoxetine or other SSRIs. The product licenses for these drugs in the US and many countries specifically indicate that they have not been shown to work for hospital depression – they have not been shown to work for sicker patients. The clinical trials that have been conducted have been exclusively in out-patients – not the sicker group of patients. These trials and the fact that the drugs do not work for sicker patients make it clear that these drugs are not more effective. They are in fact singularly less effective than older tricyclic agents in clearing up the disorders afflicting those who are most at risk of suicide.

I felt no need to discuss this issue in detail, as anyone up to date with the issues would appreciate (I thought) the above points that I've mentioned – that the excess risk associated with fluoxetine and SSRIs does not stem from sicker patients being given these drugs.

In the new manuscript you received, this point however is discussed and is discussed specifically in light of the Donovan study.

Comments 2, 3 and 7

Your reviewer is wrong on a number of points. The study by Khan et al was not a study in the first instance, it was a meta-analysis. It did not look at the issue of suicide and SSRIs. It was a paper that was most concerned with the issue of placebo and suicide. There was no systematic investigation by these authors of the issue of SSRIs and suicide.

As I make clear in the new manuscript submitted to you, any effort to look at the question of SSRIs and suicide can potentially utilise data from the Khan et al paper. This then gives rise to the question of whether the data should be expressed in terms of patient exposure years as was done by Khan et al. I have argued that this is not appropriate. It would be interesting to have your reviewer's comments on the position I take which is explicitly laid out in the new manuscript. When you take the absolute figures provided by Khan et al then the risk on SSRIs is increased compared with placebo.

In both manuscripts, I invite the readers and by extension this reviewer to do is to consider the following point. If the risk on SSRIs is increased or even identical to placebo, given that the data that show this risk to be the same as or greater than placebo are the same data that give rise to company claims that their drugs reduce suicidality for some patients, and both your reviewer, most of your readers and I would agree with this point, it follows necessarily that there is a corresponding triggering of problems in other patients.

This leads on to a consideration of the relative risks associated with agents that can both ameliorate and trigger a problem. Your statistical reviewer I would have thought should be asked for their opinion on the insistence by SSRI producing companies that unless their agents have been demonstrated to show a doubling of relative risk of suicidal acts compared to placebo that there is no evidence that their drugs cause any problem. If the reviewer were to accept this argument, it seems to me that they would have little option but to accept the argument that pertussis vaccination should also be shown to show a doubling of the relative risk of brain damage compared with the non-vaccinated state.

What I did in the rejected manuscript was to make perhaps a foolhardy attempt in an all to brief a space to flag up this issue. Of course with greater space I would have made it clear that the variability of any estimate of a 0.5 relative risk would be important. I was assuming that readers would take it that there was little variation around this figure of 0.5. The point I was making was that from clinical trials on older agents compared to placebo that the relative risk with these older agents compared with placebo appears to cluster around the 0.5 figure, but yet clinical wisdom is that these older agents can in their own right trigger suicidality. Clearly the risk benefit ratio is such that it is still prudent to treat more severely ill patients with these older agents but that's a different point.

I would invite both the Editors of the journal as well as the statistical reviewer to consider the following. From both a moral and scientific point of view but most particularly from a legal point of view, there is no onus on me to prove that SSRIs cause people to become suicidal. The onus lies with the companies to prove that their drugs do not cause this problem or else to warn about possible hazards. Against this background a relative risk of 1.0 is significant in the following sense - it makes it impossible for the statistical reviewer of this paper or anyone representing any of the SSRI companies to claim on this basis that there is good evidence that the drugs do not cause suicidality. Indeed following the discussion above had the clinical trials of the various SSRIs in question given rise to a relative risk of 0.5 to 0.7 and thereabouts with very little variability in the estimate, it

would still not be possible for the companies to claim that their drug did not cause a problem.

I would be greatly obliged if your reviewer or anyone else who has an interest in these issues could point out to me the error in this argument. I have sat down with a number of epidemiologists and statisticians and gone through this point and no one to date has been able to show me the error in the argument. It follows morally, scientifically and legally from this, given the weight of the rest of the evidence that there is an onus on companies to warn and to advise monitoring – an onus they have resisted for a decade. This can be framed in terms of statistical null hypotheses or in a variety of other ways, but at the end of the day is what this controversy is all about.

Comment 4

It appears to me that the reviewer has missed the point here. I agree that clinical trials may well be and indeed should be considered as epidemiological studies. In this regard it is quite telling that the tobacco companies have argued very successfully in court that epidemiology does not provide evidence of cause and effect. All that epidemiological studies and RCTs provide is evidence of frequency of associations. I agree fully with the tobacco companies on this point. The tobacco companies have argued that the evidence that is available for SSRIs is the kind of evidence that they would need for demonstrating cause and effect in the area of tobacco and lung cancer. Conversely the SSRI companies, in some instances advised by the same lawyers, argue that the evidence of the problem emerging on drug treatment going away when the drug treatment is halted and re-emerging when treatment is re-instituted and evidence of a dose response relationship is not causal, but rather that randomised control trials and epidemiology is needed.

However the specific point in the original article, which the reviewer may not be aware of, is that it was the MCA who had described these studies as epidemiological studies. Not I. Part of the issue therefore arose out of my concerns to cram too much into the original article. In addition to taking on the issue of the SSRIs I was clearly taking on the regulatory response to the problem. If a medical student were to call a number of these studies epidemiological – they would fail their exams. The new manuscript omits all reference to regulatory responses or patents and focuses solely on the issue of SSRIs and suicidality.

Comment 5

It seems extraordinary to me to suggest that it would be highly unethical to design a study to test the hypothesis of whether fluoxetine induces suicide or not. Lilly and the FDA spent a better part of two years designing exactly such a study. No one in the process suggested that this was a highly unethical venture to be involved in. The pills ended up in blister packs, the investigators had been recruited but the study did not take place.

The lack of ethics it would appear to me lies rather in a position of having a series of drugs on a market, for which there are good grounds to believe may well be causing a problem, and failing to take genuine steps to address this problem.

The data on suicide do not have to be derived from clinical trials and studies designed to test the efficacy of the drug. There are a range of other ways that data on suicide could be obtained – for instance the Donovan studies. More to the point are the healthy volunteer studies that are referenced in greater detail now in this revised paper. Finally however studies designed to test the efficacy of the drug that included scales designed to be specifically sensitive to the emergence of suicidal ideation would of course be a further way to move this issue forward. Lilly designed exactly such a scale. However it has never been used either in a rechallenge study or in the conventional studies of efficacy with which your reviewer is happy but I am not.

Comment 6

In the last three comments on this page the reviewer appears to become somewhat high-handed. There are only two studies on suicide rates in primary care. It would have been helpful if the reviewer had been able to point me toward others. I've lectured on this issue and written on this issue regularly and have never had anyone point out any other studies to me.

In the new manuscript, I include a reference to a study undertaken with a colleague, aimed at trying to model suicide rates in primary care in the UK – this is under review. This helps to take care of the point made by the reviewer about a comparison across countries not being appropriate. However there's a further issue here. The figures for primary care in the UK cannot be much higher than the ones provided for Sweden and Holland or otherwise there would be a suicide rate in Britain that was several times higher than the currently observed rate. Your reviewer does not seem to take into account some of the implications of the points that he or she may be making.

Comment 7

Again it is somewhat unfortunate for the reviewer to suggest there are “probably others”. Firstly the study by Khan et al was not a study as such, and it was certainly not a study of the issue of suicide and SSRIs as has been outlined above. Having been in court twice on this issue and having been deposed on several other occasions on this issue, I am quite sure that with the literature search processes available to some of the largest pharmaceutical corporations on the planet, had their been other studies I would have been faced with these other studies. I think the Editors of the journal can have some confidence therefore if I have not cited other studies and the reviewer has not provided reference to other studies that there are no other studies.

Comment 8

Assuming that the statistical review comes from a professional statistician, I am surprised that he or she has seen fit to venture into the area of patents and the implications that these might have for patient leaflets. It would have seemed wiser to leave this issue alone.

The handling of the issue appears to me to betray lack of feel for the dynamics of the situation. The reviewer is clearly right that the information contained in patents only rarely if ever feeds its way through into information for physicians or patients. However

given the controversy associated with the SSRIs and given that the information details on R minus fluoxetine have been featured on the front page of major newspapers it seems inconceivable to me that some reference to the details contained in the patent for R minus fluoxetine and specifically the fact that it was claimed to be less likely to provoke suicide than the parent compound would not have ended up being part of the information that would have had to be presented to physicians and patients.

The situation is academic in that this compound is not going to be developed. The possibility of its development, however, pointed to a situation that I indicate I feel was grotesque. In this your reviewer and I are at one in the sense of that it would take something highly unusual for information in a patent to end up in for instance a summary of product characteristics. The fact that Lilly have not challenged newspapers like the Boston Globe, that they stand accused in court of perpetrating a fraud by virtue of holding this patent, and that the development of R minus fluoxetine has been shelved suggests that there was substance rather than otherwise to the comment that I made.

Summary

Having made all the above comments, and it should be clear from my covering letter that I've made these comments in greater detail and more forcefully than I would do in the ordinary course of events, I agree with the reviewer on a number of points. The original piece tried to do too much. It was foolhardy to try to review the evidence on SSRIs and suicidality, in a brief piece that also put forward rather subtle methodological points and took on board issues of patents. I appreciate the work by your reviewer as it has helped crystallise some of the above issues and made it clear that the most appropriate piece would be one that was rather straight forwardly focussed on the central question of SSRIs and suicidality, leaving the other issues to be picked up, if at all, in another or other articles.

Our Ref: DH/JT

25 June 2001

Drs Virginia Barbour/Richard Horton
The Lancet
84 Theobald's Road
London
WC1X 8RR

Dear Drs Barbour/Horton

Many thanks for your recent letter regarding manuscript 00/12340. I can see how you would have had problems publishing this paper in the light of the criticisms you received.

I can also see how with these particular issues at this point in time that a viewpoint article, particularly one that brings in hanging issues to do with drug patents and novel issues to do with relative risk and condenses all of these into an extraordinarily confined space, has problems.

Accordingly I enclose a revised paper. This moves away from being a viewpoint piece toward being a systematic review. It cannot be a systematic review in that no studies have been specifically done to address the issues in question. However this piece does cover all of the available evidence and lays that evidence out systematically. I would like to submit it for your consideration.

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine

CAN SSRIs TRIGGER SUICIDE?

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Meta-analyses of Suicidality on SSRIs

There has been controversy for a decade as to whether SSRI antidepressants can trigger suicidality in vulnerable individuals. No studies designed to investigate these issues have ever been undertaken (1-6). This brief review will therefore cover meta-analyses, randomised controlled trials in recurrent brief depression, epidemiological studies, case studies and healthy volunteer studies germane to the issue.

The clinical trials on zimelidine, the first SSRI, suggested there were a greater number of suicide attempts on it than on comparators. Montgomery however demonstrated that while this might be the case, zimelidine appeared to do better than comparators in reducing already existing suicidal thoughts (7,8). A similar analysis demonstrated benefits for fluvoxamine against a backdrop of a higher than expected suicide attempt rate in clinical trials (9). Similar problems have emerged for other SSRIs and similar analyses have been undertaken, for example for paroxetine (10,11). The best known analysis of this type was undertaken following controversy with fluoxetine; in 1991 Lilly published an analysis of some of their antidepressant clinical trials indicating that “data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients” (12).

The Beasley analysis has a number of methodological problems, which apply to a greater or lesser extent to all other such exercises (13). First, none of the studies included in the analysis were designed to test whether fluoxetine could be associated with the emergence of suicidality. Second, only 3,067 patients of the approximately 26,000 patients entered into clinical trials of fluoxetine were included in the meta-analysis. Third, no mention was made that benzodiazepines had been co-prescribed in the clinical trial programme in order to minimise the agitation that Lilly recognised fluoxetine could cause. Fourth, no reference was made to the 5% of patients who dropped out for anxiety and agitation, the very problem that was at the heart of the argument. Fifth, no mention was made that some of the trials and investigators whose work was being reported had had their work questioned by the FDA. Sixth, the analysis in the case of fluoxetine and for other SSRIs depends critically on Item 3 of the Hamilton Rating Scale for depression; this approach to the problem is one that FDA officials (14), Lilly personnel (15) and their own consultants (16) made it clear was methodologically unsatisfactory. Despite all steps, there was an excess risk of suicidality on fluoxetine in terms of actual suicide attempts.

Internal papers from Lilly indicate that as of 1986 Lilly’s entire clinical trial database consisted of approximately 8,000 patients (17). My analysis of this gives a suicide or suicide attempt rate attributable to fluoxetine of 10 per 1,000, with approximately 4.3 per 1,000 on placebo and 1.5 per thousand on comparator antidepressants.

This difference between SSRI, comparator antidepressants and placebo is paralleled in Pfizer’s entire depression clinical trial database as of 1991, where my analysis of the figures indicate that the relative risk of suicidal acts on sertraline versus placebo was 1.9 (18). This is consistent with the reported rates of suicide attempts on milnacipram and tricyclic antidepressants compared to SSRIs in Pierre Fabre’s clinical trial database of approximately 8,000 patients, where the rate for SSRIs appears to be 3 times the rate for other antidepressants (19).

These findings are also consistent with figures from a recent analysis of the rate of suicides and suicide attempts in a selected group of trials on sertraline and paroxetine submitted to the FDA (20). This analysis was undertaken to answer the question whether it was ethical to continue using placebos in antidepressants trials rather than to determine whether SSRIs could trigger

suicidality. Given its aim, the study analysed the figures in terms of patient exposure years. This methodological step may be appropriate for placebo therapy but is inappropriate for the assessment of a problem that had been clearly linked to the first days or weeks of therapy. When the figures for sertraline and paroxetine are analysed without using patient exposure years, the relative risk of these two SSRIs compared to placebo was 1.14, and compared to comparator antidepressants was 1.22.

Broadly speaking across all these analyses, whether done by the companies on selected data or otherwise, there is an excess of suicidal acts on the SSRI. Interesting methodological considerations open up in the case of an agent that can both reduce and provoke suicidality. Finding increased numbers of suicidal acts in the same sets of trials that give rise to claims that these drugs can reduce suicidality and a relative risk of suicidal acts of 1.0 or greater on SSRIs compared to placebo can most parsimoniously be explained by proposing that to exactly the same but inverse extent that these drugs reduce suicidality in some they must be triggering it in others.

**Studies in Recurrent
Brief Depression**

When the controversy about SSRIs and suicide first emerged, Lilly in cooperation with the FDA designed a challenge-rechallenge study, with a new scale designed to be sensitive to the emergence of suicidal ideation, to investigate the issues further. This study never happened. Neither were conventional studies of efficacy with scales sensitive to the emergence of suicidal ideation undertaken. But three studies in patients with recurrent brief depression were undertaken. This is a patient group in which the findings of suicide reduction might best be demonstrated and suicide provocation, correspondingly, most easily concealed.

In 1994 Montgomery et al claimed that such a study of fluoxetine indicated a lack of association between fluoxetine and suicide provocation (21). But the published paper contains figures on much fewer than the target population, and of those recruited more than half dropped out, making it impossible, in the absence of convincing data on reasons for drop-out, to say that fluoxetine had no effect on the emergence of suicidal ideation. An unpublished analysis of these results that found placebo superior to fluoxetine ($P = 0.006$), indicating a general worsening of patients on fluoxetine, makes it even more likely that fluoxetine did engender suicidality (22).

This interpretation is consistent with data for suicide attempts on paroxetine in a trial for a recurrent brief depression (23). This study had a projected annual rate of suicide attempts in its paroxetine arm of 45 compared to 12 in the placebo arm, when it was terminated early. A proportion of the clinical trial data was reported (24) but the figures for suicide attempts, which were most serious in terms of both frequency and outcome on paroxetine, were not reported.

A final study in this patient group undertaken by Verkes et al (25) also compared paroxetine and placebo. This study reported that paroxetine reduced suicidal ideation and acts in the surviving patient group. The study clearly demonstrates that a number of patients who have suicidal ideation may improve on this drug – but this is something that has never been contested. However 75% of both the paroxetine and placebo groups had dropped out by the end of the study, leaving 19 out a projected 100 patients for analysis, and in the absence of detail on drop-outs it is impossible to decide whether paroxetine had precipitated suicidal ideation in some.

“Epidemiological” Studies

A series of “epidemiological” studies have been appealed to in this debate. Some are put forward as evidence that there is no problem with fluoxetine. The first is a one-column letter involving no suicides (26). The second is a selective retrospective post-marketing chart review (27), involving

no suicides, which analysed by the ACNP, the FDA and others show a 3-fold increased relative risk of emergent suicidality for fluoxetine versus other antidepressants (28).

A third was conducted by Warshaw and Keller on anxious patients (29), in which the only suicide occurred in a patient taking fluoxetine. More importantly, of the 654 patients in this study only 192 got fluoxetine. This was not a study designed to test fluoxetine's capacity to induce suicidality, nor should it be termed an epidemiological study. A fourth study on 632 patients, conceived 20 years before fluoxetine was launched and instituted 10 years before launch, had only 182 patients who had got fluoxetine at any point (30). This was clearly not a study designed to establish whether fluoxetine might induce suicidality. Nor was it an epidemiological study.

The fifth is a post-marketing surveillance study (31). While containing a large number of patients, it only compared SSRI antidepressants to each other and hence cannot answer the question of whether the risk of suicide is raised compared with non-SSRI antidepressants or non-treatment. The reported death rate within 6 months of starting treatment was approximately 3 per 100 for each of the major SSRIs and the data on suicides and suicide attempts were in line with clinical trial data above.

There are a further series of studies. One is a set of post-marketing surveillance studies that have compared SSRI with non-SSRI antidepressants and found a clear differential in the rate of induction of suicidality with SSRIs more likely to induce suicidality than non-SSRIs (32, 33).

A second was a study of 212 suicides by Donovan et al, which demonstrated a statistically significant doubling of the relative risk of suicide on SSRIs compared to tricyclic antidepressants (34).

A third study of 2,776 acts of deliberate self-harm by Donovan et al (35) shows a doubling of the risk for deliberate self-harm on SSRIs compared with other antidepressants. This study has been criticised for not being randomised and for not having a placebo group. Were the patients more likely to harm themselves preferentially prescribed SSRIs and did the results arise for this reason? These criticisms however can be answered by two sets data outlined above. First, the placebo controlled studies of paroxetine and fluoxetine in recurrent brief depressive disorders suggest that if patients at greater risk of deliberate self-harm are being preferentially prescribed SSRIs, their greater risk of self-harm is increased further by the SSRI. Second, the figures from the 1986 fluoxetine RCT database, where the risk of self-harm is randomised across groups, give an identical relative risk of self harm between tricyclic antidepressants and fluoxetine to that reported by Donovan and in this set of studies, the figure for self harm in the placebo group was less than half that in the fluoxetine group.

A final study was undertaken by Jick and colleagues (36). This was a study of 143 suicides following 172,000 scripts for antidepressants in primary care in the UK. It produced a statistically significant doubling of the relative risk of suicide on fluoxetine compared with the reference antidepressant, dothiepin. Controlling for confounding factors such as age, sex and previous suicide attempts, left the relative risk at 2.1 times greater for fluoxetine compared to dothiepin and greater than for any other antidepressant studied, although statistical significance was lost in the process. The projected suicide rate for fluoxetine was 187 per 100,000 patient years, and 270 per 100,000 patient years in those recently prescribed the drug. The figure of 270 per 100,000 patient years maps precisely onto post-market surveillance figures for paroxetine (37).

The conclusions to be drawn from these figures depend on the actual or projected rates for suicide in treated or untreated primary care depression in the UK. The traditional rates of a 15% lifetime risk for suicide for affective disorders are derived from hospitalised samples of melancholic depressives in the pre-antidepressant era. The only figures available for suicide rates in primary care depression come from Sweden (38), which gives a figure of zero per 100,000 patient years, and from Holland, which gives a figure of 33 per 100,000 patient years (39). Utilising a database of 2.5 million person years and 212 suicides from North Staffordshire, Boardman and Healy have modelled the rate for suicide in treated or untreated UK primary care depressives and find it to be of the order of 30 per 100,000 patients years (40). Set against these figures, the findings of the Jick study point to an increased relative risk of suicide on fluoxetine.

Controlled Case Studies

The academic debate regarding SSRIs and suicide started in 1990, when Teicher, Glod and Cole described six cases in which intense suicidal preoccupation emerged during fluoxetine treatment (41). In subsequent correspondence, these authors related this problem to the generation of akathisia. They noted that there appeared to be a dose response relationship, that the problem cleared up once fluoxetine was reduced in dose or discontinued, and that it reappeared on re-exposure to fluoxetine. They also noted that a number of patients later responded to MAOIs or had a prior history of good response to MAOIs.

Criticisms of these cases referred to the complicated clinical profile of these tertiary referral centre patients, and to the use of fluoxetine in higher than normal clinical dose, as well as the role of concomitant medication. The possibility that the concomitant medication might have minimised the problem was commented on by no one, even though Lilly as it turns out had been using concomitant medication to minimise this kind of problem in their own clinical trials.

Teicher, Glod and Cole's study was followed by others, from distinguished centres, and from authors noted for their expertise on akathisia (42-46). These studies again demonstrated a dose response relationship, challenge, dechallenge and rechallenge relationships as well as the emergence of an agreed mechanism by which the effects were mediated and demonstrations that interventions in the process could ameliorate the problems (47). A series of reports of suicidality and akathisia on sertraline and paroxetine after these were launched (48) point to SSRI-induced suicidality being a class effect rather than something confined to fluoxetine.

The induction of suicidality on SSRIs therefore by 1991 had arguably been demonstrated convincingly according to conventional criteria for establishing cause and effect relationships between drugs and adverse events as laid out by clinical trial methodologists (49,50,51), as well as company investigators (52,53,54), medico-legal authorities (55) and the Federal Courts (56). All that remained to do was to demonstrate the frequency with which the problem was happening. Scientists from Eli Lilly as well as outside experts and FDA experts collaborated for months on designing a rechallenge protocol that would establish the frequency of the problem. A rating scale designed to be specific to the emergence of suicidal ideation was constructed, the investigators were lined up, pills were prepared in blister packs. But this trial never happened.

Healthy Volunteer Studies

The debate on SSRIs and suicidality has centred around the relative contributions stemming from the disease, depression, and from the treatment. Healthy volunteer studies have the power to clarify this issue. In a recent study, giving 4-8mgs of reboxetine or a 50-100mg dose of sertraline, in a double blind randomised cross-over design to 20 medical, nursing and administrative colleagues, we found that two volunteers became intensely suicidal (57). The

chances of two perfectly normal people becoming actively suicidal in the course of any two week period during the year is approximately 2000 – 1 against (58).

Few of the healthy volunteer studies done by SSRI companies as part of their phase one work are published. Among the published studies with sertraline, one by Saletu and colleagues demonstrates a clear dose dependent induction of agitation with sertraline and contains statements that in a dose dependent fashion sertraline reduces wellbeing and has detrimental effects on affectivity (59,60). In one of the few published paroxetine studies (61), where there has been a 15% drop out rate on paroxetine among healthy volunteers, with none on amitriptyline, a summary includes a statement that “antidepressants are poorly tolerated in healthy volunteers”. Added to this can be set a study with sertraline where “[O]f 12.. healthy volunteers entered into this study, five in the first week of the study were randomized to sertraline, and seven to placebo. And of the five randomized to sertraline, all dropped out in the course of the first week for what appears to have been fairly severe anxiety or agitation..” (62).

These findings are consistent with a recent review I have conducted of all of the Phase 1 healthy volunteer studies on paroxetine (N=34 studies), in which agitation appears in up to 25 % of volunteers, with evidence of a dose response relationship and challenge-dechallenge effects (63). This study series includes one suicide.

Similar statements about the benzodiazepines being poorly tolerated by volunteers could not be made. The significance of this is as follows. The antidepressants were clearly recognised as being hazardous from their first use. This hazard was once rationalised by the notion that they would be given to individuals who were at risk and that the hazard the drugs posed would be off-set by the reduction in the hazard of treatment effected. In the course of the 1990s, however, there has been a wholesale switch from diagnosing anxiety states, which were treated with Valium, to diagnosing depression and using SSRIs (64). This patient group new to antidepressants is at minimal risk of suicide. The findings from studies giving SSRIs to healthy volunteers would appear on the face of it to sit poorly with a lack of warnings for this group of agents and their widespread, unmonitored use for this primary care patient group through the 1990s.

Coda.

Evidence from meta-analyses, randomised controlled trials, epidemiological studies, controlled case studies and healthy volunteer studies all separately indicate that there are grounds to believe that SSRIs may make some takers suicidal. When these lines of evidence are combined, the case is strong enough to suggest that there is a moral onus on companies marketing these compounds to warn about their hazards and to advise close monitoring during the early stages of treatment. Scientifically, if they wish to claim that there is no hazard on their drug, the burden of proof lies with the companies to prove their drug does not cause a problem, rather than with a reviewer to prove that it does. Legally, furthermore, a failure to test makes a failure to warn particularly problematic. Regulatory statutes in fact require companies to warn about potential hazards if they are serious – even if the case is not proven.

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Please quote ref: VB/Dtc 01/6436

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Dear Dr Healy

Thank you for your revised manuscript. I have read it carefully and discussed it with Richard Horton. We feel strongly that what the debate on SSRIs and suicide needs at this point is a formal review of the evidence available, and that your review is not it. We are therefore rejecting your manuscript again, but if you were to do a more formal review, along the lines of a meta-analysis, and with input of a statistician or epidemiologist experienced in such studies, we would look at it.

Yours sincerely

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c.c. Richard Horton

