Our Ref: DH/JT

31 December 1997

Professor David Nutt
Editor
Journal of Psychopharmacology
University of Bristol
Psychopharmacology Unit
School of Medical Sciences
University Walk
BRISTOL
BS8 1TD

Dear David

Enclosed is an article which hopefully will be one of the first you have in the New Year. This is a piece that has been looked over by Dec Doogan and Roger Pinder. Roger in particular suggested a number of changes and the version you are seeing now incorporates all of those. Even before that however he thought the piece was topical, raises an issue that needs raising and could potentially contribute. He was quite keen that the whole thing be pitched in a way that persuaded companies to take up some of the points being raised and build them into clinical trial protocols.

The issue however as you will see is not without its controversial aspects. If you feel even before sending it out for review that its unlikely to be a piece that you want perhaps you could let me know and I can go elsewhere with it.

Regards,

David Healy

PS I've copied you some correspondence with Jonathan Green. If you have any thoughts about this, let me know.

Our Ref: DH/JT

12 January 1998

Professor David Nutt
Editor
Journal of Psychopharmacology
University of Bristol
Psychopharmacology Unit
School of Medical Sciences
University Walk
BRISTOL
BS8 1TD

Dear David

Enclosed is a two page change to what was pages 25 - 27 of Suicide in The Course of Treatment (X3) and a revised manuscript (X3). Accidentally we sent you an older version of the manuscript which contains an error in the calculations. We've also changed the country to which the calculations refer - the UK rather than the US.

There would seem to be two ways forward. Either you could send the revised manuscript out to your reviewers and ask them to bin the older version or you could play spot the deliberate error with your reviewers and see whether any of them come up to scratch. This would tell you something about your reviewers. I suppose another possibility might be to hold on to the revised version if particular reviewers raise problems with the section on pages 25-27 you can see whether the revised version would meet the criticism they make.

Regards,

David Healy

JOURNAL OF
PSYCHOPHARMACOLOGY

Reply to: **David J. Nutt**, DM MRCP FRCPsych
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Editors:
David J. Nutt, DM MRCP FRCPsych
Martin Sarter, PhD

3 March 1998

Dr David Healy
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Dear David,

re: **Suicide in the course of the treatment of depression**
MS no 002/98

I am pleased to say that we now have comments from 2 referees on your manuscript. The main consideration is that you should shorten the length of the paper by a third. Referee 2 makes several comments, all of which are reasonably straight forward and should present no problems for you. Referee 1 on the other hand makes several important comments, all of which should be met in your revised version.

When you resubmit after making changes, please could you in a covering letter, detail the changes you have made by addressing the specific points of each referee. It would also greatly help if in one copy of the revised version you could highlight those areas of the manuscript which have been altered. Please send 3 copies of the revision.

In addition, your manuscript should be prepared according to the enclosed guidelines and an exact copy of the final version should be provided on disc.

I look forward to receiving your revised version in due course.

Yours sincerely,

David Nutt

Professor

SAGE Publications, 6 Bonhill Street, London EC2A 4PU, UK

Ref 1

REF: MS NO 002/98

SUICIDE IN THE COURSE OF THE TREATMENT OF DEPRESSION

DAVID HEALY ET AL.

This is a very weak paper that presents an inadequate and biased review of a topic of some interest. Some examples of the many points that need attention include the following:

Page 6/7 quotes extensively the negative reports from open studies of suicide provocation, eg. Teicher Healey, etc. but fails to provide balance by giving numbers or the results of blinded control studies, Beasley, Montgomery. Argues for akathisia as a cause but again does not provide data. Opinion appears to be given preference to data.

1

Page 8. In the argument that moclobemide is less effective, no references are given of efficacy studies. Again, opinion is given before an adequate unbiased review of the literature has been undertaken. All the papers reporting a clomipramine moclobemide comparison should be considered and discussed. The only source for this section is one paper by Isaacson showing a very poor attention to the literature.

2

Page 9. The journalistic approach devalues the scientific literature. For example; "Eli Lily" denied the claim by Beasley 91 Nakielury 94. The author fails to consider the analysis of the CSM, or an independent placebo controlled study of suicide attempters of Montgomery et al. This amounts to biased reporting.

3

Page 12. The authors misinterpret the analysis of item 3 of the HAMD and do not have the courtesy of making it clear that Beasley et al reported a significant increase of de novo emergence of suicidal thoughts and acts on placebo compared with fluoxetine. The attack on the sensitivity of item 3 is not based on reported data on the item but merely the authors unsubstantiated opinions. They should consider other data using this same analysis which showed sensitivity with other SSRIs (Montgomery Dunner Dubar 1995, O'Hevanger 1995).

4

Page 12. The criticism of item 17 of the HAMD misquotes the item. Item 17 is an item rating loss of libido, not sexual function. The authors do not seem to appreciate the important difference between interest and functioning.

5

Page 13. The authors confused akathisia and nervousness, sometimes quoting one (page 9) sometimes both together (page 13). No review of the prevalence of akathisia, which is low, is given from published data. The authors instead quote one case report paper of Lipinsky and claim, without quoting data that akathisia/nervousness is found in 30% of SSRIs. The authors should give adequate references and discussion of the incidence of akathisia and nervousness separately for all SSRIs from large data sets.

6

Page 14. The Clewes reference is inadequate. Were these data presented or published in an abstract? A better reference would be Wernicke, et al. The definition for inclusion of the 42 side effects listed by Plewes et al are not given and this misleads the reader. Were they the 42 side effects with a prevalence of 1% or more? The authors should be specific and explain to the reader whether the data support a prevalence of less than or more than 1%. This section is confused and argumentative without a balanced review of the literature.

7

The section on the inadequacy of clinical trials with the authors' preference for open observations is tedious, poorly constructed and lacking in data.

Page 21. The authors quote the earlier Henry data but do not elaborate. Here they extensively quote the Jick analysis in primary care. No attempt is made to put the Jack data into the context of the Henry England and Wales data. The authors go entirely on the Jick data project 189 deaths for fluoxetine per 100,000 patient years. They do not turn to the OPCS data or the NHS prescribing figures or the IMS data as Henry and colleagues do to test their assumptions. This section reveals substantial bias.

8

Page 22. The authors confuse suicide and suicide attempts, overdose deaths on one agent alone and on multiple agents.

9

Page 25. The section on epidemiology fails to quote any epidemiology reference. The authors quote 10% of the adult population as depressed but fails to review the literature or to specify if this is point prevalence or one year data. The authors produce no data to support their assumption of relative risk of suicide with severity and carelessly bandy figures around based on their assumptions.

10

The references are full of omissions and carelessness, page numbers are erratically given or withheld. Healy and Savage 1998, Reserpine exhumed is not an adequate reference. Lipinsky in the paper turns up as Lipinski in the references. Moller 1990 has no paper title or reference details.

11

JOURNAL OF PSYCHOPHARMACOLOGY

REFEREE'S REPORT FORM

Referee No: 2
Manuscr No: 002/98

Authors: Healy et al

Title: Suicide in the course.....

PLEASE RETURN 3 COPIES OF THIS REPORT TO THE EDITORIAL OFFICE

This paper deals with a very important topic which well deserves an airing. I think it should be published but should be shortened somewhat to make it more digestible for the reader. In particular, the section between pages 13 and page 20, while containing some very interesting material, could be shortened quite considerably without loss of important content. Overall I think that the paper ought to be reduced in length by a third.

Abstract The word 'curing' in line 2 is inappropriate. Line 9 - it would be better if the authors put 'suicide during treatment'.
Page 11 Ham-D should be put in full.
Page 12 A fullstop is needed after 'borne in mind'.
Page 17 The sentences beginning in the final line are unclear, and the word 'treatment' should be used after 'drugs'.
Page 25 The final paragraph needs readdressing. The percentage quoted for depression (10%) would appear to be the annual rate whereas the number of suicides should be based on the lifetime prevalence of depression. In the second sentence the authors are referring to the annual number of suicides, not the 'annual suicide rate'. In the second half of this paragraph, the figure of 50% for suicides without depressive disorder is probably too high on the basis of recent psychological autopsy studies.

Page 33 The Healey and Savage (1998) reference is in press according to page 3. The journal should therefore be cited.

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JT/DH

10 March 1998

Professor David J Nutt
Editor Journal of Psychopharmacology
The Psychopharmacology Unit
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University Walk
Bristol BS8 1TD

Dear David

Re: **Suicide in the Course of the Treatment of Depression**
Ms 002/98.

Many thanks for offering us the opportunity to reply to the points raised by your reviewers. Broadly speaking we think we can meet these. You asked for the paper to be shortened in length. It has been. The text up to the references has had 29% of its material removed. The paper may still look long but this is because it is written in a fairly large font etc. The text length is just over 5000 words where as it was almost 7500.

Referee 2.

As you mentioned the points here were not particularly hard to deal with. The paper has been greatly shortened, hopefully without loss of content. The points in the abstract and on pages 11,12 and 17 have all been taken care of.
The most substantial point which was on page 25 has also been handled in some more detail - we pick this point up in the responses to referee one. The point regarding the Healy and Savage reference has been taken care of and the journal, the British Journal of Psychiatry, is now cited. We expect publication of this piece before June.

Referee 1

Before dealing with the specific points, it is important to note that we feel that this referee made a number of very useful comments. Retrospectively we agree the piece was too journalistic in orientation and made some sweeping claims, which other referees could perhaps have punished more severely. The original piece did unfortunately unduly 'personalise' the argument and by naming Eli Lilly specifically, we concede we produced something that can be read in the wrong light.

We have done a great deal to try and depersonalise the issues. There were sections of the piece that refer to the political and legal significance of some of the data, which clearly should not have been there in the first place and have been removed completely.

Point 1
The whole point behind this piece is that if clinical trials are not constructed specifically to answer a question, then the answers that come out of those trials cannot be retrospectively used to answer the initial question. This is a basic tenet of experimental methodology.

The referee suggests that we argue for akathisia as a cause but do not provide data. Our argument is not for akathisia as a cause so much as the review holds that a range of different people have argued for akathisia as a cause and there is a substantial amount of data to support this. There is a curiously interesting problem, however, with the data on akathisia which is noted in the course of the review. This is the fact that, in clinical trials done according to GCP, akathisia in one sense does not occur. To suggest however that it does not occur, we think, would appear to most people as an absurdity. Against this background there are inevitable problems in determining its frequency and its frequency with particular drugs. We have done the best we can in this area focusing on the fluoxetine database in particular.

Point 2
The reviewer appears to have missed the point behind the structure of the piece. We outlined 5 different possibilities that have been raised. We are not in the business of considering each of these in depth. For example the first possibility which was raised by Kielholz in 1958 was that the simple treatment of depression in itself might raise suicide rates. We note this argument but have not handled it in a great deal of depth. It could have been handled in further depth. As late as 1985 George Winokur was writing that the only treatment that reduced suicide rates was ECT and that everything else potentially increased them.

As regards the question of treatment inefficacy and moclobemide, as with the first Kielholz option, we have not opted to handle this in detail. We have taken our cue from the referee and have indicated that in our opinion the data base at present is not sufficient to permit conclusive judgements on this issue and that the possibility remains more a theoretical one rather than one that is supported by data.

What we have tried to do as regards all these possibilities in the rest of the article is to focus on the methods by which some of these questions might ultimately be resolved. What we are hoping to do is draw attention to the deficiencies in the way in which we are currently doing things. If we continue to run clinical trials etc the way we are doing we will never be able to answer some of these questions. Hopefully this point is a little more clear in the text now.

Point 3

As regards the journalistic approach we completely agree with the reviewer and have taken steps to revise this aspect of the piece throughout. We have also taken up the referees point on the Montgomery placebo controlled study of suicide attempters but have folded this piece into the study by Peter Joyce (page 9). At this point we note that one of the implications of the Joyce study is that borderline patients who might be impulsively inclined to commit suicide would on SSRIs be less likely to do so than other agents. This point however as we note does not settle the question of whether an antidepressant might trigger problems in people not particularly liable to suicide in the first instance. It remains in our opinion that no study has been designed to tackle this issue.

Point 4

Again the reviewer makes a useful point here. We have included this in the revised version and indicate the registration of de novo emergence of suicidal thoughts and acts on placebo using the Ham D (pp 9). In our opinion however this does not solve the problem. We cite experimental data to support our position. This is data due for publication in the March issue of Human Psychopharmacology which looked at the development of akathisia and suicidality in healthy volunteers given low doses of neuroleptics. The reviewer and others will be able to have access to this in the very near future (long before this paper appears) and will be able to consider whether this answers the point that they have raised or indeed more generally indicates the shape of the problems we need to tackle. We enclose a copy of this for your consideration. It didn't seem to be a good idea to lay out the full details of this particular study as it would of been extraordinarily space consuming.

Point 5

Again the referee makes a very valid point here and the entire piece has been restructured to take this into account. The piece regarding item 17 has been dropped completely and the question of sexual dysfunction has been folded into the broader question of how we rate adverse events in clinical trials (pp 11-12).

Point 6

This refers back to points raised above. The position of akathisia is extraordinarily complicated. In our concluding section we note that on the one hand there is almost universal acceptance that dysphoria/akathisia/agitation can be caused by psychotropic agents but on the other hand it is poorly investigated. The challenge must be to devise methodologies that would handle the problem satisfactorily. The least controversial approach would be to use something like the UKU systematically in the course of clinical trials. Some companies have begun to do this. Indeed our awareness of this possibility has come entirely from company sources hence the suggestion is in no way antithetical to company interests. Until such time as this practice becomes more widespread, however, its difficult to offer convincing figures other than to say that the figures that can be pulled from the fluoxetine database are about the fairest set of figures to use. Its difficult to see how we use anything more fair. Its also difficult to see how anyone could claim that the true rates can not be anything other than higher than the rates reported in this dataset given that the dataset depends on spontaneous rather than mandatory reporting.

Point 7

This picks up on the point raised above the. The Plewes reference was a poster rather than an abstract, which is enclosed. Given that this is up to date and company data it is difficult to see how anything could be a better reference.

Point 8

We feel that the referee has perhaps misread us on this point. We have cited the Henry data earlier and do so again in the concluding section and make it, we think, quite clear that these data support the use of antidepressants that are safe in overdose. The thrust in the article is to accept that this point has been made so clearly and is now so uncontroversial that little else needs to be added.

On the other hand the reason for looking more closely at the Jick study is that this remains controversial. The Henry data do not settle this controversy in that they only refer to OPCS data and NHS prescribing figures and they do not take into account all those who are committing suicide by other means.

Point 9

Again we feel that the referee may have slightly misread the issue in that one has to look at people who commit suicide by all means whether or not by overdose and whether or not by multiple agents if one is going to look at the broader question of suicide in the course of treatment. The Henry data speak specifically to the question of people who commit suicide following the ingestion of a specific toxic agent but not to those who are committing suicide for other reasons.

Point 10

The section on epidemiology has only to do with the epidemiology of suicide in patients actually taking antidepressants, as opposed to the epidemiology of suicide or the epidemiology of people who are depressed who suicide. As such there have only been two studies, both of which are substantial studies and both of which have been cited.

The subsection on epidemiology in the public domain refers to the way various figures like the 15% lifetime risk for suicide get bandied about in the media, legal settings and other contexts. On this point we have hopefully clarified the questions of lifetime risk as well as annual prevalences, as mentioned also by referee 2. An interesting point emerges, when one considers the literature as we have done - all the figures that are cited these days in this context are drawn from populations of severely depressed hospitalised patients. We have gone back and pulled out every single reference on this point. There are clear implications of this which we try now to make in a much less excited and much less journalistic manner than was made in the first paper. The main implication is that we simply do not know the lifetime risks of suicide for milder affective disorders. Intuitively they can not be as great as the risk for severe depressive disorders and practically they cannot be as great because if they were the rates of suicide in the UK population annually would have to be at least 50,000 per annum and not the 5000 per annum that they currently are. It is not possible at the moment to provide empirical rates of suicide for milder affective disorders in that to do so populations with these diagnosis have to be tracked over decades at the very least. It is possible to model this rate however and we are at present in the business of producing a paper specifically on this question (**which the Journal of Psychopharmacology can have a first option on if it wishes**).

Pursuing this point further however and picking up on the point made by referee 2, there is a substantial body of evidence that anything from 30-50% of population will have an affective disorder at some point in their life. Francis Creed is currently suggesting that the annual prevalence of affective disorders maybe as high as 50%. The National Co-morbidity Study (now referenced) gives lifetime figures of 40%. In making our calculation as regards relative risks in this revision we assume a figure of 25% - less than any of the figures. We are being very conservative in our estimates therefore and the idea that we are carelessly bandying around figures is one that we would reject. We can understand however that some of the

inflammatory language that we used in the first version of the article may have contributed to this response from one of the referees. This hopefully has been put right.

Point 11
All of the references are now tidied up. In addition to the Moller reference (1992) a further reference has been introduced on increased rates of suicide following psychotherapeutic interventions.

Its difficult to clearly mark where things have changed on the new version because so much has been removed and marking an absence doesn't seem to make sense. What we have done is to mark up key points on the old version, which is included, and have put in some page nos to revisions in the new piece in this letter.

Yours sincerely

David Healy Claus Langmaak Marie Savage

JOURNAL OF
PSYCHOPHARMACOLOGY

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14
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3 April 1998

Dr David Healy
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Dear David,

re: **Suicide in the course of the treatment of depression**
MS no 002/98

We now have comments from referee 1 on the revised version of your manuscript and this referee again makes a number of important observations. We have also taken the liberty of reviewing your paper "in-house" and to some extent have sympathy with the referee's comments.

Point 1 should be incorporated into your manuscript. At present the paper reads as an attack on fluoxetine and fails to report a balanced view from the SSRI angle. Point 2 regarding the Plewes reference is important. On reading the published abstract, (correct reference Neuropsychopharmacology 7(2) S169.) one notes that it is a Lilly publication. It would be preferable to balance this out with a more rigorous published reference comparing fluoxetine with whatever in patients; or even including a volunteer study of emergent side effects? Certainly for the reader interested in looking further, the Plewes reference is extremely scanty. Point 3 should be considered in your next revision.

In addition, I have some general comments which you may or may not choose to incorporate. The original referee 2's comments about shortening some of the sections still stands; pages 12-16 could be a good place to start, and page 16 still is still quite journalistic in style.

Specific points:

P8 - Joyce ref not in references.
P16 - "deaths from violence on fluoxetine" - violent suicides or killings??; last para, Isacsson study already quoted in similar detail on page 6.
P17 - Wheatley and Kremer 1997 not in refs, you probably mean Wheatley et al 1998.
P18 - Hagnell et al 1979 is 1981 in refs.
P20 - You touch on increased rate of suicides with psychotherapy and this is of interest. Since psychological treatments are often part of the "treatment for depression" (your title), may be

expanding this section would be useful?
P21 - You briefly mention mood changes in volunteers and suicidal ideation. A further discussion point may be that of anhedonia and its association with suicidal ideation and it being highly predictive of successful suicide (see Argyropolous and Nutt, Psychopharmacology 134:333-336 for refs).

Are there any specific questionnaires which are designed to measure suicidal thoughts that could be incorporated into clinical trials? Is anyone about to produce one? What are the ethical implications for studying suicide in the course of treatment in depression? Are you able to offer any suggestions to improve the system for reporting events?

In your revision please could you in a covering letter, detail the changes you have made in one copy of the revised version please highlight those areas of the manuscript which have been altered, so that the next revision will be easier to review. Please send 2 copies of the revision.

I look forward to receiving your revised version in due course.

Yours sincerely,

David Nutt

Professor

David - I guess you & the referee will never agree, but we will need to send it back!

Anyone

REF: MS NO 002/98

SUICIDE IN THE COURSE OF THE TREATMENT OF DEPRESSION

DAVID HEALY ET AL.

The paper remains apparently unchanged. The authors argue in their letter rather than addressing the points raised.

They still do not have the courtesy to the reader to fully report the findings of Beasley et al or Price et al which indicate if anything that fluoxetine seems to protect against suicidal acts rather than produce tem. The authors say in their letter that they have dealt with the negative findings in the placebo controlled study of Montgomery et al in suicide attempters but I cannot find the reference. Likewise, they have failed to comment on the data showing that suicidal thoughts and acts are reduced in the fluvoxamine and paroxetine databases as asked by the referee.

They continue to confuse agitation and akathisia. They do not answer the questions raised by the reviewer, but hide behind their opinions supported only by a book rather than a data based reference. The authors, for example, do not refer to the findings of Tollefson et al, which show that fluoxetine reduces agitation more than placebo, nor to the similar analysis on other SSRIs. They fail to give in their paper the fact that the Plewes et al abstract defined the symptoms as those reported in more than 5% of patients but instead accuse the authors and trials of bias. Can't they find a published reference?

The authors' grasp of the literature is modest and their grasp of data apparently absent. They have not commented on the reduction of suicide with antidepressants in the Gotland study, Rutz et al, nor on the finding from Isaacson et al that the risk of suicide was higher in the untreated population. They have not commented on the Warshaw and Keller report in the HARP data that fluoxetine treatment is associated with a significantly lower probability of suicide attempts or gestures than those not taking fluoxetine. This paper provides substantial evidence of bias rather than a dispassionate review of a serious subject. They have not referred to the substantial data sets which find that fluoxetine and other SSRIs are apparently able to reduce the emergence of suicidal thoughts or acts but prefer instead to publish once again their own unsubstantiated beliefs.

This paper lets down the authors, the journal and, frankly, the scientific community.

Our Ref: DH/JT

8 April 1998

Professor David Nutt
Editor
Journal of Psychopharmacology
The University of Bristol
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Dear David

RE: SUICIDE IN THE COURSE OF THE TREATMENT OF DEPRESSION

There is nothing like a vigorous peer review process, where the ring is held open by the editor of the journal, to confront one with the problems in an article. It's only reading the reviewers comments that you fully come to appreciate what it is you've written. There seems to me a number of differences between us and the reviewer that we've taken steps in this draft of the article to address.

One of the points is that there appear to be two issues which ideally should be kept separate. One is the issue of whether an antidepressant in certain circumstances can contribute to a suicide and the other is the public health question of what should be the national approach toward handling the question of suicides - should we attempt to vigorously detect and treat all depressive disorders?

POINT 1

In the absence of a clear statement from us in the first draft of the paper that SSRIs clearly are of benefit in depressive disorders and in reducing the suicidality that goes with depression and indeed that they may be particularly useful in patients with features of impulsive suicidality, I can quite see how a reviewer and potentially readers of the article could have been misled. This

Continued/..

is a misunderstanding it seems to me in the sense that it was always assumed by myself and my colleagues that it is useful to detect and treat depressive disorders particularly once they reach a moderate degree of severity. The article was written against a background assumption that this is the case. I accept however that this is a particularly crucial assumption and that it needs to be made explicit rather than left implicit and therefore the revised version of this article makes this point very clearly before going on to deal with the question of possible suicidality in individual cases.

This draft has taken care to distinguish between individual and population risks and for instance the question of psychotherapy has been addressed by noting that where antidepressants may in individual cases cause problems, at present the data on psychotherapy points toward possible increased population risks. This point is put rather forcefully in the conclusions section of the paper. To expand it much further would I think require a different paper (which we have submitted elsewhere).

As regards not including the references as suggested by the referee in the first set of comments, it is the case that several of the references mentioned explicitly by the referee were not included. For instance the Price reference. This refers however to a study essentially of Yellow Card reporting. This is exactly the kind of study that we criticise in the methodological section of the paper. As such we believe it is fairly worthless. Some of the other studies had been subsumed in the general section of the previous draft which stated that no studies had specifically addressed the question of emerging suicidality. This still remains the point. It's made perhaps even more clearly in this draft of the article but it is now set much more clearly against a background of noting the efficacy of SSRIs, a background that includes a number of the studies that were called for by the referee in the first instance.

We have amended the references and other points noted in your covering letter. The question of dysphoria/anhedonia as a predictor for suicidality I think is central. The Fawcett references that you used in your piece are ones that we have used in this article as well. I haven't included further detail on this in this draft as I've taken literally your instructions to reduce the amount of material further. A further 1,000 words has been removed from the piece even taking into account the insertions that were necessary to cover some of the points made above. The manuscript has now 40% of the material removed compared with the original version. I think it should be difficult for the referee to say that it remains apparently unchanged.

We are approaching a point however where it seems to me that the differences will no longer remain a matter of point of view but rather will hinge on questions of trial methodology. Perhaps if the referee feels similarly strongly about this draft of the manuscript you might consider a review plus commentary. When I review something, I'm always prepared to have the

Continued/..

comments published. A commentary on this piece that was as robust as the reviews have been would be a challenge to answer. I'm clear in my own mind what the outlines of our answer would be. Essentially the issue would be that properly designed studies have not addressed the questions being posed in this article. There are epidemiological issues as well that have not been properly addressed. A commentary and response might allow some of these issues to be developed further.

POINT 2

As regards the Plewes et al reference, I've thought long and hard about this one and feel that this is really the best reference. In order to be fair on the issue it would seem best to use the data Lilly themselves are prepared to use publicly. Anything else would be something that would be cobbled together from figures cited in the Physicians Desk Reference or some other source which would always be open to the accusation of bias on our part. The Plewes reference I feel provides data that could be very easily obtained by anyone who is interested to take the issue further if they write to the company. The relevant figures are furthermore included actually in the article.

There are a few further points you may wish to note about this. We are being very even-handed I feel in that this section of the paper. On the fact that akathisia is not included in the list here, it justified the approach that Lilly have taken the basis that akathisia is not a word used by patients. However if you look through the list more closely you will see that congestive heart failure is included. This is unlikely to be a term used by patients. I feel that we have lent over backwards here to be fair to Lilly and in actual fact what they have been doing may be somewhat slightly different to the generous interpretation/escape route that we've offered them.

As regards side-effects that occur at the 5% level, I note the point made by the reviewer and the point made in the abstract but if you look at the data a great number of these side-effects - 1/3rd or more occurred at what is clearly less than a 5% level. The tone of this whole section however has been changed by the fact that we've removed the statement that this lists 42 possible side-effects etc.

As regards whether something else would substitute better, a comparison with another agent does not seem to me to be appropriate in the sense that the issue being addressed is whether randomised control trials have shown that certain side-effects occur at a significantly greater rate on Fluoxetine compared to Placebo. This is the only publication that I can think of that addresses this point. There really isn't anyone else who would have the interest to publish anything on the question of whether particular side-effects occurred in significantly greater rate on Fluoxetine than Placebo other than

Continued/..

Lilly and hence the Lilly publications would seem to be the only one that it would be appropriate to use.

You might also like to know that we have not at any point attempted to list all the side-effects of Fluoxetine that could be related to arousal of some sort, as some critics of the drug have done. Reviewing the issues I became aware that there has been criticism from certain sources that the arousing side-effects of Fluoxetine occur in over 30% of those who take it and because of possible echoes with critics, who I would not wish to be associated with, the figure of 30% which was mentioned previously in the text has now been deleted completely. The main point is the fact that we just do not know the frequency with which these side-effects occur and won't know it until research instruments such as the UKU are used. This point is hopefully made now in a much less contentious manner than before.

POINT 3

Finally as regards to the reviewers third point this refers to a point raised earlier about the public health issue of treating depression. The discussion section of the paper has been extensively re-vamped with large amounts of material removed and a new concluding section, which takes into account the public health issues of education regarding the detection of depression and the role this might play in lowering national suicide rates. We made reference in this revised section to the Gotland Study and other data as recommended by the reviewer.

The issue of mild affective disorders is much trickier. The only prospective community-based epidemiological study of this quotes a figure of 0/100,000 patient years. Clearly this cannot be right and we've gone for figures of 25-40. But developing this fully I think is a different article.

Yours sincerely

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18 May 1998

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Dear David,

re: **Suicide in the course of the treatment of depression**
MS no 002/98

We have now had a chance to review the much-revised version of your manuscript and are happy to tell you that it is now suitable for publication in the Journal and will appear in a future edition.

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Many thanks for your contribution to the Journal.

Best wishes.
Yours sincerely

Jayne Bailey
Editorial Manager

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Suicide in the course of the treatment of depression

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Five different mechanisms have been proposed whereby antidepressant treatment might lead to suicide: first by simply ameliorating depressions more rapidly; second by an action intrinsic to the specific antidepressant effects; third by toxicity in overdose; fourth by side-effects of specific antidepressants; and finally by virtue of treatment inefficacy. Evidence from randomized control trials (RCT), controlled case studies and epidemiological studies on this question is reviewed and it is concluded that antidepressants can be implicated in some cases of suicide during treatment. Modifications of clinical trial methods and pharmacogenetic studies would yield a richer data set to explore this issue further.

Key words: akathisia; antidepressants; behavioural toxicity; case reports; suicide

Introduction

One of the first controversies of the psychopharmacological era concerned associations between psychopharmacotherapy and suicide. Although thought of as a neuroleptic, the only placebo-controlled randomized control trials (RCT) conducted with reserpine indicated that it was an antidepressant (Davies and Shepherd, 1955). A simultaneous series of reports in the *New England Journal of Medicine*, *JAMA*, the *BMJ* and the *Lancet*, however, implicated it in the precipitation of depression and suicide (see Healy and Savage, 1998). Despite early prominence, this issue has been comparatively neglected, perhaps because we do not wish to contemplate the possibility that useful treatments may on occasion be problematic. Nevertheless, there have been five distinct proposals as to how treatment might be associated with suicide and the problem of deciding what possibilities, if any, the evidence supports also raises a host of intriguing methodological issues.

Suicide on treatment: the mechanisms

Depression and suicide

Before the advent of the antidepressants, a number of authorities (Staehelin, 1955) had argued that depressed patients were likeliest to commit suicide when they were entering into or coming out of a depressive disorder. It followed that antidepressants, if they alleviated depressions without permanently correcting the underlying disease, would lead to more entries into and exits from depressed states. Suicide therefore had to be a risk of treatment and it occurred in the first studies of imipramine (Kielholz and Battegay, 1958).

Antidepressant effect and suicide

Kielholz later proposed that specific antidepressant actions might be associated with suicide. His initial impression was that the monoamine oxidase inhibitors (MAOIs), which he categorized as the most drive enhancing, were most associated with suicide attempts, followed by desipramine and nortripytline by virtue of alleviating depressive psychomotor retardation before they cleared up suicidal ideation (Kielholz, 1971). When the effects of these agents on monoamine systems were established, it appeared that there was a particular problem with antidepressants selective for catecholamine systems. A long-term maintenance study with maprotiline (Rouillon *et al.*, 1989) in which there were five suicides and nine attempted suicides on maprotiline compared with one suicide in a smaller placebo group appeared to bear out this idea.

Antidepressant toxicity and suicide

In the 1980s, a debate developed about the relative toxicity of antidepressants in overdose. This centred on the safety of mianserin, which had been associated with agranulocytosis. The argument hinged on a calculus of risks and benefits. While mianserin might be associated with lowered white cell counts, its defenders argued that it was safer in overdose than other antidepressants and that therefore its use would be associated with a lower death rate overall (Pinder, 1988). This debate led to the construction of a fatal toxicity index based on the number of deaths following use of each antidepressant as a proportion of the number of scripts written (Cassidy and Henry, 1987; Pinder, 1988; Henry, 1992). When these calculations were made, desipramine, amitriptyline and dothiepin, which are more toxic in overdose than other antidepressants, appeared to be associated with more deaths. The implication was that there might be a public health gain by switching prescriptions to less toxic compounds.

Antidepressant side-effects and suicide

Against a background that catecholaminergic agents might be more likely to be associated with suicidality and the safety in overdose of the selective serotonin reuptake inhibitors (SSRIs), the next development came as surprise. A series of case reports

(Teicher *et al.*, 1990a,b,c; Creaney *et al.*, 1991; King *et al.*, 1991; Rothschild and Locke, 1991; Wirshing *et al.*, 1992; Healy, 1994) suggested that fluoxetine might induce suicidal ideation *de novo* in a proportion of vulnerable individuals by triggering an akathisic state. This was perceived by some as an attack on fluoxetine, although Teicher *et al.* (1991) and others (Healy, 1994) saw the problem in terms of a potential that all antidepressants might have through side-effects, such as akathisia or depersonalization (Damluji and Ferguson, 1988; Healy, 1994). One problem with such side-effects early in treatment may be a risk of misattribution by the patient to a worsening of their illness.

Antidepressant inefficacy and suicide

Another possibility was raised by Isacsson and colleagues (1994), who analysed all suicides in Sweden for 1990/1991. They found that lofepramine was least likely to be found in the bloodstream of suicides, the most commonly used tricyclics were intermediate in frequency and mianserin and moclobemide were the most commonly found agents. They introduced the argument that suicide might be associated with treatment inefficacy. In support of this idea, they noted two pieces of evidence. First, there was the relatively high rate of suicides on moclobemide and low rate for clomipramine and they noted that clomipramine had been shown in clinical trials to have a superior treatment effect size to moclobemide in severe depressions. Second, a range of studies (e.g. Isacsson *et al.*, 1994) suggest that completed suicides have sub-therapeutic blood levels of antidepressants.

Suicide on treatment: methodological issues

An association between antidepressant treatment and suicide raises complex issues of causality given that depression itself is closely associated with suicidality. Depression, however, is also closely associated with sexual dysfunction and yet it has been possible to reach agreement on the existence of antidepressant-induced sexual dysfunctions. For some of the mechanisms outlined above, a causal relationship between treatment and effect (suicide) has face validity; other things being equal antidepressants that are safer in overdose should be associated with fewer deaths from suicide. For other issues, such as treatment inefficacy or the emergence of suicidal ideation, the picture is less clear. We explore these issues, using data from clinical trials, case reports and epidemiological studies, and focus on fluoxetine because the issues have been most keenly debated for this agent, although the same points apply to all antidepressants.

Clinical trials

Associations between fluoxetine and suicidality have been denied on the basis that RCTs are the only means to demonstrate cause and effect and that no trials with fluoxetine have shown the emergence of suicidality or akathisia (Beasley, 1991; Nakielny, 1994). In an era when evidence based medicine is in favour and RCTs are held up as the best form of evidence, this argument carries considerable weight. There are, however, a number of problems with the notion that RCTs are a necessary means to establish cause and effect or the best means in all circumstances.

Clinical trials and suicide

A considerable amount of work has now indicated that prior suicidality or baseline agitation need not be contra-indications to treatment with fluoxetine (Beasley *et al.*, 1991; Tollefson *et al.*, 1994). Indeed, independent studies suggest that SSRIs might be most effective in patients with borderline personality features, who might be expected to impulsively attempt suicide (Joyce *et al.*, 1994). An analysis of the fluoxetine database, looking at item 3 of the Hamilton Depression Rating Scale, indicated a fall in suicidality ratings in patients on fluoxetine comparable to that found with reference antidepressants and greater than found on placebo (Beasley *et al.*, 1991). It also demonstrated that a greater number of subjects showed item-3 increases on placebo (Beasley *et al.*, 1991). Similar findings have been reported for paroxetine (Montgomery *et al.*, 1995). Clearly, SSRIs including fluoxetine have a place in the management of depressive suicidality.

However, the use of RCTs by pharmaceutical companies is largely determined by registration requirements for evidence of some treatment effect. The patients recruited to such studies are samples of convenience, which need not represent either the general population or any vulnerable population within in it. These trials are not designed to answer the question of whether the drug on occasion can trigger an emergence of suicidality. To date, there have been no such trials. A meta-analysis of studies conducted for other purposes, using instruments that were never designed to settle this question is no substitute, given experimental indications showing patients and observers may fail to rate even intense newly emergent drug-induced suicidality (Healy and Farquhar, 1998). Quite simply, beneficial effects on suicidality in a majority of depressed patients do not outrule drug induced problems anymore than a reduction of pertussis induced brain damage outrules vaccine induced injuries.

Clinical trials and side-effects

The precise frequency with which SSRI-induced akathisia/nervousness occurs is uncertain, even though akathisia was reported very early as a side-effect of fluoxetine treatment (Lipinski *et al.*, 1989) and Ayd's (1996) *Lexicon for Psychiatry and Neurology*, states that 'fluoxetine's capacity to evoke akathisia is well recognized'. This is largely because few RCTs have been designed to establish the precise incidence of side-effects. Although not unconcerned about side-effects, regulators make judgements about primary treatment effects and on aspects of toxicity rather than on the frequency of side-effects.

In a poster review of the fluoxetine database involving 1610 fluoxetine patients and 952 placebo patients, Plewes *et al.* (1997) reported statistically significant differences between fluoxetine and placebo in rates for anxiety (12.1% versus 6.9%) and for nervousness (13.7% versus 8.8%). It can be objected that neither of these side-effects refer to akathisia. The problem here is that good clinical practice (GCP) advocates coding side-effects according to a WHO dictionary 'The International Monitoring of Adverse Reactions to Drugs Terminology' (1994). This is based on reports made by patients. Akathisia is not a word patients use. Accordingly

subjects who become subjectively akathisic must necessarily be reported under headings such as nervousness or anxiety. There is therefore a legitimate reason for not reporting akathisia but it is misleading to imply that it does not happen. Plewes *et al.* (1997) distinguish between nervousness and anxiety but, if these differ, it is difficult to see that one of them can refer to anything other than agitation/akathisia.

There is another aspect to side-effect reporting. To date, companies have only reported spontaneously mentioned side-effects, which are likely to be a small proportion of actual side-effects. Until recently, no patients were required to complete a comprehensive list of potential side-effects such as the UKU (Lingjaerde *et al.*, 1987). In the case of sexual dysfunction, early clinical trial estimates, based on spontaneous reporting, suggested a rate of 5% on fluoxetine (Stark and Hardison, 1985). Subsequent investigations with instruments sensitive to drug induced sexual dysfunction point to rates greater than 70% (Patterson, 1993). This clearly indicates how a problem can be completely missed if the means of investigation is inadequate. The situation is compounded by indications that some clinical trials are run by minimally supervised, untrained personnel, who are likely to be insensitive to the emergence of novel problems and issues (Stecklow and Johannes, 1997).

Case studies

Nevertheless, the argument goes that the Food and Drug Administration (FDA) would only register compounds on the basis of RCTs because only they, in contrast to case reports, can demonstrate causality. This is not true. Activated charcoal is licensed for overdoses with compounds such as strychnine on the basis of a single case, when Pierre Touery drank 10 times the lethal dose of strychnine and survived, having taken activated charcoal beforehand (Healy, 1997). The FDA's post-1962 statutes permit placebo-controlled trials, active comparator trials, historical controls as well as single cases to be used as the basis for a licence. The only requirement is that the procedure used has assay sensitivity. In the case of an anaesthetic, for example, falling asleep 30 s after a drug is given is so unlikely that independent observers could validly conclude on the basis of a single case that the drug had produced the treatment effect being claimed for it (Leber, 1998). Further studies would be required for registration purposes, in order to demonstrate the safety of the compound.

RCTs are needed when an expected treatment effect is relatively small or when there is spontaneous variation in the index condition or when the bias of investigators is likely to influence the results unless such controls are introduced. They are needed in the registration of antidepressants, where the treatment effect sizes of some antidepressants, relative to the spontaneous variation in milder depressions, is so small that upwards of 300 patients may be required to demonstrate significance. The emergence and resolution of akathisia is more visible and clearcut and less subject to spontaneous variation than the emergence and resolution of depression. It is rare naturally. Its occurrence following drugs is so well established that no one has ever called for an RCT to prove it although such a trial might establish the rate at which particular agents induce it.

Nevertheless, in case studies proposing an association between a clearcut treatment emergent event, like akathisia, and particular drugs there should be controls in the design. There are no controls built into associations between suicidality and antidepressants drawn simply from the spontaneous medical reports filed by individual practitioners and no credible case could be based on such reports. But case reports of this kind should not be confused with case studies, which have controls, such as a test–retest design, built into them. The results from test–retest designs can permit valid scientific conclusions to be drawn (Karch and Lasagna, 1977; Kazdin, 1982; Stephens, 1983; Girard, 1987; Beasley, 1991; Edwards, 1992; Jick *et al.*, 1992; Healy, 1994). Indeed, no less an investigator that Bradford Hill, the creator of the RCT, stated that RCTs were not the only way to assess drug effects (Hill, 1966). A test–retest design was employed by Rothschild and Locke (1991), Creaney and colleagues (1991) and Wirshing and colleagues (Wirshing *et al.*, 1991) when looking at the emergence of suicidal ideation on fluoxetine.

Another control was introduced by the eminence of the reporters. A further control stemmed from the fact that similar reports came from a wide range of independent investigators. The finding could not easily be explained in terms of the bias of one investigator or centre. Furthermore, in contrast to spontaneous medical reports, senior investigators agreed on the details of what was happening and in the Teicher series, six cases were described rather than just an isolated case, in the Wirshing series, five cases, and in the King series, a further six cases.

Finally, it is clear from reading these reports that senior investigators thought they were witnessing something different to the usual suicidal ideation that occurs in depression. There was a consistency across the reports as to what was happening, namely that suicidal ideation might be triggered by inducing akathisia/agitation. The argument therefore did not depend on an inexplicable association. It can also be noted that, at the same time, studies on suicide risk factors, conducted by the National Institute of Mental Health, pointed to levels of anxiety and agitation as the most significant predictors of completed suicides in the months following the commencement of treatment (Fawcett *et al.*, 1990; Fawcett, 1992).

Epidemiological studies

Another means to establish the impact of antidepressants on suicidality is to look at epidemiological studies. There are two studies relevant to the question of antidepressants and suicide (Jick *et al.*, 1995; Isacsson *et al.*, 1994). The Jick study, conducted in a primary care setting, looked at suicides following 172 000 antidepressant prescriptions. As dothiepin was the most commonly prescribed antidepressant in this sample, it was assigned a relative risk of 1.0, against which the risk came out at 2.1 for fluoxetine, 0.5 for lofepramine and 1.8 for mianserin. Translated into deaths per 100 000 patient years, the figure was 47 for lofepramine, 86 for dothiepin, 165 for mianserin and 189 for fluoxetine.

In the entire sample, the difference between dothiepin and fluoxetine was significantly different at 95% confidence intervals. When all confounding factors such as prior history of suicide attempt and antidepressant prescription were taken

into account, the best estimate of the relative risk of fluoxetine to dothiepin remained at 2.1, although the confidence interval—a function of sample size, which had been halved—changed. In contrast, when confounds were controlled for, the best estimate for mianserin, which had been widely promoted as being safe in overdose, fell from 1.8–1.1, suggesting that it but not fluoxetine was being prescribed to patients who were perceived to be at greatest risk.

Clearly, one study is of limited value but a number of points can be noted. First, this study refers to real life rather than to a sample of convenience. There are likely to be confounds but it is not clear what weight should be put on them. On the one hand, a proportion of imipramine prescriptions, for example, will have been given for enuresis and 10 year olds are unlikely to commit suicide. On the other hand, it is not possible to kill oneself by overdose with fluoxetine and it is likely therefore that there were a greater number of unrecorded attempted suicides from overdose with fluoxetine than there were for some other compounds. Furthermore, in keeping with an induction of akathisia, the deaths from violence on fluoxetine were proportionately higher than for other antidepressants. A further point is that before the study began it was widely accepted that lofepramine was one of the safest antidepressants, because of both its efficacy and safety in overdose, and the findings of the study confirmed this, which suggests that the study methodology was coming up with accurate results.

Finally, the Jick study does not stand in isolation. Isacsson and colleagues (1994) analysed all suicides in Sweden for 1990/1991 in a study that was larger in terms of completed suicides than the Jick study. They found the same rank ordering of suicides by antidepressant; lofepramine was the safest, the most commonly used tricyclics were intermediate and mianserin was the riskiest (fluoxetine had not then been licensed in Sweden), with an almost identical figure, 41 out of 100 000 patients/years, for lofepramine.

In addition to a low death rate on lofepramine, the other noradrenergic selective agent, maprotiline, was associated with a lower than average death rate. Combined these figures from two studies cast doubt on Kielholz's early proposal that drive enhancing antidepressants would be associated with suicides by virtue of a propensity to stimulate drive leaving suicidal ideation intact. There was a dissociation between these noradrenergic selective agents and moclobemide, however, which suggests that Kielholz's original perceptions that there might be a problem associated with MAOIs may need further consideration.

As regards the possibility that treatment inefficacy might be associated with suicide (Isacsson *et al.*, 1994), it is probably a mistake to think that treatment effect sizes are some absolute value (Healy, 1998). They only ever hold relative to specified populations, and certain populations such as patients with obsessive-compulsive disorder or adolescent depressions, who might be expected to do better on SSRIs than tricyclic antidepressants, may be inherently less likely to commit suicide. It is not clear therefore that demonstrations of greater treatment effect sizes for some antidepressants in severe depression (Wheatley *et al.*, 1998; Lopez-Ibor *et al.*, 1996) will necessarily translate into benefits in terms of reduced suicides.

Epidemiology in the public domain

In the debate about suicide and depression, a 15% lifetime suicide risk for depression is invariably cited (Guze and Robins, 1970) or a 79-fold increase in rate compared with the normal population (Hagnell *et al.*, 1981). Against such a background it is suggested that it is impossible to determine if an antidepressant causes suicide. Inskip and colleagues (1998) have updated estimates for lifetime suicide risks for affective disorders, citing a figure of 6%. However, both this and Guze's estimates are drawn almost exclusively from populations of severe and hospitalized depressives. The lifetime suicide risk for mild to moderate depressive disorders is not known but it can be modelled. Current estimates of lifetime affective disorder prevalence have risen to between 30% and 50% of the population (Hagnell *et al.*, 1981; Blacker and Clare, 1987; Kessler *et al.*, 1994). Given that the population of England and Wales is 50 million with 5000 suicides per annum, if half of the suicides are affective disorder related (2500), multiplying by 75 (an average life expectancy) and dividing by 12.5 million (25% lifetime prevalence) gives a lifetime suicide risk of approximately 1.5% for all affective disorders. A possible conclusion from this exercise is that it makes little sense to talk about a global lifetime risks of suicide for affective disorders and more sense to talk about suicide risks for severe, moderate and mild affective disorders, which might approximate to 15%, 6% and 1–1.5%, respectively.

If the annual prevalence of affective disorders is 10% (Blacker and Clare, 1987; Kessler *et al.*, 1994) and depressions account for 50% of suicides, this gives a figure of 50 suicides per 100 000 patient years for all affective disorders. Stripping out figures for severe depressive disorders suggests that annual suicide rates for mild affective disorders are probably no more than 25–40 suicides per 100 000 years. These figures offer no room for complacency when set against the Jick and Isacsson figures.

Conclusions

The data from the variety of sources quoted here present a complex picture from which simple conclusions are not readily drawn. By virtue of the variation between agents found in the studies of Cassidy and Henry, Jick and colleagues and Isacsson and colleagues, it is all but impossible not to accept that antidepressant treatment in a small proportion of vulnerable patients may be linked causally with death by suicide. This statement however, does not mean that antidepressant treatment increases the overall rate of suicide. The situation resembles that with pertussis vaccination and brain damage where overall levels of brain damage may fall after vaccination yet particular children may be adversely affected by the vaccine. The example of reserpine is relevant here. The suicides with which it was associated came from non-depressed hypertensive populations and were probably triggered by akathisia (Healy and Savage, 1998). This demonstrates the ability of a psychotropic agent to lead to the emergence of problems that cannot be easily passed off as stemming from an underlying psychiatric disorder, as do healthy volunteer studies (Healy and Farquhar, 1998).

There appears therefore to be a case that psychotropic agents can make vulnerable individuals worse while benefiting

the population at large. It can be noted that psychotherapy has been associated with increased rates of suicide on a population rather than individual basis (Moller, 1992; van der Sande, 1997). Arguments that suicides happen in the young schizophrenic seized with a flash of insight at the awful prospects ahead of them or the depressed patient with drive restored but suicidal ideation intact put little onus on the clinician. This review suggests that things may not be so simple. Clearly, bearing in mind the toxicity of certain agents in overdose is one thing but there appear to be other things they can do as well.

The subjective dysphoria that antipsychotics and antidepressants may produce remains poorly characterized. At present there is no agreement on what the overlap may be between subjective akathisia and drug induced dysphoria (Sachdev, 1995; Healy and Farquhar, 1998). Such reactions can, however, lead remarkably quickly to depressive, suicidal and violent thoughts even in healthy individuals (Healy and Farquhar, 1998). There is a need to investigate these issues more thoroughly, given the role that akathisic reactions appear to have played in this story right from the earliest use of reserpine.

Given the present state of clinical trials, the role that such reactions may play in causing problems is best teased out by means of test–retest methods. That this is the case is attested to by senior clinical trialists such as Lasagna (Karch and Lasagna, 1977), epidemiologists such as Jick, pharmaceutical company investigators such as Stephens of Glaxo (Stephens, 1983), Girard of Synthelabo (Girard, 1987), Beasley of Eli Lilly (Beasley, 1991) and others. If data from clinical trials are to play a greater part in informing the debate, there is a twofold need. One is for trials designed to specifically address the issue. The other is for a more comprehensive and less discretionary recording of the adverse effects of treatment. This might be achieved by incorporating mandatory self-ratings of side-effects using instruments such as the UKU.

As regards lessons to be learned from the current dataset, it appears that antidepressants selective to noradrenergic systems do not pose problems to the extent that was once proposed, although paradoxical worsening of depression on these agents has also been noted (Damluji and Ferguson, 1988). The picture as regards the MAOIs remains less certain. There seems some possibility that at least one SSRI, fluoxetine, may be associated with higher rates of suicidality in certain individuals. It remains unclear whether this is a problem likely to affect all SSRIs or only those SSRIs used in particular populations. If akathisia is the mechanism by which this effect is mediated, then this is a problem that can be minimized by prescribers being aware of the possibility and advising patients accordingly.

It should be noted that other side-effects, such as depersonalization or urinary retention, mediated through other systems, also have the potential to cause problems. The entire area of distress induced by adverse events and strategies to minimize these problems is deserving of further investigation. It is opportune to raise the issue of antidepressant induced suicidality when the possibility of greatly minimizing such reactions has now emerged. From the early 1960s, there were good pharmacogenetic indications that some individuals responded preferentially to MAOIs while others responded to serotonin reuptake inhibiting tricyclic agents (Pare *et al.*, 1962). Similar indications emerge from the fluoxetine and akathisia data. There would therefore seem to be some pharmacogenetic basis for adverse responses to selective agents. Clinical, scientific and other considerations all suggest that this area should be the focus of intense development.

If it is conceded that antidepressant treatment in some instances can cause problems, there is a separate public health question as to how this should impact on national programmes to reduce the incidence of suicide by enhancing the detection and treatment of depression. For moderate to severe depressive disorders, there are good indications that detection and treatment reduce suicide rates (Rutz *et al.*, 1995). Furthermore, Isacsson *et al.* (1994) suggested that a greater number of depressives died from suicide because they were not treated than may have died because of the adverse effects of any particular antidepressant. Finally, better detection and treatment of depression in Sweden during the 1980s was possibly associated with a national decline in suicide rates (von Knorring and Bingefors, 1998). Pharmacotherapy may also have benefits across diagnostic categories. It will clearly reduce suicide rates in schizophrenia and probably also in some personality disorders (Montgomery and Montgomery, 1982).

The picture is less certain for milder affective disorders, where it remains unproven that lifetime prevalences for suicide can be reduced. In such circumstances, detection and treatment trials are clearly warranted but there is an increasing onus on prescribers and companies to acquaint themselves with the hazards of treatment, to inform the patient on how to handle these and to monitor the impact of treatment.

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