Our Ref: DH/JT

4 November 1999

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

As you may have seen or have been told, there was a lengthy piece in the Guardian Weekend Supplement on Prozac on Saturday October the 30th. I enclose a photocopy and a set of background materials. One is a research brief on the piece. A second is a liability time-line, which refers to internal documents from Eli Lilly that are now in the public domain as a result of the Forsyth case.

In brief I believe the Prozac story represents one of the most significant bioethical issues of our time. There are however two very specific aspects of it that I wish to focus on in this letter which I believe may be of concern to the MCA.

The first point, mentioned in both the Guardian article and the background briefing, is the question of legal jeopardy in which we currently place patients we recruit to clinical trials as these are at present conducted.

The problem is that the Prozac story indicates very clearly that Lilly has used side-effects data collected by spontaneous report methods to argue that neither akathisia nor emotional blunting of any sort occur on Prozac and therefore neither of these effects could possibly contribute to suicides or homicides on this drug. Now even if you disregard the RCT evidence, the epidemiological studies, the test re-test studies as well as Lilly's own internal memoranda indicating that Prozac causes people to commit suicide, the fact that Lilly have behaved in this way on this issue suggests that patients are in

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considerable legal jeopardy if either Lilly or other pharmaceutical companies treat the side-effects data that emerges from clinical trials in this way.

You will not need this point spelt out in detail but for example the side-effect data on sexual dysfunction with the SSRIs collected by spontaneous reporting methods appeared to indicate a problem occurring at a 5% level of frequency where systematic checklist approaches later indicated an incidence around 50%. Unless complemented by systematic checklists, the side-effect data from spontaneous reporting methods on this issue of sexual dysfunction would indicate that the problem barely exists and patient data could conceivably have been used to argue just this point in court. This would, I'm sure you would agree, be entirely inappropriate. It constitutes a state of affairs amounting to legal jeopardy.

I raise the problem in part because there is a very simple answer to it. Some national group, such as the United Kingdom, could very readily remedy things and not only for psychiatry but for all of medicine world-wide. As you will know all major clinical trials these days are multi-national and multi-site. Should UK ethical committees insist, if side-effects data are collected by spontaneous reporting methods, that the consent form should indicate clearly that these data will only be used for marketing purposes and that they have no validity for legal purposes, the current poor situation as regards collection of clinical trial data could effectively continue without putting patients in a state of legal jeopardy.

An alternative would be for ethical committees to state that they would prefer systematic checklists. A great number of companies I have talked to have indicated that they too would prefer this.

Were the United Kingdom to stand firm on an issue like this the rest of the world would have to change as the same protocols apply cross-nationally.

The second issue has to do with the clinical liability that prescribers of Prozac in this country presently run. There was an ambiguous outcome to the Forsyth case, further details of which I would be happy to relay to you. In brief the critical issue for us as prescribers are that lawyers viewing this case will henceforth, unlike the lawyers in the Forsyth case, target both the company and the prescriber whereas in the Forsyth case only the company was targeted. This means that prescribers who may be essentially blameless will find themselves in court, the strategy being to enquire of them whether they have ever been informed in lectures, symposia or other forums that there were hazards of this type associated with Prozac, that these hazards could be forestalled by appropriate warning and minimised by appropriate antidotes.

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My informal research on this point suggests strongly that very many general practitioners as well as A&E Dept doctors and others have recognised a phenomenon of patients becoming suicidal on SSRIs (Prozac in particular) within two or three weeks of starting treatment. Far from advocating a switch of treatment at that point they frequently advise the patient to continue treatment. This is disastrous. The advice is offered in the apparent belief that this indicates that the drug is working to increase drive and in due course will lift the person's mood. It is not. The evidence is compelling that just this kind of patient is at the very greatest risk of further serious adverse events and that a risk of suicide of possibly 1/1000 prozac takers is converted into a 1/10 risk by doing just this.

Both of these points, it seems to me, must be of concern to you. The issues are quite different to any problems that were ever raised in relation to benzodiazepine or SSRI dependence, where there is considerable ambiguity involved in deciding what constitutes dependence. In this case there are very clear internal company documents and a pattern of behaviour, possibly stemming from legal advice, that is inconsistent with prescription only arrangements.

Based on RCT evidence from a number of companies, epidemiological studies and other sources, at a conservative estimate I believe one person per week has killed themselves in the UK for every week that Prozac has been available over and above the number that would have done so if the same patients had been left untreated and one person per day has attempted suicide with unknown consequences for their future risk of suicide. I would be happy to go through this evidence with you, if this would help and indeed I would be happy to have the error of my ways pointed out if anyone can see a problem with my figures or logic.

Against the background outlined above, I feel particularly impelled to act as I am doing now in writing to you having been the convenor and author of a report on childhood psychopharmacology for the British Association for Psychopharmacology, which supported the prescription of psychotropic drugs to children and teenagers in appropriate circumstances and with appropriate monitoring. This document has not led directly to increased rates of prescribing of SSRIs to adolescents in this country but it has done nothing to put a brake on what has been a dramatic increase in recent years. Unfortunately, I now find my in-tray filling with files on teenagers committing suicide within a week or two of commencing Prozac. It is this that makes the problem difficult to walk away from.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Department of Health

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
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Our Ref: 37-KHJ-0100
Your Ref: DH/JT

7th January 2000

Dear Dr Healy

Thank you for you letter and enclosures of 4 November relating to Prozac and suicide. The points you raise have been noted with interest and I have the following comments.

You make a suggestion that more information on adverse reactions to investigational products could be obtained by having a checklist of expected events and reactions that each patient is asked to fill in or respond to. This technique is used in some clinical trials already and may provide additional information as you suggest. New methods are being researched to try and identify safety signals from large databases of safety data. The MCA has been involved in some of this research.

It is important to emphasise that only a relatively few patients are exposed to a medicine in clinical trials before it is marketed. This means that relatively rare adverse reaction to the product will not be detected in clinical trials. For this reason the UK introduced the Black Triangle Scheme to monitor the spontaneous reports from newly marketed products more intensively during the first few years or until a sufficiently large number of patients would have been exposed to it. Therefore, focussing on safety data from clinical trials in formulating an opinion of the safety of a drug or of its potential to cause any one reaction may be difficult. Post-marketing safety data is vital to establish the safety profile of a new medicine.

One of the primary roles of the Medicines Control Agency is to ensure that prescribers and patients are adequately informed about their medicines to allow them to use it as safely and effectively as possible. Your letter raises the issue about warnings currently given to prescribers on the risk of suicide in early treatment with Prozac and other antidepressants.

The Prozac Summary of Product Characteristics (SPC) currently contains the following statement:

'As improvement may not occur during the first two weeks of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs'

We have carried out an initial review of data collected via the Yellow Card Scheme. The number of reports of suicide, akathisia, aggression and related terms spontaneously reported via the scheme are shown in the table attached. It is important to note that a report of a suspected adverse reaction does not necessarily meant that it was caused by the drug. The numbers of reports in the attached table should be seen in the context of the huge usage of Prozac. Over 7,000 reports of suspected adverse drug reactions have been received in association with Prozac in the UK. It is also worth noting that media publicity surrounding a particular issue can stimulate the reporting of adverse drug reactions.

An analysis of onset times of reaction fro these terms showed that the majority although not all, of these reactions occurred within the first few weeks of treatment.

The issued of suicide associated with fluoxetine was first reviewed by the Committee of Safety of Medicines in 1990 and it was concluded that the available evidence did not support an increased risk of such problems with fluoxetine. We are continuing to keep this matter under close review.

If you are aware of any further information on this matter, we would be very pleased to receive it.

Yours sincerely

Dr Keith Jones
Director & Chief Executive

Table of UK ADROIT reports of suicide, akathisia, aggression and related terms.

Term	Number of Reports
Aggression	165
Agitation	315
Akathisia	25
Non-accidental overdose	9
Overdose NOS	18
Parasuicide	1
Suicidal Ideation	98
Suicide (accomplished)	44
Suicide Attempt	54

Our Ref: DH/JT
Your Ref: 37-DHJ-0100

19 January 2000

Dr Keith Jones
Director & Chief Executive
Department of Health
Medicines Control Agency
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Dear Dr Jones

Many thanks for your letter of the 7th of January 2000. In your letter you mention that it must be emphasised that only a relatively few patients are exposed to a medicine in clinical trials before it is marketed. I accept this of course. However I believe that there is a large amount of unpublished randomised control trial data from these relatively few patients that confirms rather conclusively that fluoxetine and other SSRIs compared with placebo raise rates of suicide attempts.

I have no idea how the MCA stands as regards unpublished data on suicide attempts. You may be interested to know that the FDA has recently required all companies to submit data on just this issue for currently marketed antidepressants. Given that this data is being prepared anyway It might be worth your while to consider requesting the companies to forward it to you also.

If you do proceed down this route, I would be very happy, if you wished, to inform you as to whether the data that I know that exists and is currently unpublished features among the data that will have been submitted to you.

Quite aside from unpublished and unsubmitted data however there is a published meta-analysis by Pierre Fabre of their drug Milnacipran currently

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under scrutiny by the MCA in which I believe you will find that SSRIs have a significantly elevated rate of suicide attempts compared to either Milnacipran or TCAs.

You then raise the point about the warning on Prozac. I think this is quite inadequate. There are published clinical studies of children with OCD becoming suicidal on Prozac. This suicidality does not stem from a depressive disorder.

Furthermore on this point I enclose a first draft of a study that I have been involved in with colleagues. This is currently submitted for publication. I would hope you would keep the contents confidential but as you will see it is quite clear from this healthy volunteer study that within two weeks of going on Sertraline two of our healthy volunteers became seriously and significantly suicidal. This is not a suicidality that was inherent in any depression that they had. None of our volunteers were depressed or ill in any way.

It seems to me that this study significantly changes the terms of the debate. By the time you have received this letter I will have presented the data at the Institute of Psychiatry. I will shortly be presenting the material as well in the Department of Psychiatry in Oxford.

There is another issue that my letter to you raised which you don't appear to have addressed in your response. This is the issue of legal jeopardy. You note that I have suggested that there are ways to collect the data of adverse reactions with investigational compounds that may improve the informational content of trials. This is one thing. It's something however that is only required in one sense if companies treat the data coming out randomised control trials the way Lilly and other SSRI companies have been treating the data that have come out of their randomised control trials. The fact that data on adverse effects that have occurred has not been recorded has been used to argue that the effects themselves did not happen. As I understand it this means therefore that the patients who went through these clinical trial programmes, in a rather precise use of the term, have put both themselves and all the rest of us in a state of legal jeopardy. I would be most interested in your thoughts on this particular matter and ideas about how it can be remedied.

This is a matter that I will be working as hard as I can to raise the public profile of in weeks and months to come. If you have any thoughts on the issue I would be very grateful to receive them as it may influence the approach I take when raising the issues.

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On this issue as well as on the issues raised by the enclosed study I would hope to hear from you in the near future.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Encs.

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
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22nd February 2000

Dear Dr Healy

Thank you for your letter of 19th January 2000 to Dr Jones on the subject of antidepressants and suicide and for enclosing a copy of your study. Your letter has been passed to the Post-Licensing division of the MCA for response, since monitoring the safety of licensed medicine is our responsibility.

We will be considering the study on the emergence of antidepressant induced suicidality very carefully and will get back to you in due course. We would be interested to see a copy of the full study report if this is available.

We not that you consider the warning relating to suicide in the Prozac SPC to be inadequate and as new information emerges, we will consider any implications this may have for the warnings in product information.

Turning to your point about the collection of adverse reaction data in clinical trials, you mention that patients who went through these clinical trial programmes have put both themselves and the rest of us in a state of “legal jeopardy”. We would be grateful for further clarification of what you mean by “legal jeopardy”.

Yours sincerely

Miss Sarah Wark
Senior Scientific Assessor
Post Licensing Division

Cc
Dr K Jones MCA/Dir
Dr J Raine MCA/PL
Dr P Waller MCA/PL

Our Ref: DH/JT

28 February 2000

Miss Sarah Wark
Senior Scientific Assessor
Post-Licensing Division
Department of Health Medicines
Control Agency
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1 Nine Elms Lane
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SW8 5NQ

Dear Miss Sarah Wark

I will be very happy in due course to send you a copy of the full study report when this is available. It may however take some weeks or even some months before I can forward this to you.

In the meantime it is my understanding that a number of the studies with various different antidepressants that have been conducted with healthy volunteers as part of a series of pre and post registration tests have noted similar reactions to the ones that I have reported in our study. So much is this the case, that there is a general understanding in the field, certainly among the older practitioners working with different pharmaceutical companies, that strange reactions of this type are almost to be expected from healthy volunteers. 20 or 30 years ago the rationale for accepting such reactions was that antidepressants would never be given to anybody who wasn't depressed and that there were clearly differences between the brains of people who were hospitalised cases of endogenous depression compared with normal volunteers.

These rationales have vanished as depression has extended to the point where cases of what were Valium are now cases of Prozac. The most commonly prescribed use for Prozac it seems to me, and many of the other SSRIs, is for anxiety and stress reactions. These are the people whom I see regularly becoming suicidal on these drugs. This is a group of patients in whom it is not clear that there are likely to be any great differences between their brain states and those of healthy volunteers.

My understanding is that there are many people in the field whom the MCA could consult who would be able to confirm this position. There is also likely to be a considerable amount of data that companies have but whether they have submitted this to you or not is less clear to me.

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I think the study on Sertraline induced suicidality in healthy volunteers is directly relevant to the question of suicide in the Prozac SPC that you say you will consider in the event that new information emerges. I feel this is new information directly relevant to the Prozac SPC. I think it's highly likely that Lilly in addition to other companies will have data of the kind that I have referred to above.

As regards Legal Jeopardy I have consulted with a number of lawyers on this and all appear to agree with me.

The situation as I see it is as follows. Patients entering clinical trials have a range of adverse effects which are not at present being coded for either at all or satisfactorily. In the case of side-effects not coded for satisfactorily these include problems such as suicidal ideation, which are coded for under depression. Akathisia is not coded for. Emotional indifference or emotional blunting or disinhibition are not coded for.

This is an understandable situation. It is understandable and perhaps acceptable if in the absence of figures to support a proper incidence for these problems, marketeers for a company claim that the incidence of these side-effects is zero. Everybody knows, you included I'm sure, that side-effect data commonly marketed by companies is hopelessly inadequate and underestimates the true extent of the problems probably by a sixfold factor. The legal jeopardy arises when patients who suffer from an adverse effect on the drug to the extent that they consider a legal action are then faced with a company denying that the drug causes the problem based upon the way the side-effect data have been coded in their clinical trials. This could happen to you or me or Dr Jones. Take the side-effects that have happened on Prozac for instance, and the way Lilly have handled the data on this issue in both court cases last year and in print in academic journals within the last 18 months. It is this that constitutes a state of legal jeopardy.

I would be very grateful if you could confirm for me that our understandings coincide on this point. If they do not, and you consider that this state is not a state of legal jeopardy, I would be very grateful if you cold explain to me exactly why not. I would not want to mislead any more people than I might have already misled by including this understanding of current practices in any more articles or books that I write.

I would be very grateful therefore to hear back from you on this point specifically.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Our Ref: DH/JT

3 April 2000

Dr Keith Jones / Philip Hunt
Director / Department of Health
Medicines Control Agency / Richmond House
Market Towers / 79 Whitehall
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LONDON / SW1A 2NS
SW8 5NQ

Dear Dr Jones/Lord Hunt

RE: DANGERS OF ADVERSE REACTIONS TO SSRI'S

Some time back I submitted to you a draft of some developments during a randomised Placebo Control Trial in Healthy Volunteers that we undertook in this department. I have since been deposed in a legal case in the United States and in the course of that deposition it has become clear to me that it is a matter of considerable legal importance whether you have had any remotely similar reports filed with you since the development programmes of various SSRIs started in the early 1980s.

By remotely similar reports I mean studies in which any of the SSRIs were given to healthy volunteers and reactions ranging from anxiety and agitation through to other psychic disturbances emerged and were reported to you.

A further issue emerges if you have such reports on file. Clearly the approach that I would have taken to our ethical committee in North Wales when undertaking the studies that I undertook would have been completely different had such information been available to me. If you have information other than our particular study there are implications for any other healthy volunteer studies that may at present be undertaken within the United Kingdom or indeed world-wide.

This is a particularly acute issue for me at present as I have been approached some months back by a television programme within the United Kingdom due

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to air later this year which will consider some of the ethical and scientific issues surrounding healthy volunteers studies or self experimentation. This is an area where clearly I could unwittingly do considerable harm albeit with the best possible intentions. I would appreciate some response therefore from you on these questions and indeed even more than a response - some guidance would be helpful. As I believe I have indicated before I would be happy to meet up to show my hand more fully on some of these issues and to get the benefit of the experience of considering issues such as this within your agency.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

CC Paul Flynn MP Newport West, House of Commons, LONDON

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
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27 April 2000

Dear Dr Healy

3rd APRIL 2000 LETTER REGARDING SSRIs

Thank you for your letter of 3 April to Philip Hunt and myself on the subject of SSRIs.

We are currently considering the important issues you raise and looking into your request for information about SSRI volunteer studies. Your request is being considered within the terms of the Code of Practice to Government Information. The information you request is taking some time to collate and it is possible that we will be unable to respond fully to your request with the twenty days recommended in the Code. As soon as this is done we will write to you in full.

Thank you for your offer of a meeting, which we will keep in mind.

Yours sincerely

Dr Keith Jones
Director and Chief Executive
Medicines Control Agency.

KHJ/ftkf

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From the Office of the Chief Executive

David Healy
Director
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16 May 2000

Dear Dr Healy

I am writing further to my acknowledgement. I apologise for the delay in responding to your letter of 3 April regarding the dangers of adverse drug reactions to SSRI's. We are currently collating information in response to your question and a full response will be sent to you shortly.

Once again please accept our apologies. Many thanks for your understanding in this matter.

Yours sincerely

Polly Penrose
Office of the Chief Executive.

Cc Lord Hunt

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
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4 May 2000

Dear Dr Healy

Thank you for your letter of 28th February. Please accept my apologies for the delay in responding.

Thank you for your explanation of what you mean by 'legal jeopardy'. You ask specifically for our comments on this.

You state that a pharmaceutical company could deny that their drug caused a particular problem based on the way side effects are coded in clinical trials. When establishing the causal relationship between a suspected adverse reaction and a drug, all available evidence should be evaluated, not simply clinical trial data. Many adverse reactions are identified through monitoring of the drug in general clinical practice which are not evident in the clinical trials.

The basis for your argument is that certain adverse reaction terms are not being coded for satisfactorily during clinical trials. The Medical Dictionary fro Regulatory Activities (MedDRA) is the internationally accepted medical terminology for use in drug regulation. I was developed under the auspices of the International Conference on Harmonisation and was based in the MCA's own medical dictionary. I would like to point out that the terms that you specifically mention – suicidal ideation, akathisia, emotional indifference and disinhibition are all coded for in MedDRA.

You mention that side effect data produced by pharmaceutical companies is inadequate. Under European law, pharmaceutical companies are under continuing obligation to provide information relevant to the safety of licensed medicines to regulatory authorities. Both pharmaceutical companies and regulators are responsible for ensuring that appropriate action is taken in response to new evidence and for ensuring that product information reflects the available information on that drug. Indeed it is in the interests of the company to ensure that all adverse effects are labelled.

Yours sincerely

Sara Wark
Senior Scientific Assessor
Copy: Dr J Raine MCA/PL
Dr P Waller MCA/PL

Our Ref: DH/JT

8 May 2000

Sarah Wark
Senior Scientific Assessor
Medicines Control Agency
Market Towers
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Dear Dr Wark

Many thanks for your letter. I'm not clear whether you've answered my question or not.

Let me expand slightly. The issue is not simply the adequacy of coding of side-effects. There are a range of related issues. For example, you may include terms such as emotional indifference and suicidal ideation in MedDra but if the coding of side-effects is done by spontaneous reporting methods then the likelihood of significant side-effects being picked up is greatly reduced. Second at present, on the basis of clinical trials that are not designed to detect for example phenomena such as suicidal ideation or akathisia the lawyers for companies producing SSRIs are putting pressure on judges to dismiss cases that do not demonstrate by randomised control trial methods a twofold increase in the relative risk on the SSRI compared to placebo.

Given that this is the case, I have in publications recently, one of which has gone to the Chairman of every ethical committee in the country (the Bulletin of Medical Ethics and IJRSM papers enclosed) suggested that ethics committees and indeed patients consider their position as regards clinical trials, even to the extent of not permitting participation in the case of ethics committees and not actually participating in the case of patients. I've done so on the basis that it seems that participation in trials of this sort, when companies are prepared to use the data in this way does constitute legal jeopardy.

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It's possible that no one will pay any heed to me. It's possible that no one will pay any heed to anything that I've written. At this point in time unless advised to the contrary by yourself and the MCA that a state of legal jeopardy does not apply in these circumstances, I would envisage when interviewed on radio or potentially television on some of these issues over the next few weeks giving similar advice.

Should anyone of those who might participate in clinical trials or those who grant ethical permission for the trials to take place begin to pay heed to what I'm saying, there could be substantial implications for the pharmaceutical industry base in this country. In the circumstances, if the point I'm making is incorrect I would as I've mentioned before greatly appreciate being informed exactly why it is incorrect. Your letter of May the 4th does not allay my fears or provide explanations as to what points I'm making might be incorrect.

As regards MedDra, clearly having a dictionary which includes the terms suicidal ideation, akathisia, emotional indifference and disinhibition is a step forward. I wonder could I ask you when this came into force. Could I also ask you whether pharmaceutical companies are obliged to use it. I understand there were dictionaries with terms like suicidal ideation available to Eli Lilly to use in their clinical trials of Prozac but they did not use these dictionaries. The same I suspect is true of Pfizer and other SSRI producing companies.

Finally you mention that it is in the interest of companies to ensure that all adverse effects of their drugs are labelled. This is only the case in situations where they are at any risk of losing legal actions. Otherwise sales can be maximised in situations where adverse effects can be concealed. You may be interested to know that one of the isomers of Prozac was patented some time back and at present the patent is jointly owned by Eli Lilly and others. The patent application mentions that the isomer is less likely to cause akathisia and suicidal ideation that the parent compound causes. The induction of suicidal ideation is not something that you will currently find in the label for Prozac or indeed for any of the other SSRIs. This is hard to reconcile with a state of affairs where a company can take out a patent on a compound on the basis that the parent compound (Prozac) does cause these problems which does not appear your label and stands to make millions if not billions of dollars as a consequence. (I have attached extracts of this patent)

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

CC Dr J Raine, MCA
Dr P Waller, MCA
Mr Paul Flynn MP

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
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26 June 2000

Dear Dr Healy

Thank you for your letter of 8 May. I am sorry that you remain unsatisfied with our responses to the question of 'legal jeopardy'.

We are trying to understand what you mean by 'legal jeopardy'. It seems to us that the key to what you are referring to is in you r statement 'the lawyers for companies producing SSRIs are putting pressure on judges to dismiss cases that do not demonstrate by randomised control trial methods a twofold increase in the relative risks on the SSRI compared to placebo'.

It is difficult to comment on this in the absence of a set of factual circumstances of without knowing whether or not the type of argument you mention has actually been successful. It is also difficult to see how this argument could adversely affect a participant in a clinical trial. It is fair to say that until a situation does arise where a participant in a clinical trial is adversely affected in court proceedings by his participation in a clinical trial, it is not possible to say that a state of legal jeopardy exists. The most on could say is that there is a possibility of such a state arising. The remoteness or otherwise of that possibility will depend on the circumstances in each case.

Turning to your specific questions about the Medical Dictionary for Regulatory Activities (MedDRA), this was adopted by international Conference on Harmonisation Steering Committee as the international medical terminology for regulatory activities in July1997. It was not made available until a Maintenance and support Services Organisation (MSSO) had been appointed (in April 99). MedDRA is now available from the MSSO – a company called TRW – on subscription. The use of MedDRA is currently recommended in guidelines for the pharmaceutical industry. The FDA have announced intention to mandate the use of MedDRA for electronic adverse drug reaction reporting by companies. Europe is considering mandating the use of MedDRA

I hope you find this information useful

Yours sincerely

Sarah Wark
Senior Scientific Assessor

cc. Dr K Jones – MCA/CE
Dr R Raine - MCA/PL
Dr P Waller – MCA/PL

Our Ref: DH/JT

30 June 2000

Sarah Wark
Senior Scientific Assessor
Medicines Control Agency
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Dear Dr Wark

Many thanks for your letter. Apologies for the confusion that I appear to have caused. You do however appear to have got hold of the wrong end of the stick. Perhaps this has been because my efforts to try and explain the problem have fallen down somewhat, owing in part to the fact that the issues appear to me to be blindingly simply and to involve legal jeopardy.

The state of legal jeopardy that I'm referring to is not one that applies to any participant in a clinical trial. The legal jeopardy applies to you and me or to anyone who takes potentially any pill at all but certainly something like an SSRI.

The jeopardy arises from the fact that should you or I suffer an adverse event from an SSRI that the company in question will claim that their drug could not have caused the problem by virtue of the fact that the clinical trials they ran didn't record the particular problem that we may be concerned to take an action about.

Clearly in some instances clinical trials will not record adverse events – ones that occur at a frequency of say 1 in 10,000 for example. In this case, companies would not be able to use their clinical trials basis to argue the point one way or the other. However in the case of side-effects that occur much more frequently that should have been picked up in clinical trials, where it is clear these events almost certainly did occur in the clinical trials but were not

Continued/..

coded for, the use of this clinical trial data by companies then to argue that you or I did not suffer the adverse event in question is potentially problematic.

It's particularly problematic in our current era of evidence based medicine when the usual methods of determining cause and effect have been suspended in favour of the supposed evidence that comes from the supposed gold standard method for determining cause and effects – the randomised control trial.

As regards whether this type of argument is currently being used by companies in legal proceedings at present, I can tell you that it certainly is.

From your letters I have no indication to date that it would be incorrect for me to advise patients against participation in clinical trials generally on the basis that they may be putting their relatives and families in a state of legal jeopardy. It appears that I should even be able to say that I've consulted on this matter with the MCA who have not indicated that there is anything essentially incorrect about the argument that I'm making. The only difference between us at present appears to be my awareness of the fact that clinical trial participation has de facto resulted in states of legal jeopardy for a large number of people whereas you seem aware of the theoretical risk rather than an actual hazard.

As previously I would invite you to correct this interpretation if it appears to be incorrect in any way. I appreciate however that there may be difficulties for you in making any clear pronouncement in this area.

Many thanks for the clarification that MedDRA was not used in clinical trials during the development of the SSRIs or indeed has not been used to date.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Our Ref: DH/JT

5 July 2000

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

It's now over three months since I wrote to you enclosing details of a healthy volunteer study that had been conducted in North Wales and requesting details of any other healthy volunteer studies that might have been submitted to you in the course of development work on other SSRIs.

I realise my request places you in an extraordinarily tricky position but equally I am faced with something of a dilemma.

My dilemma is this. Given our study and the existence of other studies of which I'm aware which have shown a much higher rate of akathisia/agitation in healthy volunteers on SSRIs, I am absolutely sure that Ethical Committees would not permit further studies of SSRIs in healthy volunteers to take place without clear warnings and close monitoring. Even were an Ethical Committee prepared to sanction such a study, the insurers who indemnify these studies for University Departments might well refuse to do so even in the presence of clear warnings and close monitoring. I would imagine if either you or I worked for such an insurance agency this is quite possibly the line we would take.

Yet the SSRIs are available in this country and for the most part are being prescribed to individuals who have stress reactions of various sorts – individuals who come close to healthy volunteers in many respects. They are being prescribed without warning and without monitoring even in children.

Continued/..

I can see almost any move you might make in this area has far reaching implications. I on the other hand have little option but to make a move if only because of the healthy volunteer studies that may be in train or being contemplated around the country. At some point someone is bound to ask me what the MCA are doing about all this. Perhaps you'd like to tell me.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ
Telephone 0207-273 0763, Room 14-201
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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

10th July 2000

Dear Mr Healy

Thank you fro your letter dated 5th July 2000 regarding the, “Dangers of Adverse reactions to SSRI’s”. This will be answered shortly.

Yours sincerely

Paul Edwards
Office of the Chief Executive

Cc Philip Hunt.

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

26 July 2000

Dear Dr Healy

Thank you for your letters of 3 April and 5 July 2000. I apologise for the delay in responding to your request for information about adverse reactions to Selective Serotonin Reuptake Inhibitors in volunteer studies. A summary of information on adverse events reported by volunteers given SSRIs is attached for your information.

The Committee on Safety of Medicines has recently re-considered the possible association between SSRIs and suicidal behaviour. As you are aware, a number of epidemiological studies and analyses of clinical trial data have failed to find an association between fluoxetine and increased suicidal behaviour. Whilst the reporting rate of suicidal behaviour for all SSRIs through the Yellow Card scheme has been low in recent years, there continue to be anecdotal case reports of suicidal behaviour associated with fluoxetine, and CSM will continue to closely monitor this issue.

The CSM noted that it is general clinical experience that the risk of suicide may increase in the early stages of treatment with any antidepressant. The Committee considered that prescribers and patients should be made aware of this in product information, and patient information leaflets in accordance with the recommendations of the CSM.

I trust this provides the information you require.

Dr Keith Jones
Director and Chief Executive.

Copy Lord Hunt, PS(L)

ADVERSE EVENTS FROM SSRI VOLUNTEER STUDIES

Fluoxetine (Prozac)

There have been 29 studies where fluoxetine was administered to healthy volunteers. The studies involved 397 subjects who were taking fluoxetine in the dose range 1mg/day to 110mg/day for periods ranging from 1-45 days. Some adverse events were reported in these studies, including nervousness , anxiety, irritability and jitteriness. There was no occurrence of suicidal behaviour.

There are also 79 publications involving administration of fluoxetine to 1,266 healthy volunteers. The doses ranged from 5 to 80mg/day for periods ranging from a single dose to 3 months of continued administration. No events relating to suicidal behaviour were reported. Psychological assessments were conducted in 5 studies and demonstrated that fluoxetine has no effect on the mood of healthy individuals.

Paroxetine (Seroxat)

There were 645 subject sessions (occasions on which a single dose of paroxetine was administered to a volunteer) in single dose studies (dose range 15mg to 70mg) and 381 volunteers were administered paroxetine in repeat dose studies (dose range 20 to 40mg). Most volunteers took paroxetine for between 2 and 28 days, although 16 took paroxetine for 42 days.

There were no reports of suicidal thoughts in any of the volunteer studies. There were a few reports of ‘emotional lability’, however these reactions were not found to be related to suicidal thoughts or behaviour. Some volunteers reported anxiety, nervousness and agitation while taking paroxetine, however the most commonly reported adverse events were nausea, diarrhoea, drowsiness, somnolence and insomnia.

Lustral (sertraline)

In studies contained in the sertraline hydrochloride International Registry Dossiers (IRD-1 And –2), Oral Concentrate IRD, and Renal/Hepatic Supplement, there have been over 50 studies in normal healthy volunteers involving over 800 subjects, the majority of subjects were male, although some studies did include females. The sertraline dose range was generally 50 to 200mg and sertraline was administered in both single and multiple doses. The duration of multiple dose studies was normally less than 30 days. There was no occurrence of suicidal ideation, suicide gesture or attempt or completed suicides.

There are a few reports of agitation, anxiety, nervousness, abnormal thinking and hyperkinesias among the safety data collected in these studies. These

were described as mild or moderate in all cases. No serious psychiatric events were reported.

Faverin (fluvoxamine)

There have been 95 volunteer studies involving 1300 subjects who received fluvoxamine. Fluvoxamine was administered in single or multiple doses for up to a maximum o f4 weeks. The dosage range administered was 10-30mg/day. A search of the database did not reveal any cases of suicide, suicide attempt, suicidal ideation or related adverse events from spontaneous reporting or rating scale data in non-patients volunteers exposed to fluvoxamjine.

Cipramil (citalopram)
There have been 30 volunteer studies involving 421 subjects (176 subjects in single dose, and 245 subjects in multiple dose studies).

There were no cases of suicide or suicide attempt. Adverse events reported which may be relevant were as follows: 4 reports of hyperkinesias, 2 reports of depersonalisation and abnormal thinking and single reports of agitation and depression. From the available data, there was nothing to indicate the occurrence of suicidal thoughts.

Summary

There are some reports of mild or moderate psychiatric reactions including nervousness, anxiety and agitation among the safety data from volunteer studies with the SSRIs. However, there is no evidence that suicidal behaviour or severe psychiatric reactions have been reported during healthy volunteer studies involving any of the SSRIs.

Our Ref: DH/JT

3 August 2000

Dr Keith Jones
Director and Chief Executive
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

Many thanks for your letter of July 26th. Unfortunately for all of us, your reply raises more questions than it answers. From what you have sent, it seems to me that you are passing on summaries of their data presented to you by the companies. I have no doubt that you are doing this in good faith but this is where the problems start.

I am sitting here with a study in front of me that is incompatible with the summary on sertraline you have presented. I am bound by a confidentiality agreement not to divulge this to anyone. But from a legal deposition I have recently been involved in, which could be forwarded to you, and from prior discussions with the study investigator, I can tell you that this was conducted by Ian Hindmarch. It was conducted before suicide on SSRIs became an issue. The significance of this is that no-one would have had cause to explicitly code for suicidality. However for a company to say to you regarding this study that there was no suicidality would be misleading. Suicidality may not have been reported but this is clearly a different state of affairs.

This latter point applies to the Hindmarch and no doubt to many other studies. In the Hindmarch study all subjects randomised to sertraline dropped out within days with reactions that were clearly of a psychiatric nature. The fact that all dropped out and did so with the problems reported on the original form is incompatible with a description of the problems as mild to moderate.

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The descriptions of these reactions that I have in front of me, combined with our healthy volunteer study, would I am certain give all ethical committees and the insurers of healthy volunteer studies a problem sanctioning studies of this type. They might permit a study to go ahead but only with warnings and close monitoring. I am fairly certain that you would make a similar judgement were you an ethics committee chairman or were you working for an insurer. Given this, I can only believe that the MCA have not received the document I am privy to. And if you have not received this document, in how many cases have you received copies of the original studies?

Where do we go from here? I feel I have little option but to draw attention to the situation by whatever means I can - the situation being that mature medical and nursing people would not be let take these drugs without detailed warnings and monitoring while children and an ever larger number of healthy individuals with stress reactions of one sort or another are being given these agents without any warnings or monitoring. Your forthcoming advice in Current Problems in Pharmacovigilance, it seems to me, will do nothing to help the situation and indeed may even aggravate it. The idea that patients thought to be at risk should be carefully monitored implies that patients already seriously suicidal may be made worse and those who are less obviously depressed are not at risk. In fact, I think the evidence all points the other way. It is those a GP might think were least at risk who in fact are at the greatest risk.

As regards your contention that there are a number of epidemiological studies that have failed to find a risk, this is clearly not the case. The only epidemiological study of any substance was done by Jick and colleagues and this produced an extremely worrying finding. If there are other epidemiological studies perhaps you could refer me to them.

As regards proper analyses of clinical trial data, these have not failed to find an association. There have been 2 analyses. One conducted by Pierre Fabre, finding a greatly increased rate of suicidality on SSRIs. The other by Beasley is so seriously flawed that it provides grounds for concern if you or the CSM are depending on this (see enclosed). My analysis of other company clinical trial databases gives a significant increase in suicide and suicide attempt rates on a range of SSRIs. An article by Khan in the Archives of General Psychiatry this April also shows an elevation in risk as does an as yet unpublished analysis by Ross Baldessarini of Harvard. In many of these analyses the SSRIs show up as having an elevated risk compared to placebo where the older or other antidepressants have a lower rate than placebo.

Continued/..

Perhaps you would let me know where you propose to go from here. At the very least you might let me know whether I am incorrect to assume you are depending on summaries provided by the companies and that you have not had sight of the original Hindmarch study. Unless I hear from you to the contrary, I will report my understanding of the situation as I have outlined it and leave others to decide whether this is appropriate or not.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

CC Lord Hunt, Department of Health, Richmond House, 79 Whitehall, London, SW1A 2NS

Mr Paul Flynn, Member of Parliament for Newport West, House of Commons, London, SW1A 0AA

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

08 August 2000

Dear Dr Healy

SSRIs and Suicide.

Thank you for your letter dated 03 August 2000 regarding continued correspondence concerning the relationship between SSRIs and suicide.

I have raised this letter with Dr Jones and have made him aware of your concerns. A response shall be forwarded to you as soon as the necessary information has been complied.

Yours sincerely

Ms Fiona Tetlock
Private Secretary to the Chief Executive,
Medicines Control Agency.

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
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Gwynedd LL57 2PW

23 August 2000

Dear Dr Healy

Thank you for your further letter of 3 August on the subject of SSRIs and suicidal behaviour.

Our summary on volunteer studies that was provided with my letter of 26 July was based on data provided by the marketing authorisation holders for these products. We do have access to the Hindemarch study, but would comment that the pattern of severe adverse effects and drop outs seen in this small study was not replicated in any other study involving sertraline. We are, however continuing to review these data.

You ask for a list of the epidemiological studies considered by the CSM. These are attached. The references you mention in your letter have also been reviewed, however it is not felt that they provide evidence that would warrant regulatory action other than that which is currently underway.

It may be helpful if I explain in more detail the regulatory action we are taking in relation to this issue. As part of an exercises to standardise and update all SSRI SPCs the following warning about suicidal behaviour is being added to all SSRI SPCs :

'As improvement my not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved, and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery'

The CSM considered that this statement accurately reflects the current knowledge on this issue. However they also considered that it was important

that patients and the families of patient were made aware of a possible risk of an increase is suicidal behaviour and we are currently asking marketing authorisation holders for the SSRIs to add the following statement to patient information leaflets:

‘Occasionally, thoughts of suicide or self harm may occur or may increase in the first few weeks of treatment with < >, until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences.’

I would like to assure you that we are taking this issue very seriously and will look carefully at any further evidence which becomes available. The CSM has advised that this issue should be kept under close review.

Yours sincerely

Dr Keith Jones
Director and Chief Executive.

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Our Ref: DH/JT

1 September 2000

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

Thank you for your letter of the 23rd of August. Far from being reassured by it however I find a number of grounds for even more concern.

My first but perhaps least pressing concern is with the fact that as I take it from your letter the summary you sent me essentially is one that you passed on from the different companies. If this is the case I cannot see how you can be in a position to say that there aren't similar problems to those found in the Hindmarch study with either Sertraline or other SSRIs.

Secondly you characterise the Hindmarch study as small. It may be small in absolute numbers compared to some other studies but for the most part these other studies involving healthy volunteers were single dose studies. The Hindmarch study was in fact a very powerful study from a statistical point of view given its double blind nature and given its conclusive results. I'm sure your statisticians could provide you with figures for relative risk for Sertraline compared to placebo in this study.

A second point regarding this Hindmarch study is that you now, with our study, have a further study involving a similar pattern of severe adverse effects to sit with the Hindmarch study. It is my understanding that these two studies on their own would be sufficient to grant a licence to Pfizer for the use of Sertraline as a drug to produce agitation and apprehension.

Continued/..

In my letter of the 3rd of August I invited you to answer the question whether, given these two studies, you as the Chairman of an Ethics Committee or an Insurer for healthy volunteer studies would permit a healthy volunteer study involving Sertraline to take place without monitoring and warning. Your letter of the 23rd provides no answer to this question. Can I invite you once more to answer?

An alternative question would be how you predict the Chairs of Ethics Committees or Insurers would be likely to respond to this scenario. I would hope to be able to tell you how they respond soon. It would be useful to have your prediction on the record first.

A further concern I have is the list of studies, which you have listed in the reference section as epidemiological studies. None of these other than the Jick Study is an epidemiological study. I'm staggered that you can consider any of the others as being epidemiological studies. I'm sure you will agree that an epidemiological study should sample a very large section of the population or indicate what steps were taken to ensure the sample that is being used is representative of the population. This is standard methodological procedure. None of the studies you've listed other than the Jick Study did this and none were designed to test the question of whether Prozac or any other SSRI can cause suicidal ideation.

The Leon study was a study involving 640 odd patients that was conceived 20 years before Prozac was launched and begun 10 years before it was launched. Only 180 odd patients got Prozac. This was not an epidemiological study and not a study to design to test whether Prozac could cause suicidal ideation.

The Warshaw and Keller study is a study of anxiety disorder patients with only 654 patients of whom again 180 odd got Prozac and the only suicide in this study was on Prozac. This is not an epidemiological study, furthermore neither the Leon nor the Warshaw and Keller study can be regarded as in any way disinterested research.

As regards the Fava and Rosenbaum study this is a study that you may or may not know has been repeatedly reanalysed by FDA officials and a range of other personnel and everybody else other than Fava and Rosenbaum find that the ratio of emergent suicidality on Prozac compared to other antidepressants in the study shows a relative risk of 3.0 or greater.

The Jick study for most epidemiologists that I have consulted provides very strong evidence implicating Prozac in not just the emergence of suicidal ideation but completed suicide.

Continued/..

Perhaps you have not looked at the above studies yourself and therefore are unaware of how inadequate they are for the purposes you appear to be now putting them. Perhaps you have depended on advisers. I enclose a report written by I believe an adviser to the CSM/MCA around the 1990 period when the controversy about SSRIs and suicide first emerged. This adviser was also an adviser to Eli Lilly and other SSRI producing companies around this time. The enclosed report is a paper produced for Lilly, dealing with what later came to be called the Beasley Meta-analysis/paper. I don't suppose you have a similar report on record from this period. If not I would imagine that most observers would be deeply worried by the discrepancy between the advice being given to you by your advisers on this issue compared with the advice the same advisers will have been giving to some of the companies involved. Whatever you or other observers will make of the discrepancy between the enclosed report and the advice given to you, the discrepancy between advice that the studies you cite (other than the Jick study) are epidemiological studies and what is generally held to be an epidemiological study raises questions of basic scientific literacy.

On the regulatory action you are proposing to take, can I respectfully suggest to you that this will lead to deaths. It will do so because of the following.

As phrased your additional wording says that the possibility of a suicide attempt is inherent in depression and that it is general clinical experience with all antidepressants that the risk of suicide may increase in the early stages of recovery. There is some truth to this statement.

However a great number of patients, perhaps the majority who get SSRIs either do not get them for depression or for depression that has a significant suicide risk associated with it. These are primary care nervous conditions that do not have a significant risk of suicide. They are more like the healthy volunteers in the Hindmarch study and our own study than they are like classic depressive who are at high suicide risk.

Clearly in both the Hindmarch and our own study apprehensive ruminations and suicidal preoccupations emerged in healthy volunteers. There was no hint of depression in any of those involved. There would appear to be a clear drug induced component in both these studies that provide you with sufficient grounds to include some reference to this in your proposed wording.

Unless your wording indicates that the treatments may in their own right add a further risk of emergent suicidality to whatever risk is inherent in depressive disorders themselves your advice will lead to a situation where patients who worsen on treatment will be kept on that treatment by their General Practitioners in the belief that it is only in this way that the suicide risk can

Continued/..

ultimately be lowered. This is mistaken advice that is going to increase the rate at which patients move from emergent suicidality to suicidal acts.

But it will also do something else. By blocking off a recognition of the association between the drug and emergent suicidality, you are going to force patients who suffer from this side effect to consider themselves flawed in some way because of these developments. This in turn can be expected to have a significant negative impact on their future wellbeing, mental state and risk of suicide.

On the point you make that it is general clinical experience that this can happen with all antidepressant therapies, I would agree with you but I would also suggest that you write to Professor Ross Baldessarini at McLean Hospital, Harvard University who can give you figures on just this issue. Professor Baldessarini has been working on figures based on new drug applications to the FDA, presumably the same clinical trials that you have had available to you. From this material he has constructed relative risks for SSRIs, tricyclic antidepressants, placebo and other treatments. These risks differ dramatically and significantly between all antidepressants with the SSRIs posing a greater risk than older tricyclic antidepressants in inducing suicide attempts in the course of clinical trials. The relative risk is probably four to fivefold greater for SSRIs. Professor Baldessarini I believe would be able to provide you with the figures were you to approach him, although given the material he is working from you should have everything in-house. There is also the recently published analysis by Khan et al using the NDAs for the SSRIs showing an increased relative risk of emergent suicidality on SSRIs compared to placebo. I would have thought you would want your advice to physicians and to patients to reflect the data accurately. I do not believe the proposed advice does so. I don't intend to speculate as to why you might not wish to accurately reflect the data.

Finally please let me apologise for any infelicities there may be in the tone of this letter. Pointing out basic facts about epidemiological methodology may be advising you how to suck eggs and may be completely out of place in a letter such as this. My tone stems from the fact that I find the situation that has evolved increasingly incredible.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

CC Paul Flynn, MP Newport West

PPK/LH
Dextra Court, Basingstoke
4th October 1990

DEPOSITION EXHIBIT
28

To: Dr. Bob Thompson - c/o Erl Wood

cc: Dr. L. Herrero - Indianapolis
Dr. A.J. Weinstein - Indianapolis

Bob,

Re: Expert reports from Prozac suicide briefing package

Please find enclosed the reports from [redacted] and Dr. [redacted] and Dr. [redacted] has drafted his report but I do not have a final version to hand.

I thought it was useful to give these to you as one package. Enclosed are a number of suggestions, particularly from [redacted] and [redacted]

There are some areas where additional data or data clarification would be useful, particularly [redacted] comments. Also published data may be useful eg. the maprotiline study, and we may be able to generate significant new data from our known studies eg. the French long term study.

[redacted] report is objectively critical but it contains a number of constructive suggestions which I think we should address. He is likely to be a significant factor in any regulatory deliberations in the U.K.

I look forward to your comments on the expert reports and would also suggest that we continue to maintain contact with the five experts and continue to bring them up to date with new information. I would also like to be able to respond specifically to those who have raised points of information or made suggestions about additional analyses.

Several of them also highlighted their view that we as a company should encourage scientific discussion of the suicide area in a specific meeting and present data on various subjects including Prozac which would refute the Teuscher claims. As I mentioned to Allan before, this suggestion has come up before and I think personally there would be merit in handling this through a one day symposium such as we ran for the hypoglycaemia meeting. I realise that this is a sensitive area but I would again value your inputs on this.

Regards,

Dr. Patrick P. Keohane
Medical Director U.K. and Ireland

Does Fluoxetine provoke suicidal thoughts: Comments on the Fluoxetine Safety Report July 17 1990.

It comes as no surprise that the issue of suicidality and fluoxetine has surfaced as a problem for Lilly since I predicted it would some four or five years ago. At that time the general view was that antidepressants cannot cause suicide but a number of events and studies have helped to change the perspective. As you know the legal battle about mianserin has sensitised the CSM and other regulatory bodies to the suicide issue as well as changing the law and allowing suicide attempts to be considered in the regulatory process.

As you know there were questions about the agitation and stimulating properties attributed to fluoxetine and there were fears that this might increase suicidality. The issue was raised as a question to be addressed with several European regulatory authorities before a licence was granted. You may remember that I covered this issue in my expert report for the English and later in greater detail for the Dutch and German authorities.

It is for this reason I felt that Lilly would be wise to undertake a formal prospective study in this area. As you know I proposed to examine the effects of fluoxetine or placebo in a group of multiple suicide attempters. At the time you will remember Lilly did not think this study had a high priority which was reflected in the low level of funding of £150 - £300 per patient. I nevertheless regarded this as a sufficiently important issue, to carry out the study using my own resources in my own time. This study when complete should answer the question one way or the other and may be able to address the issue of when the attempts occur on placebo which will produce a baseline needed to interpret the fluoxetine data.

The report that you sent me was disappointing. It is certainly interesting but I found the background analysis somewhat inadequate and the links between the different data analyses disjointed. I found the report difficult to follow and it was difficult to understand why the particular analyses used were adopted and others rejected.

The report failed to take account of two important pieces of information and it is a serious omission that they are neither mentioned or discussed. There is no mention of the metanalyses of the fluvoxamine data published by Wakelin, which was based on analysis of the Hamilton Scale Suicide item. In this report the entry scores on the Hamilton Suicide item were used to subcategorise the sample. Those with a score of 2, 3 or 4 were found to have a better outcome on fluvoxamine and imipramine than placebo but more importantly in those with a score on the Hamilton item 3 of 3 or 4 there was a significant advantage for fluvoxamine over both imipramine and placebo. These data are important because it provides rather strong evidence with a different 5-HT uptake inhibitor supporting the view that there is a selective advantage in treating suicidal patients.

Since these data are published it is reasonable to expect Lilly to have performed the same analysis and if it is not reported the assumption may well be that fluoxetine has a less favourable effect.

Another major omission from the background review and from the discussion in the report is the significant finding in a very large placebo controlled long term study that Maprotiline provokes suicide attempts compared with placebo. The number of suicide attempts in short term treatment is likely to be comparatively low. The importance of this study is that it reveals the power of a prospective placebo controlled long term study to test whether a drug is associated with more or less attempts than placebo. Since your report neither mentions this result nor comments on suicidality measured in the long term efficacy study of fluoxetine it may be thought that Lilly has something to hide. In the light of the Maprotiline finding a proper analysis of the fluoxetine long term study in terms of attempts is a necessary minimum.

The analysis of the data is sufficient as far as it goes but there are a number of points I thought were either not quite correct or inadequately explained.

1. No explanation is given as to which placebo controlled studies were included in the analysis and which are excluded. The report analyses data from only 5 placebo controlled trials but it is widely known that there are more placebo controlled trials than this. Suicide attempts are relatively rare in trials and the decision to report on a smaller number of trials than the full data base may appear as evasive. In any event selective reporting in your data requires adequate explanation which is missing.

The same unexplained restriction appears to hold for the reference controlled studies. Any suggestion that the full data base is not being examined with raise the thought in some minds that the dat6a are potentially misleading.

2. The records of suicidal ideation in the adverse reactions derived data is rather low. This may be because this kind of data is not systematically asked for and therefore is erratically collected and unreliable. A better measure of this would be the total number of patients in trials scoring HRS item 3 with a score of 2, 3, or 4. A comparison of this data collected during the trials with the reports of suicidal ideation or on ADR reports would give a better idea of the incidence of suicidal thoughts during the double-blind studies.

By the same token there is inadequate reporting of the incidence of the suicidality of the patients entering the double blind studies with scores on the HRS suicide item (3) with scores of 2 or more. You report significantly higher numbers entering the study on TCA with HRS item 3 scores of 3 or more but do not give the actual numbers so that it is difficult for an independent assessor to get a proper idea of the data.

This group with a score on entry of 2, 3, or 4 on the HRS item 3 suicide item may be regarded as the "partially at risk" group and an analysis of the change in this item in fluoxetine, comparator antidepressants, and placebo groups would most easily provide data on the effect of these agents in provoking or reducing suicidal thoughts or acts.

3. The largest pool of data is clearly available on the Hamilton Scale which was used in most of the studies. A proper analysis on item 3 of the Hamilton gives a better idea of suicidality than the adverse drug reactions based data. However, the Hamilton suicide item is poorly constructed and cannot be used to separate suicide attempts from suicidal ideation. I expected that your report might have commented on this. A better measure of suicidal ideation would be expected in analysing the suicide item of the MADRS, which is a purer measure of suicidal thoughts uncontaminated by attempts. A metanalysis of the MADRS suicide item would reasonably be expected, taken from those trials which used this scale.

4. A further weakness in the report is the failure to take account of the relationship between suicidality and duration of treatment. The dropout rate is the fluoxetine and placebo data is not equal and so therefore the period of exposure to drug and placebo is not equal. Likewise the dropout rates of the comparator and fluoxetine are not equal and a subsidiary analysis of the data from the controlled trials which takes account of this should be made. I am not sure whether this would materially affect the case in the analysis you present but I would expect it to be both carried out and discussed. This is important in view of the report that non-fatal suicidal acts occurred a mean of 57 days after staring treatment.

Conclusion

On the data presented in this report it would seem that fluoxetine is not much different from placebo or comparator antidepressants in affecting suicidal thoughts and acts taken together. The analysis is patchy and apparently not done on the full pool of blinded placebo and reference controlled data which is available to the company. It is therefore suspect particularly since it contradicts published data.

The best data to examine the long term clinical effects of fluoxetine and placebo would be the large placebo controlled one year prophylactic study. I can see no reference to these data which is surprising, and means that no comment from blinded studies on the effect of fluoxetine in the longer term can be made.

The failure to take account of the duration of treatment in the fluoxetine placebo and fluoxetine comparator comparisons also weakens the analysis and adds a further bias.

The report refers in an offhand manner to the recent change in product labelling, to warn of suicidal ideation associated with fluoxetine. This conveys to me, and, I believe, most clinicians, that Lilly is convinced that the data support the presence of a relationship between fluoxetine and the provocation of suicidal ideas. It is difficult to understand why this report provides no

evidence to support this, and increases the feeling that other data not presented here must have helped to persuade Lilly of the existence of a causal relationship.

Overall the report is disappointing. The review is patchy and inadequate. The analysis undertaken are not in line with published data and do not give the numbers involved and provide limited data on the main question. The conclusions of the report contradict the recent change in produce labelling and this adds to the impression that the question of whether fluoxetine provokes suicidal thoughts or not has not been properly considered.

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ
Telephone 0207-273 0763, Room 14-201
Facsimile 0207-273 0282/0675

From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

4 September 2000

Dear Dr Healy

Re: SSRIs and Suicide.

Thank you for your letter dated 1 September 2000 regarding previous correspondence concerning the connection between SSRIs and suicide.

Dr Jones has been made aware of your letter and a response will be forwarded to you as soon as the necessary information has been gathered.

Yours sincerely

Paul Edwards
Administrative Assistant to the Directorate.

Cc Paul Flynn

Our Ref: DH/JT

8 September 2000

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

I would appreciate if the minutes of any meeting held during the course of the last year by the CSM or the MCA on the question of any conceivable association between antidepressants and suicide could be forwarded to me along with any paper that has been prepared for either committee related to this issue and in particular any assessment that has been undertaken of either the Healthy Volunteer Study that I submitted to you or the Hindmarch Study.

Please treat this as a formal request for information under the code of practice on access to Government information.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ
Telephone 0207-273 0763, Room 14-201
Facsimile 0207-273 0282/0675

From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

11 September 2000

Dear Dr Healy

Re: Your request for minutes of any meeting held in relation to antidepressant and suicide.

Thank you for your letter dated 8 September 2000 regarding your request for minutes of any meeting held in relation to antidepressants and suicide. Dr Jones has been made aware of your letter.

Your request is being dealt with as a formal request for information under the code of practice on access to Government information as you requested. A reply will b e sent to you shortly.

Yours sincerely

Paul Edwards
Administrative Assistant to the Directorate.

Our Ref: DH/JT

13 September 2000

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

I understand there have been letters from Sarah Wark from your Pharmaco Vigilance Group recently to SSRI companies saying that the CSM has recently reviewed the issue of SSRIs and Suicidal Behaviour. The conclusion apparently was that the available study data did not support a causal association between SSRIs and Suicidal Behaviour. I would greatly appreciate if you could let me know exactly what study data were considered. I would also appreciate any reports that were prepared for this meeting.

I also understand that the letter to the different companies refers to a recent SSRI Core Safety Exercise. Again on this issue I would appreciate any papers or minutes or other relative material relating to this exercise. As in my previous letter please consider this a formal request for information under the code of practice on access to Government information.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

14 September 2000

Dear Dr Healy

CORRESPONDENCE RE SSRIs.

Thank you for your Fax dated 13 September 2000 requesting further information under the code of practice on access to Government information.

Your request has been forwarded to the relevant department and a response will be forwarded to you as soon as the necessary information has been gathered.

Yours sincerely

James Carolin
Office of the Chief Executive.

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

25 September 2000

Dear Dr Healy

I am sorry that you remain unsatisfied with previous responses to you letters. I wonder if, rather than continue with written correspondence, it would be more productive if you were to meet with staff in the Post-Licensing Division. This would provide an opportunity to discuss your concerns in detail and to ensure that all the relevant information on this issue is considered. If you would like to contact Dr June Raine, Director Post-Licensing, the appropriate arrangements can be made.

Yours sincerely

Dr K Jones
Chief Executive.

MEDICINES CONTROL AGENCY

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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

5 October 2000

Dear Dr Healy

I am writing further to your letters of 8th and 13th of September 2000 asking for copies of assessment reports relating to SSRIs under the Code of Practice on Government Information (the Code).

Before we can meet you request, we have to consider whether any of the information contained in these reports is subject to commercial or other confidentialities and, if any of that information has originated from a third a third party, it may also be necessary to seek their views on its disclosure. That action is consistent with the advice contained in the Code but as consequence I regret that I will not be able to let you have a final reply within the 20 working days recommended in the Code.

I will, of course, send a full reply as soon as possible.

Yours sincerely

Dr Keith Jones
Director & Chief Executive.

MEDICINES CONTROL AGENCY

To:	Ms Jackie Thomas (Secretary to Dr Healey)
Phone:	01248 384452
Fax:	01248 371 397
From:	Dr J M Raine
Company:	Medicines Control Agency Market Towers 1 Nine Elms Lane Vauxhall London SW8 5NQ
Phone:	0171 273 0400
Fax:	0171 273 0675
Date:	24 October 2000
Pages including this cover page:	2

Comment:

Jackie

Dangers of Adverse Reactions to SSRIs

Further to our telephone conversation this morning I write to confirm the date and time of a meeting which has been arranged for the 23 November 2000 at 2.00 p.m to discuss the dangers of adverse reactions to SSRIs. Present at the meeting will be Dr June Raine, Dr Patrick Waller, Ms Sarah Wark, and Professor Stephen Evans.

I have attached a map of the surrounding area for Dr Healy as requested.

Eugenie E Elson
Secretary to Dr June Raine

Our Ref: DH/JT

25 October 2000

Dr June Raine
Director of Post-Licensing
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

Many thanks for the further details about the meeting on November the 23rd. I would appreciate any information you can provide on Professor Evans and Dr Waller – their background and interest in this issue.

Is it open to me to bring another to this meeting?

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine.

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ
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From the Office of the Chief Executive

David Healy
Director
Division of Psychological Medicine North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

17 November, 2000

Dear Dr Healey

SSRIs and Suicide

I am writing to let you know that, unfortunately, we have had difficulty in bringing our planned meeting for 23 November 2000. Specifically our expert from the Committee on Safety of Medicines in now unable to join us on that day.

I am sure you will agree that it is important that the meeting encompasses all the appropriate expertise. I hope that we will be able to re-organise for 13 December, in the afternoon, and would be grateful if your secretary could lket mine know if this is suitable from your point of view.

I am very sorry for any inconvenience.

Yours sincerely

Dr JM Raine
Director, Post-Licensing Division.

Our Ref: DH/JT

20th December 2000

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

A quick follow-up note to express my thanks for the meeting last week.

You've asked for a number of items. One was further details of our healthy volunteer study. I enclose three posters.

Another item concerned FDA considerations of a class-wide labelling on the antidepressants. I include a legal liability time-line on some of the Prozac cases. I refer you bullet point number 30. I can obtain the documents behind this for you if you wish. Clearly this is Lilly's position in the midst of the crisis.

I also include a memorandum from Paul Leber, dated 15th/ 7/1992.

I at one point mentioned that I was hoping to get hold of some of the trials of SSRIs in conditions other than depression to see what the effects on suicidality there were. It seemed to me that at one point you thought that I might be able to get these results to you. I may in due course but there will be a considerable amount of analysis involved and the material will probably remain under a confidentiality order for some time to come. You really ought not wait for me to provide these results for you. I am sure that within the CSM/MCA there should be some access to this material and some capacity for you to work on it yourselves.

Continued/..

Finally you asked me for a possible form of words for a warning, here are some options.

“Although it is well known that patients suffering from depression are at a heightened risk of suicide, the risk may increase further during drug therapy, particularly during the first few weeks of treatment. Patients should be warned that, if they feel worse during the course of treatment with an antidepressant, they should notify their physician immediately. They should be told that it may not be a matter simply of their depression not improving or getting worse, but a reaction to the medication causing their inner turmoil. Patients receiving an antidepressant should be closely monitored particularly during initial drug therapy”.

Alternatively, "SSRIs are known in some instances to cause akathisia and excitement or turmoil that can provoke assaultiveness and suicide in vulnerable individuals. Close supervision is indicated for all patients for whom they are prescribed".

I also referred to the fact that an article had later appeared in the BMJ, the first version of which contained a useful form of wording. After commenting on the suicide and three suicide attempts on sertraline versus none on placebo, this runs as follows: Since the introduction of tricyclic antidepressants, it has been known by clinicians that patients are at increased risk of suicide during the first few weeks of TCA therapy. For this reason, a close supervision of depressed patients given TCA was recommended. Our findings support this observation and stress that although SSRIs have low toxicity in overdose, their use does not negate the responsibility of the clinician to administer good clinical follow-up as with the traditional TCAs.”

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Our Ref: DH/JT

5 January 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

Please find enclosed an article that has recently come out. It would seem germane to the debates we've been having. While not an epidemiological study on the scale of the Jick study it is substantially better designed than many of the studies referred to as epidemiological studies in Dr Jones' letter, that we've discussed earlier. This shows a doubling of the risk of deliberate self harm on SSRIs compared with other antidepressant drugs.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Encs

Our Ref: DH/JT

1 February 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

It is now almost two months since I came to see you. I wonder whether there has been any progress?

I made a small error when I gave you the original wording by Professor Malt from Norway as regards a possible warning for SSRIs. Malt's original wording was as follows:

"One patient on sertraline committed suicide, and three others reported increasing suicidal ideation which prompted premature stop of the treatment, in contrast to just one case on mianserin and none on placebo. Since the introduction of the tricyclic antidepressants, it has been known by clinicians that TCA could increase suicidality in the first week. For this reason a close supervision of depressed patients given TCA was recommended"

I made another error when asked whether the 400mg Sertraline dose used in the healthy volunteer study by Saletu et al (which I left you a copy of) was outside the normal clinical dose range. I suggested that it was but of course it is not.

Many months ago I asked for a copy of material on the SSRI Core Safety Exercise. Is there any sign of this coming my way?

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

12 February 2001

Department of Health
MEDICINES CONTROL AGENCY

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Dr David Healy
Director
North Wales Department of Psychological Medicine
University of Wales College of Medicine
Hergest Unit
Gwynedd Hospital
Bangor
Gwynedd LL27 2PW

Dear Dr Healy

Re: Pfizer Healthy Volunteer Study

Thank you very much for your letter to Dr Jones dated 12 February 2001. Dr Jones is out of the office at present, but will be shown your letter on his return, whereupon a full response will be coordinated and sent to you accordingly.

Yours sincerely

Sharyn Robertson
Assistant to Directorate

Dir\offtyp\trs/ack/healy22.02.02

Our Ref: DH/JT

12 February 2001

Dr Keith Jones
Director
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Jones

Further to my letter of 3rd August 2000 to which you replied that you had indeed seen a copy of the Pfizer Healthy Volunteer Study that had led to me writing to you in the first instance, I wonder if I could ask whether you had at that point or have now seen the full version of that study. I ask because I am aware that there are several summaries of this study. You could conceivably have seen a summary and still be concerned about the pattern of serious adverse events that you noted.

My question can be rephrased as follows: How many pages was the version of the Hindmarch study you had in front of you as of August 2000? I hope this doesn't seem too trivial a question to ask.

Following your suggestion that I meet with Dr Raine, you may be aware that I have done so. It is not clear to me however that we have agreed on any way to move the issues that concerned me forward. That being the case should the issues come up in public, I at present would feel warranted to indicate that I have discussed my concerns with the MCA and they have not offered me any information that would allay those concerns.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

CC Dr June Raine

Department of Health

MEDICINES CONTROL AGENCY

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23 March 2001

Dr David Healy
Director
University of Wales College of Medicine
Division of Psychological Medicine
North Wales Department
Hergest Unit
Ysbyty Gwynedd
Bangor
Gwynedd LL57 2PW

Our ref: OG/OO/O25

Dear Dr Healy

I am writing further to your request of 8 September 2000 to Dr Jones, made under the Code of Practice on Access to Government Information (the Code – copy enclosed), for the minutes and assessment report relating to CSM consideration of the issue of suicidal behaviour and SSRIs. Please accept my apologies for the delay in replying.

I am enclosing a copy of the assessment report and tabled paper which were considered by CSM in June of this year, and the relevant extract from the minutes of that meeting. As you will see, parts of the assessment report and the minutes have been edited under the exemptions outlined in the Code, which place certain restrictions on the disclosure of information. We have concluded that disclosing this information would not be appropriate because either it is likely to be addressed in legal proceedings (exemption 4(a) of the Code). Or could facilitate and unwarranted invasion of an individual's privacy (exemption 12 of the Code).

If you have a query about this letter, please contact me. If you are unhappy with our decision, you may ask for it to be reviewed. A senior member of the Agency who has not so far be involved with your request will undertake that internal review. If you wish to ask for a review, you should write to Dr June Raine, at the above address, in the first instance.

If you remain dissatisfied, you may ask a Member of Parliament to make a complaint on your behalf to the Ombudsman (known officially as the Parliamentary Commissioner for Administration) who may decide to conduct his own investigation.

Yours sincerely

Miss Sarah Wark
Senior Scientific Assessor
Pharmacovigilance Group

Copy: Dr K Jones MCA/PL
Dr June Raine MCA/PL
Dr P Harrison MCA/PL

ADVERSE EVENTS FROM SSRI VOLUNTEER STUDIES

Fluoxetine (Prozac)

There have been 29 studies where fluoxetine was administered to healthy volunteers. The studies involved 397 subjects who were taking fluoxetine in the dose range 1mg/day to 110mg/day for periods ranging from 1-45 days. Some adverse events were reported in these studies, including nervousness , anxiety, irritability and jitteriness. There was no occurrence of suicidal behaviour.

There are also 79 publications involving administration of fluoxetine to 1,266 healthy volunteers. The doses ranged from 5 to 80mg/day for periods ranging from a single dose to 3 months of continued administration. No events relating to suicidal behaviour were reported. Psychological assessments were conducted in 5 studies and demonstrated that fluoxetine has no effect on the mood of healthy individuals.

Paroxetine (Seroxat)

There were 645 subject sessions (occasions on which a single dose of paroxetine was administered to a volunteer) in single dose studies (dose range 15mg to 70mg) and 381 volunteers were administered paroxetine in repeat dose studies (dose range 20 to 40mg). Most volunteers took paroxetine for between 2 and 28 days, although 16 took paroxetine for 42 days.

There were no reports of suicidal thoughts in any of the volunteer studies. There were a few reports of ‘emotional lability’, however these reactions were not found to be related to suicidal thoughts or behaviour. Some volunteers reported anxiety, nervousness and agitation while taking paroxetine, however the most commonly reported adverse events were nausea, diarrhoea, drowsiness, somnolence and insomnia.

Lustral (sertraline)

In studies contained in the sertraline hydrochloride International Registry Dossiers (IRD-1 And –2), Oral Concentrate IRD, and Renal/Hepatic Supplement, there have been over 50 studies in normal healthy volunteers involving over 800 subjects, the majority of subjects were male, although some studies did include females. The sertraline dose range was generally 50 to 200mg and sertraline was administered in both single and multiple doses. The duration of multiple dose studies was normally less than 30 days. There was no occurrence of suicidal ideation, suicide gesture or attempt or completed suicides.

There are a few reports of agitation, anxiety, nervousness, abnormal thinking and hyperkinesias among the safety data collected in these studies. These were described as mild or moderate in all cases. No serious psychiatric events were reported.

Faverin (fluvoxamine)

There have been 95 volunteer studies involving 1300 subjects who received fluvoxamine. Fluvoxamine was administered in single or multiple doses for up to a maximum o f4 weeks. The dosage range administered was 10-30mg/day. A search of the database did not reveal any cases of suicide, suicide attempt, suicidal ideation or related adverse events from spontaneous reporting or rating scale data in non-patients volunteers exposed to fluvoxamjine.

Cipramil (citalopram)
There have been 30 volunteer studies involving 421 subjects (176 subjects in single dose, and 245 subjects in multiple dose studies).

There were no cases of suicide or suicide attempt. Adverse events reported which may be relevant were as follows: 4 reports of hyperkinesias, 2 reports of depersonalisation and abnormal thinking and single reports of agitation and depression. From the available data, there was nothing to indicate the occurrence of suicidal thoughts.

Summary

There are some reports of mild or moderate psychiatric reactions including nervousness, anxiety and agitation among the safety data from volunteer studies with the SSRIs. However, there is no evidence that suicidal behaviour or severe psychiatric reactions have been reported during healthy volunteer studies involving any of the SSRIs.

10 SSRIs and Suicidal Behaviour

10.1 The committee noted the paper and **Tabled Paper 111**

10.2 The committee were informed that the previous reviews of fluoxetine and suicide in the early 1990's had concluded that it was likely that fluoxetine was not causally associated with suicidal ideation, however information on high risk patients was lacking and concern remained.

10.3 The committee considered the data collected since the last review, and the relevance of the recent publication of case reports of suicidal ideation in healthy volunteers given sertraline.

10.4 The committee noted that there had been anecdotal reports of suicidal behaviour associated with fluoexetine, mainly in patients with complex psychiatric histories. The committee also noted that it was general clinical experience that patients taking any antidepressants may develop an increase in depressive symptoms, including suicidal behaviour , in the first few weeks of treatment. The committee commented that it was impossible to answer the question of whether fluoxetine and/or other SSRIs caused suicidal behaviour in a small subpopulation of patients. They considered that this issue should be kept under review and formally revisited every 2-3 years.

10.5 The committee noted with interest the publication by Dr Healy which reported suicidal behaviour occurring in healthy volunteers given sertraline. The committee felt that these reactions were difficult to explain, however data on from the marketing authorisation holders on adverse reactions experienced by volunteer given SSRIs were reassuring.

10.6 The committee concluded that the available study data did not support a causal association between fluoxetine or other SSRIs and suicidal behaviour. They noted that the spontaneous reporting rate of suicidal behaviour for all SSRIs had been low in recent years, and that high reporting rates in the early 1990's were likely to be a result of the intense publicity surrounding the issue at that time.

Department of Health

MEDICINES CONTROL AGENCY

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27 March 2001

Dr David Healy
Director
University of Wales College of Medicine
Division of Psychological Medicine
North Wales Department
Hergest Unit
Ysbyty Gwynedd
Bangor
Gwynedd LL57 2PW

Dear Dr Healy

Re: SSRIs and the risk of suicide

Thank you for your letters of 20 December and 5 January enclosing further information as discussed to our meeting of 13 December. I am very sorry indeed for the delay in response. Thank you also for your letter of 12 February to Dr Jones.

We found the meeting last December extremely helpful and have read with interest the further information that you have sent. We are seeking expert advice on the new data. Thank you also for your proposals for revised wording for the patient information leaflets. We are currently in the process of implementing the wording in patient information leaflets as agreed by the Committee on Safety of Medicines in June 2000. As you know the CSM warning does not, on the evidence available, attribute causality, but does give advice that medical attention should be sought.

In relation to your question to Dr Jones, the date relating to the Hindmarch study which was available to us in August of last year was a synopsis (4 pages long). We have since received further information and are considering how to further investigate the adverse effects experienced by volunteers. When we have received the information we have requested from all marketing authorisation holders, we will again seek expert advice.

You should already have received documentation relating to the CSM discussion on SSRIs and suicide and should be hearing shortly form Miss Sarah Wark with a copy of the paper on the core safety exercise for SSRIs.

We look forward to receiving the further information when this is available. I note your closing comments to Dr Jones and would stress, as we did at the meeting, that this issue is under ongoing review, that we are keen to receive any new evidence and to re-evaluate risk and benefit, and that our CSM experts will be kept informed.

Thank you again for your help.

Yours sincerely

Dr June Raine
Director – Post-Licensing Division

O1C27.1-(SW)JR1

Our Ref: DH/JT

4 April 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

RE: SSRI'S AND THE RISK OF SUICIDE

Many thanks for your letter of the 27th March 2001.

As regards the data relating to the Hindmarch study, you will no doubt know better than I that there should be many sets of data including a study report by the sponsors, the raw data from the actual study which will often involve assessments by the investigators themselves as well as by the subjects and further data which may include specific comments on the study by company monitors etc. All the above appears to be fairly standard for many of these studies with the resulting documentation coming in three or four distinctly different bundles and often running to over 100 pages worth of material. A four page synopsis certainly does not tally with the material that I have reviewed of this particular study.

When with you before Christmas, I mentioned the Saletu study. There has been a further publication of this study Saletu B & GruNberger (1998), Drug Profiling By Computered Electro Encephalography and Brain Maps: With special consideration of Sertraline and it's psychometric effects. Journal of Clinical Psychiatry 49, 8(Suppl), 59-71. Between the two published versions it is now clear that there is a dose dependent agitation produced by Sertraline and the suggestion made to me by Professor Evans at the MCA meeting that the reported difficulties on the drug may not refer to individual subjects taking

Continued/..

Sertraline appears not to be the case. The set of side-effects that I outlined in the meeting do refer to distinct individuals.

There is a further study published with Paroxetine (Warrington et al), Warrington SJ, Dana-Haeri J, Sinclair AJ (1989). Cardiovascular and Psychomotor Effects of Repeated Doses of Paroxetine: A comparison with Amitriptyline and Placebo in healthy men. Acta Psychiatrica Scandinavia 80, (Suppl 350), 42-44. Referring to the drop out of several healthy volunteers while taking Paroxetine this study, the authors state that antidepressants are poorly tolerated in healthy volunteers.

The problem this poses to both you and me is this. As far as I am aware no similar statements could ever have been made about the benzodiazepines. The wholescale switch then from prescribing benzodiazepines for minor nervous problems to prescribing SSRIs for minor nervous problems is one that is fraught with difficulties. The relative risk a drug is of course not some absolute value, it is proportionate to the risk posed by the condition being treated for. Where more serious depressions are being treated the poor tolerance of the compound is less of a problem. Where the population being treated is at minimal if any risks of suicide however such problems need necessarily to be seen in a completely different light.

At this stage I have reviewed the preponderance of healthy volunteer studies conducted by both Pfizer and SmithKline prior to submission of their initial licensing applications. At present our discussions are restricted by legal orders to the few phrases about the Hindmarch study that appear in my deposition, the published Saletu and Warrington studies as well as our own study here in North Wales. I can assure you however that the rest of the data I have reviewed are broadly consistent with the position that can be deduced from the published literature.

It may also be worth noting that in the File on Four programme which ran on BBC Radio 4 last year a General Practitioner stated that many GPs recognise the problem and will do something like prescribe concomitant benzodiazepines to minimise the problem during the early phrases of treatment with an SSRI and not a tricyclic. It is also the case that consultant psychiatrists up and own the country from the very early 1920s on have been doing something similar. It seems to me to be an extraordinary situation to have a problem that is so widely recognised on the one side with people instituting prophylactic treatment to avoid the problem or prescribing antidotes to minimise the problem without there being any warning in the data sheets.

In two weeks time I am due to give a public lecture in North America on just these issues. It will probably contain statements that I have consulted with the

Continued/..

MCA on the issue of studies which have been described as epidemiological studies and no one from the MCA has challenged characterisation of these studies as not epidemiological studies.

The other point that my talk will include is the fact that a variety of people working for Pfizer including Roger Lane and Christine Blumhardt as well as Ian Hudson and David Wheadon working for SmithKline and Charles Beasley working for Lilly as well as independent experts retained by these companies such as John Mann and Daniel Casey have all testified in the course of the last year that since the controversy with SSRIs and suicide blew up that no research designed to explore the link between SSRIs and suicide has been instituted. The current position as I understand it is that one study was designed in conjunction with the FDA, this was a re-challenge study, but it never took place.

For a variety of other factors aside from the interest in the issue of SSRIs and suicide, this lecture in Toronto is likely to receive media coverage. I think there is a real chance that the issue of SSRIs and suicidality will become increasingly salient in weeks to come. I will post you the transcript of the talk in a few weeks time. I plan to make this available widely.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

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Our Ref: DH/JT

7 June 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

You may or may not have heard that yesterday in Cheyenne, Wyoming a C Court found Glaxo SmithKline guilty on several accounts including the count that Paroxetine can cause suicidality, that it specifically did so and contributed to the wrongful death of Don and Rita Schell as well as Deborah and Alyssa Tobin and that the company had been responsible for a failure to test and a failure to warn. You may also be aware of a verdict in the Hawkins case in New South Wales some weeks ago where a Supreme Court Judge made it clear that in his opinion Mr David Hawkins would not have murdered his wife but for the influence of Sertraline.

In the course of my work as an expert witness in Tobin versus SmithKline I got the chance to look at SmithKline's healthy volunteer database in Harlow. Their characterisation of this for you was that: "There were no reports of suicidal thoughts in any of the volunteer studies. There were few reports of 'emotional lability', however these reactions were not found to be related to suicidal thoughts or behaviour. Some volunteers reported anxiety, nervousness and agitation while taking paroxetine, however the most commonly reported adverse events were nausea, diarrhoea, drowsiness and insomnia".

What I found was that approximately 25% of the volunteers in the studies that I reviewed which were all of the healthy volunteer studies done prior to the filing of this drug for registration in the US and in the UK – 34 studies

Continued/..

approximately in all. These yielded a 25% agitation, nervousness/akathisia rate. Some of the multiple does studies in healthy volunteers lasting 2-3 weeks yielded an up to 85% withdrawal rate in the volunteers.

All of their healthy volunteer studies were supposed to have been made available to me but not all were. Of the ones that were missing there was trace correspondence left in once indicating that the investigator had never witnessed such a level of problems in a study with healthy volunteers. Another study was a single dose study which in a dose dependent fashion yielded a 75% rate of severe adverse events most of which involved the central nervous system. There were other disturbing indications from one of the other missing studies.

Volunteers who had participated in the programme went on to suicidal acts. The relationship between their intake of paroxetine and later suicidal acts is a matter about which neither you nor SmithKline Beecham should be sanguine.

These studies were for the most part done on company employees. None of the studies bar the missing ones were done by investigators with a background in psychiatry. The investigators were general physicians with a primary interest in gastrointestinal problems who could not have been expected to detect mental problems of this sort that have concerned me and I would have thought should concern you.

My testimony in this case also bore witness to sealed studies and other unreported data. It commented on the Montgomery Baldwin Study which yielded a projected rate of 45 suicide attempts in a group of recurrent brief depressive disordered patients on paroxetine per annum versus 12 on placebo. The figures were not statistically significant in great part one has to suggest because the company had terminated the study early. This termination and subsequent non-publication I would imagine the jury will have found and others will find significant.

Dr Hudson, currently of the MCA, was a witness for SmithKline in this case. He may well be able to give you further details on some of the issues involved. His testimony involved repeated reference to the fact that SmithKline Beecham cannot decide whether their drug had caused problems such as the wrongful death of Don and Rita Schell or Deborah and Alyssa Tobin or the wrongful deaths of many other people whose deaths have been reported to SmithKline even when these reports have been accompanied by the opinions of their treating physicians that the drug had indeed contributed to the problem. Dr Hudson's testimony was that until controlled trials or other similar studies had proven in general that paroxetine could cause such problems that the company could not make decisions on any specific case.

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This appears to me a Black Hole defence. It is entirely conceivable that tens of thousands of suicides could disappear into this Black Hole without either SmithKline Beecham, Pfizer or Eli Lilly being called upon to make any judgements as to whether their drug was contributing to the problem. The lack of evidence from randomised controlled trials or epidemiological studies in this context is not evidence of a lack of a problem. It stems explicitly from failures of SmithKline Beecham, Pfizer or Lilly to do the requisite studies. Both David Wheadon and Christine Blumhardt from SmithKline as well as Roger Lane from Pfizer and Charles Beasley from Eli Lilly along with outside experts such as Daniel Casey and John Mann have testified under oath in the course of the last year that there have been no studies undertaken by any of these companies or others that have been designed to test whether the SSRIs could cause a problem. I believe that this will in due course be seen for the extraordinary state of affairs that it is.

I think what will also be clear is that SmithKline Beecham recognised the presence of withdrawal syndromes in their volunteers from the early to mid 1980s. That withdrawal syndromes occurred at a much higher rate than occur on benzodiazepines. Nevertheless they applied for and have received from you and other regulators a licence to claim that their drug is effective in the prophylaxis of depression and these claims have been based on designs which almost certainly are designs better suited to show the presence of a withdrawal syndrome than designs suited to demonstrate prophylaxis in depressive disorders. A great number of people have in recent years been told that when they begin to feel ill on discontinuing treatment that this is the recrudescence of their mood disorder rather than a discontinuation syndrome from their drug. I would imagine that a great many such people and others on their behalf will feel extraordinarily let down and angry when faced with the evidence that I've been faced with.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Department of Health
MEDICINES CONTROL AGENCY

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8 June 2001

Dr David Healy
Director University Of Wales College of Medicine
Division of Psychological Medicine
North Wales Department
Hergest Unit
Ysbyty Gwynedd
BANGOR
Gwynedd LL57 2PW

Dear Dr Healy

Re: SSRIs and the risk of suicide

Thank you for your letter of 4 April 2001 and for your fax of 7 June 2001.

We have reviewed the studies that you have referenced. These provide evidence that sertraline and paroxetine may be associated with CNS activation. I would like to point out that agitation is listed as an adverse effect in the Summaries of Product Characteristics of all SSRIs.

Thank you for informing us about your lecture in Toronto and for faxing us a copy of the lecture. Your letter of 20 December enclosed posters relating to your healthy volunteer study. As discussed at our meeting in December 2000, we are very interested to receive the full report of this study and would be grateful if you would confirm when this will be available.

Your fax of 7 June outlines your views on the recent court case in the USA. The Committee on Safety of Medicines (CSM) will be considering data from volunteer studies involving SSRIs in July 2001. We would be very interested to receive any data from the recent trial in the USA that you consider would be relevant for CSM to consider.

Yours sincerely

Dr June Raine
Director
Post-Licensing Division

JRHEALY08062001

Our Ref: DH/JT

19th June 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
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SW8 5NQ

Dear Dr Raine

RE: SSRI'S AND SUICIDE

Many thanks for your letter of the 8th June. As regards the listing of agitation as an adverse effect in the Summaries of Product Characteristics of all SSRIs there are a number of ambiguities. First neither the BNF nor the ABPI versions of these list agitation as an adverse effect for Seroxat for instance. I have little doubt that there is such a listing in some Summaries of Product Characteristics but perhaps you can tell me whether there is any evidence as to the likelihood of GPs for example reaching for the individualised SPCs of each of the SSRIs rather than for their BNF or for a copy of the ABPI Compendium.

Given the listing in the SPCs of each SSRI, the next question that arises is whether this is likely to be interpreted as a warning or a statement of causality or rather something of a dismissal of a link.

This question seems to me to be critical. If your interpretation is that the information being presented to physicians is that agitation can be caused by SSRIs (and the data fully supports this interpretation), then it seems to me almost logically impossible for you then to advise any physicians that thoughts of suicide or harm that may emerge in the course of treatment are linked to their illness rather than directly to the agitating drug with which they are being treated.

Continued/..

I am pleased to see that you will be reviewing some aspects of the Healthy Volunteer work that has been done. In the light of previous correspondence that I've had with both yourself and Dr Jones it does seem that you've in almost all instances you have had summaries of this data prepared for you by the companies rather than the raw data. I hope you will have access to the full data set. Many of the views that have been expressed to you by SmithKline for instance such as their view that nausea and side-effects like drowsiness were the most commonly occurring side-effects in their healthy volunteer panels are strictly speaking correct but I believe you will see that agitation occurs in up to 25% of the volunteers exposed to paroxetine in multiple-dose studies. It is very difficult in the light of this to see how you cannot avoid a warning about the occurrence of agitation and the consequent occurrence of suicidality or other problems that might be reasonably linked to agitation in patients being treated with Seroxat or other SSRIs.

In SmithKline's healthy volunteer panel you will also find that there was a suicide. It happened some weeks after treatment had been discontinued. Quite reasonably in these circumstances at that historical point in time the investigators did not link the suicide to paroxetine at that point in time. However it may be time to re-open the question of what happened to this volunteer.

The first point is that none of the investigators were trained to elicit problematic behavioural or mental effects emerging on these drugs. The volunteer in question will not have been systematically or properly assessed at the time of paroxetine intake. There has to be a considerable chance that the volunteer suffered in much the same way that the healthy volunteers in the study we ran in this department suffered. Without the index of suspicion we had as to the possibility of a problem we would not have unearthed the findings that I subsequently wrote up and have sent to you. Contained in the article that was published in Primary Care Psychiatry is a reference to the fact that our volunteers took several weeks to recover their mental equilibrium following what had happened to them. There was a clear causal connection between the suicidality that emerged with drug treatment and disappeared once the treatment had stopped but in addition both volunteers were left with severely impaired self confidence, dysphoria and nervousness for weeks and in one instance over two months afterwards. Had either committed suicide during this period I would not have felt able to reassure you or anyone else that the Sertraline that we had given them which had made them suicidal for the first time in their lives had not contributed to the subsequent suicide. In fact there would have to be a strong index of suspicion that it had contributed, albeit in ways that have not yet been properly mapped out. In the light of this I think that it is impossible for SmithKline Beecham to deny a possible link between paroxetine and the suicide of one of their healthy volunteers.

Continued/..

Quite apart from the impact on our volunteers' self confidence of being made suicidal by a drug, there is a further aspect contributed by withdrawal effects

from the drugs. In the case of Seroxat in healthy volunteers these have been noted to include abnormal dreams and thoughts and agitation. What none of us know at this stage is how long such withdrawal is likely to go on. This merges into the question raised above of the long-term impact of our healthy volunteers. You may wish to note and perhaps even consult with Professor Merton Sandler formerly of the Pathology Department in Queen Charlotte's Hospital, London who took a single dose of reserpine in the early 1960s as part of his research and was significantly dysphoric for a month afterwards.

I have certainly clinically seen patients with mild conditions treated for short periods of time suffer for three months after discontinuing Seroxat. SmithKline's healthy volunteer work amply bears out these possibilities. It would be very difficult for either them or you or me to out rule therefore a contribution from this source to the death of their healthy volunteer.

This issue raises the role of SmithKline Beecham's awareness of withdrawal in their healthy volunteers when they then made an application to the MCA for a licence to prevent relapse in depression claiming that patients re-randomised to placebo who became unwell were suffering from a relapse of their depression. This seems to me to be extraordinarily deceitful in the light of their own healthy volunteer work and concerns about the question of withdrawal from their drug from a period 10 years earlier.

You must know, but I'll repeat for you, that there are many hundreds and almost certainly thousands of patients around the country who find, when they attempt to reduce the dose of their medication, they feel very unwell. They are now being told by general practitioners around the country and this message is reinforced by the pharmaceutical companies that this is a return of the depressive or nervous condition for which they were being treated. It is no such thing. Any minimal awareness of the nature of physical dependence syndrome, the point at which they emerge following the reduction in a dosage regime and their liability to clear up following the reinstitution of treatment, as opposed to the general failure of new depressive episodes for instance to clear up following the reinstitution of treatment, makes it almost certain that for the vast majority of people affected in this country what is involved is a withdrawal syndrome rather than a new depressive episode.

As things stand at present you are compounding the injury of physical dependence by condoning the message currently being delivered that this is not physical dependence. This message is a message that will injure the self-esteem of those to whom it is being given inappropriately and will in its own right have long-term consequences.

Continued/..

I will enclose with the posted version of this letter the article involving the further data from our healthy volunteer studies that has been submitted for peer review.

As regards data from the recent trial in the United States I'm sure that you could get the trial transcript in its entirety from SmithKline Beecham overnight if you requested it. What you should also request are details of the Montgomery study in intermittent depressive disorders conducted around 1992//93. This was a placebo controlled study of paroxetine in this patient group that yielded a projected annual rate of 45 suicide attempts in the paroxetine treated group versus 12 suicide attempts in the placebo treated groups. As Mr Charles Preuss the lawyer for SmithKline mentioned to me in the trial in the United States, these results were not significant. I have little doubt however that the jury found that the early termination of the study and non-publication of the results extremely significant.

You may also care to know that the most serious suicide attempt occurred in the paroxetine treated group and involved what SmithKline refer to as spinal injuries. This case led to an action against St Mary's hospital.

Finally it may well be time for you to consider some of the following possibilities. How much of the literature being presented to you by companies supporting their position is ghost written, published in non-peer reviewed supplements to journals, or published in journals of which one of the authors is an editor. I think any decent survey of the relevant material that companies are likely to bring to legal trials in this area for instance the studies cited by SmithKline in the Tobin trial, will show that a goodly proportion of that material falls into one or other of the above categories.

You may not feel that it's your area of responsibility to police issues like this. My problem is that I'm fairly certain that every other arm of Government that I could turn to will respond similarly. This is not a reassuring situation. In the current parlance, it doesn't smack of joined up government.

Yours sincerely

David Healy
Director
North Wales Department of Psychological Medicine

Our Ref: DH/JT

2 August 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

I thought I'd sent you a letter on 19 June 2001 but not having received an acknowledgement of its receipt I've begun to doubt whether it went or not. I would of course be most interested in any answer to the questions raise in the letter.

I wonder if I could as some further questions also. Given the fact that there are moves to harmonise European labelling at the moment, and given that the wording you proposed to SmithKiline Beecham, Glaxo and Lilly was presumably in harmony with what you perceive to be the requirements of the harmonisation programme and given that the companies refuse to accept the proposed working and indeed have significantly changed it, I would have thought that the issue would need to be raised at a European level. I wonder therefore if I could, in addition to the minutes from any CSM/MCA consideration of these issues, which I have previously asked you for, I could ask you to forward minutes relevant to any consideration of these issues you have had in the European context – that is minutes from either internal MCA meetings or with the European regulators.

A further question arises from the CSM Current Problems Bulleting number 21 from 1988. In this you warned of the ability of Benzodiazepines to precipitate suicide an aggressive reactions. This is a confident an unambiguous warning. However in the light of current debate about what problems the SSRIs may cause I have to note it that the 1988 warning had been placed there without benefit of clinical trial or other epidemiological data. I, of course, think that your approach then was appropriate. But I have to note that it is inconsistent

with your approach now. Can I ask you how you think this potentially embarrassing inconsistency should be addressed?

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine.

Cc Dr Keith Jones

DECLARATION OF INTERESTS: A CODE OF PRACTICE FOR MEMBERS OF THE MEDICINES COMMISSION AND SECTION 4 COMMITTEES AND SUB-COMMITTEES

INTRODUCTION

1. This code of practice guides members of the Medicines Commission and associated committees as to the circumstances in which they should declare an interest in the pharmaceutical industry.

2. The advice of the Commission and the Committees concerns matters which are connected with the pharmaceutical industry and it is therefore desirable that members should have a good understanding of the work of the industry. It is also desirable that some members should have some practical experience of the scientific problems of product development.

3. The pharmaceutical industry relies heavily on the advice of doctors, veterinarians and pharmacists outside the industry in, for example, the universities. To avoid any public concern that commercial interests might affect the advice of the Commission and Committees, Ministers have decided that the arrangements which govern relationships between members and the pharmaceutical industry and information on significant and relevant interests should be on public record.

SCOPE AND DEFINITIONS

4. This code applies to members of the following bodies:

(a) Medicines Commission
Under section 2 of the Medicines Act 1968, the Chairman and members of the Medicines Commission are appointed by Ministers after consultation with such organisations as they consider appropriate.

The membership must include persons who appear to Ministers to have a wide and recent experience of, and to have shown capacity in, the practice of medicine, the practice of veterinary medicine, the practice of pharmacy, chemistry and the pharmaceutical industry. Appointments are for a term of 4 years.

(b) Section 4 Committees
The Committee on Safety of Medicines, the Veterinary Products Committee, the British Pharmacopoeia Commission and the Advisory Board on the Registration of Homoeopathic Products are committees established under section 4 of the Medicines Act 1968. Ministers appoint the Chairmen and members of the Section 4

Committees. The term of office is usually 3 years.

(c) Sub-Committees
Section 4 Committees may establish sub-committees, and appoint their Chairmen and members. The following sub-committees are currently functioning: Sub-Committee on Biologicals; Sub-Committee on Chemistry, Pharmacy and Standards; Sub-Committee on Pharmacovigilance; the Medical and Scientific Panel; and the Appraisal Panel for Human Suspected Adverse Reactions.

5. In this code, "pharmaceutical industry" means:

(a) Companies, partnerships or individuals who are involved with the manufacture, sale or supply of medicinal products * subject to the licensing provisions in the Medicines Act, or the requirement to obtain a certificate of registration under the Medicines (Homoeopathic Medicinal Products for Human Use) Regulations.

(b) Trade associations representing companies involved with such products.

(c) Companies, partnerships or individuals who are directly concerned with research, development or marketing of a medicinal product* which is being considered by the Commission or one of the Committees or Sub-Committees.

References to "the pharmaceutical industry" include cases involving a single company.

6. In this code, "the Department" means the Department of Health, or in the case of the Veterinary Products Committee, the Ministry of Agriculture, Fisheries and Food.
(**Includes homoeopathic products*)

DIFFERENT TYPES OF INTEREST

7. The following is intended as a guide to the kinds of interests which should be declared. Where a member is uncertain as to whether an interest should be declared he or she should seek guidance from the Department or, where it may concern a particular product which is to be considered at a meeting, from the Chairman at that meeting. **If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.**

8. However, neither members nor the Department are under any obligation to search out links between one company and another, for example where a company with which a member is connected has an interest in a pharmaceutical company of which the member is not aware and could not reasonably be expected to be aware.

Personal Interests

9. A personal interest involves payment to the member personally. The main examples are:-

   (a) **Consultancies:** any consultancy, directorship, position in or work for the pharmaceutical industry which attracts regular or occasional payments in cash or kind.

   (b) **Fee-Paid Work:** any work commissioned by the pharmaceutical industry for which the member is paid in cash or kind.

   (c) **Shareholdings:** any shareholding in or other beneficial interest in shares of the pharmaceutical industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

Non-Personal Interests

10. A non-personal interest involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:-

   (a) **Fellowships:** the holding of a fellowship endowed by the pharmaceutical industry.

   (b) **Support by the pharmaceutical industry:** any payment, other support or sponsorship by the pharmaceutical industry which does not convey any pecuniary or material benefit to a member personally but which does benefit his/her position or department eg.

      i. a grant from a company for the running of a unit or department for which a member is responsible;

      ii. a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which the member is responsible. This does not include financial assistance for students;

      iii. the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.

11. Members are under no obligation to seek out knowledge of work done for or on behalf of the pharmaceutical industry within departments for which they are responsible if they would not normally expect to be informed.

DECLARATION OF INTERESTS

Declaration of interests to the Department

12. Members of the Commission, the Committees and Sub-Committees should inform the Department in writing when they are appointed of their **current personal** and **non-personal** interests. Only the name of the company and the nature of the interest is required; the amount of any salary, fees, shareholding,

grant etc. need not be disclosed to the Department. An interest is current if the member has an on-going financial involvement with the pharmaceutical industry, eg. if he or she holds shares in a pharmaceutical company, has a consultancy contract with the pharmaceutical industry, or if the member or the department for which he or she is responsible is in the process of carrying out work for the pharmaceutical industry. Members are asked to inform the Department at the time of any change in their **personal** interests, and will be invited to complete a declaration form once a year. It would be sufficient if changes in **non-personal** interests are reported in the annual declaration form following the change. (Non-personal interests involving less than £1000 from a particular company in the previous year need not be declared to the Department.)

Special position of Chairmen

13. It is not appropriate for the Chairmen of the Medicines Commission and the Section 4 Committees to have any current personal interests in the pharmaceutical industry.

14. The position of Sub-Committee Chairmen is the same as for all other members, since Sub-Committees report to the main Committee rather than giving advice in their own right.

Declaration of interests at meetings and participation by members

15. Members are required to declare relevant interests at Commission, Committee or Sub-Committee meetings, and to state whether they are personal or non-personal interests and whether they are specific to the product under consideration or non-specific.

16. A member must declare a **personal specific** interest if he or she has **at any time** worked on the product under consideration and has personally received payment for that work, in any form, from the pharmaceutical industry. The member shall take no part in the proceedings as they relate to that product, except at the Chairman's discretion to answer questions from other members. If the interest is no longer current, the member may declare it as a **lapsed personal specific** interest.

17. A member must declare a **personal non-specific** interest if he or she has a **current** personal interest in the pharmaceutical company concerned which does not relate specifically to the product under discussion. The member shall take no part in the proceedings as they relate to the product, except, at the Chairman's discretion, to answer questions from other members.

18. A member must declare a **non-personal specific** interest if he or she is aware that the department for which he or she is responsible has at any time worked on the product but the member has not personally received payment in any form from the pharmaceutical industry for the work done. The member may take part in the proceedings unless he or she has personal knowledge of the product through his or her own work or through direct supervision of other people's work, in which case

he or she should declare this and not take part in the proceedings (except to answer questions).

19. A member must declare a **non-personal, non-specific** interest if he or she is aware that the department for which he or she is responsible is **currently** receiving payment from the pharmaceutical company concerned which does not relate specifically to the product under discussion. The member may take part in the proceedings unless, exceptionally, the Chairman rules otherwise.

20. The examples of "personal", "non-personal" and "current" interests given in the previous paragraphs should be read in the context of paragraphs 7, 8 and 9. "Taking part in the proceedings" includes both speaking and voting. A member who is in any doubt as to whether he or she has an interest which should be declared, or whether to take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether a member with an interest shall take part in the proceedings.

21. If a member is aware that a product under consideration is or may become a competitor of a product manufactured, sold or supplied by a company in which the member has a **current personal** interest, he or she should declare an interest in the company marketing the rival product. The member should seek the Chairman's guidance on whether to take part in the proceedings.

RECORD OF INTERESTS

22. A record is kept in the Department of:

    (a) names of members who have declared interests to the Department on appointment, as the interest first arises or through the annual declaration, and the nature of the interest;

    (b) names of members who have declared interests at meetings of the Medicines Commission, Section 4 Committees and Sub-Committees, giving dates, names of relevant products and companies, details of the interest declared and whether the member took part in the proceedings.

PUBLICATION

23. Information about interests declared by members to the Department will be published each year with the Annual Reports of the Medicines Commission and Section 4 Committees (normally published in July) and are available on the website of The Medicines Control Agency (http://www.mca.gov.uk).

CODE OF PRACTICE FOR MEMBERS OF THE MEDICAL AND SCIENTIFIC PANEL (Adopted January 1997)

1. The Code of Practice relating to the declaration of interests in the pharmaceutical industry applicable to the Veterinary Products Committee ("the General Code of Practice") continues to apply to the Medical and Scientific panel. The following paragraphs of this code shall, however, additionally apply to the Medical and Scientific panel. In case of any conflict between the provisions of this Code and the General Code of Practice, this Code shall apply.

2. Members of the Medical and Scientific Panel should, at the next meeting of the Panel following the commencement of involvement in question, declare that they have become involved in court proceedings relating to human health aspects of exposure to organophosphorus (OP) sheep dips. If no meeting of the Panel is to take place within one month of the commencement of the involvement, the member should make such a declaration directly to the Chairman. "Involvement" in court proceeding would include providing or agreeing to provide expert advice in connection with OP sheep dips to a party to existing or proposed court proceedings, and agreeing to appear as a witness in court in the case.

3. The requirement to make a declaration under paragraph 2 shall be subject to the general rules of medical confidentiality relating to particular individuals.

4. After giving a declaration under paragraph 2 above, the member concerned shall declare at any future meeting of the Panel, and, as appropriate, at any time to the Chairman as set out in that paragraph, any changes in his/her involvement, such as whether agreement has been given to act as a witness following the giving of advice.

5. Section 118 of the Medicines Act, 1968 prohibits a member from disclosing (a) information which they have obtained solely by virtue of their membership of the Panel, (b) details of deliberations of the panel, or (c) advice given or proposed to be given to the Veterinary Products Committee by the Panel or any advice which has been or is proposed to be given to Ministers comprising the licensing authority. However, disclosure is allowed if the member is discharging duties as a member of the Panel, if the information, deliberations or advice are already in the public domain or if consent to disclosure has previously been given by the licensing authority. These requirements of the Medicines Act may create a conflict if a member is involved in court proceedings in relation to the duty of disclosure to the court. In such cases, the member should first consult the Panel Chairman who should seek advice of the licensing authority with the objective of obtaining consent to disclose the information, deliberations or advice in question.

6. Other than as provided above, members of the Panel shall declare in the same way as described in paragraph 2 above, any occasions when they have agreed to conduct research, in return for payment, connected with OP sheep dips.

7. If the circumstances arise in which, in the opinion of the Chairman, a declaration by a member of the Panel not otherwise provided for by this code or the General Code of Practice is necessary in order to ensure the proper conduct of the Panel, the Chairman, may require a member of the Panel to make such a declaration, and he may then give directions in accordance with paragraph 7 above.

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17 October 2001

Dr D Healy
Consultant Psychiatrist and Senior Lecturer
Hergest Unit
Ysbyty Gwynedd
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LL57 2PW

Dear Dr Healy

First, may I thank you for seeing my colleague, Harry Owens, recently. I understand that you requested information about Zyprexa (olanzapine) and suicide.

Please find enclosed published articles relating to your question.

I trust that this information will be of interest to you.

Yours sincerely

Linda Loades (Mrs) BSc, MSc
Medical Information Officer

CC: Ms Margaret (Harry) Owens O46P

Encs:

Zyprexa Summary of Product Characteristics

Beasley CM, Sayler ME, Kiesler GM *et al* The influence of pharmacotherapy on self-directed and externally directed aggression in schizophrenia. Schizophrenia Research 1998; **29**(1-2):28.

Fung M, Tran P, Beasley C *et al* Suicidal risk in patients treated with the novel antipsychotic olanzapine.Eur Neuropsychopharm 1998; **8** (Suppl 2): s223

Meltzer HY Suicide and schizophrenia: Clozapine and the InterSePT study. J Cliln Psych 1999; **60** (Suppl 12): 47-50

Meltzer HY, Anand R, Alphs L. Reducing suicide risk in schizophrenia. CNS Drugs 2000; **14**(5): 355-365

Meltzer HY. Treatment of suicidality in schizophrenia. Annals NY Academy of Sciences 2001 (Apr); 932:44-60.

Tran PV, Hamilton SH, Kuntz AJ *et al.* Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. Journal of Clinical Psychopharmacology 1997; 17(5):407-418

Our Ref: DH/JT

24 October 2001

Mrs Margaret Owens
Specialist Medical Representative
Eli Lilly & Company Ltd
C/O The Hergest Unit
Ysbyty Gwynedd
BANGOR
LL57 2PW

Dear Harry

The material that came back from the company as regards suicides was really not particularly helpful. It was quite different to what I'd asked for. I've printed out a page here with question marks inserted. This is a table from the trial submitted to the FDA for a licence for each of the new generation antipsychotics. It comes from an article by Khan et al in the American Journal of Psychiatry in September. What I need to try and do is fill in the question marks. Any help that you can be with this would be greatly appreciated.

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine

Our Ref: DH/JT

16 November 2001

Dr June Raine
Director of Post-Licensing Division
MCA
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Dr Raine

I wrote to you almost half a year ago on issues to do with suicidality and SSRIs as well as physical dependence on SSRIs. I followed up the original letter a few weeks later enquiring about the review of healthy volunteer studies that the MCA/CSM were scheduled to undertake in July of this year.

I haven't had a reply to either letter. I am still interested in your response to the issues raised in both letters. I would also be interested to see a copy of the minutes dealing with the meeting in which the healthy volunteer work was considered.

I enclose with this letter an article that contains details that must be of some concern to you. It appears that the categorisation of suicide and suicide attempts in their clinical trials by some of the pharmaceutical companies as placebo suicides and suicide attempts is incorrect. Some of these occurred during the washout period of clinical trials. When a correction is made for that the current database of clinical trials submitted to you and to the FDA in application for licenses for the most recently licensed set of antidepressants shows that they collectively raise suicide risks statistically significantly. The increased risk is statistically significant for paroxetine on its own.

As you will see from the enclosed article there is a great deal of other data which fits in with this finding.

Continued/..

I would be grateful for the comments of the MCA on the implications of the data collected in this article and indeed the comments of any expert reviewers you may care to show this article to.

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine

Encs.

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29 November 2001

Our Ref: LLNO-20011107103511

Dr D Healy
Consultant Psychiatrist and Senior Lecturer
Hergest Unit
Ysbyty Gwynedd
Penrhosgarnedd
BANGOR
Gwynedd
LL57 2PW

Dear Dr Healy

Thank you for your letter concerning suicide attempts during clinical trials with olanzapine, which was forwarded to us by Harry Owens. I am sorry that you did not find our previous letter on this subject helpful.

Your question was referred to our parent company in the USA, but unfortunately the specific data your requested are not available.

Yours sincerely

Dr Alexander Simpson
Medical Director – UK & ROI

CC: Margaret (Harry) Owens 046P
Linda Loades, Medical Information

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Dr David Healy
Director
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7 December 2001

Dear Dr Healy

Re: SSRIs and the risk of suicide

Thank you for your letter of 19 June 2001 which enclosed your study report, and your further letters of 2 August 2001 and 16 November 2001 to Dr June Raine. I have been asked to respond. I am sorry about the long delay in responding to your queries. During this time we have been reviewing the information you have provided.

We have been looking for information that would address your question of the evidence base for warnings about the increased risk of suicide. We have been unable to answer this from the available files, however we will contact you further on this issue.

In your letter of 19 June, you mention that agitation is not currently listed in the Seroxat SPC or in the BNF. This term was added to the Seroxat SPC earlier in the year and the new SPC should now be available. Agitation is among a number of psychiatric reactions listed as an undesirable effect in the SPC. There is a statement to the effect that psychiatric effects of SSRIs may be difficult to distinguish from the underlying disease.

The difficulties of distinguishing any psychiatric effects of SSRIs from the underlying disease was acknowledged by CSM in their review of data in relation to suicidal behaviour in June 2000. As you are aware from the minutes of that meeting:

'The Committee commented that it was impossible to answer the question of whether fluoxetine and/or other SSRIs caused suicidal behaviour in a small subpopulation of patients.'

It is for this reason that the CSM recommended continuing to keep the issue under review. We planned that CSM would consider further date in July 2001, however CSM consideration of this issue has been delayed in order to allow us to follow further lines of enquiry. This will include your study report and other data reference in your letters. We are aware of the volunteer who committed suicide a number of weeks after completing a volunteer study involving paroxetine. This information will also be included in the assessment to be presented to CSM in the near future. We will let you know the outcome of this consideration. You ask for details of the personnel involved in the review of SSRIs. As is our normal practice, assessments are carried out by medical and scientific staff in the Pharmacovigilance Group of the Post-Licensing Division. The assessment report is then presented to the CSM and to other experts in the field if necessary.

You ask if there are criteria regarding links to interested parties for outside experts. I am assuming by this that you mean interests in the pharmaceutical industry. We have a published Code of Practice which deals with this issue which I enclose.

Your raise the issue of withdrawal reactions associated with SSRIs. It has been known for many years that withdrawal reactions has been associated with paroxetine. An article in 'Current Problems in Pharmacovigilance' in 1993 highlighted 78 reports of withdrawal reactions associated with paroxetine which has been reported via the Yellow Card Scheme. A detailed review in 1998 of data by MCA/CSM did not reveal evidence to support an association between SSRIs and a dependence syndrome, however it was recognised that all SSRIs are associated with withdrawal reactions. The results of this review were published in 'Current Problems in Pharmacovigilance' in September 2000. This issue was also reviewed in detail by the European scientific advisory committee, the Committee on Proprietary Medicinal Products (CPMP). Its conclusions can be found on the European Medicines Evaluation Agency Website.

The symptoms most commonly reported via the yellow Card Scheme following discontinuation of an SSRI are dizziness, nausea, fatigue, tingling sensations and sleep disturbances. In terms of duration of withdrawal reactions, analysis of our database suggests that the majority of withdrawal reactions with SSRIs last for less that 89 days, however there are reports of withdrawal reactions lasting considerably longer. Warnings about withdrawal reactions are present in the SPCs and PILs for all SSRIs.

Your further requests relate to European harmonisation of product information for SSRIs. The warnings concerning withdrawal reactions have been introduced on a Europe-wide basis, based on those proposed in the UK. In relation to the minutes of European discussions relating to SSRIs and information about the current harmonisation procedures, may I refer you to the EMEA.

Your also make reference to a lack of transparency on behalf of pharmaceutical companies. I would like to assure you that it is the responsibility of the MCA to police such issues, and we would be very interested to receive any evidence of which you are aware.

Yours sincerely

Ms Sara Wark
Post-Licensing Division
Copy: Dr K Jones MCA/Dir
Dr J Raine MCA/PL

Our Ref: DH/JT

7 December 2001

Alan Milburn
Secretary of State for Health
Department of Health
Richmond House
Whitehall
LONDON
SW1

Dear Mr Milburn

RE: ADVERSE EFFECTS AND PRESCRIPTION ONLY STATUS

I'm copying this letter to Dr Keith Jones of the MCA as I suspect you will wish some input from the MCA on this point and copying him in on the letter may expedite the process. There would seem very little point in writing to Dr Keith Jones on his own as any letters that I have written to the MCA recently have not bee answered.

As a historian of psychopharmacology I have been particularly interested in the question of prescription only status of psychotropic and other drugs. My understanding is that one of the primary reasons for prescription only status is so that physicians, who it is thought will be in a better position to quarry out information about the hazards of drugs, than you for instance would be, when to treating you, will quarry out such hazards and will factor such issues into account when deciding on what medication to give you for whichever complaint you should present with.

In a recent series of articles in the Archives of General Psychiatry and the American Journal of Psychiatry, a research group in Michigan have presented data from the published literature and from trials submitted to the FDA on both antidepressants and antipsychotics and the numbers of suicides in those trials both on new antidepressants and new antipsychotics as well as older antidepressants and older antipsychotics and on placebo.

Continued/..

As an aside companies have it would appear in some instances coded as placebo suicides and suicidal acts, suicides and suicidal acts that did not happen on placebo. I have written to the MCA, alerting them to this but have received no response from them on the significance of this which I believe is methodologically indefensible.

But to come to the main point, as you will see from the enclosed table of studies on antipsychotics in the case of Lilly's Olanzapine and AstraZeneca's Quetiapine the data published by Khan et al show gaps for suicide attempts. In order to determine what the risks of treatment might be, it is very important for a clinician such as me to have these gaps filled in. The companies have the data. There is however no way to access this data within the public domain. The scientific literature apparently does not contain the answers. The only way to access the data is through the companies. As I understand the legal basis for prescription only arrangements, there is a moral and probably a legal requirement on companies to supply this data if a request is made for it.

I have written to AstraZeneca and to Eli Lilly. The responses from both companies were initially unsatisfactory. Follow-up letters in the case of Eli Lilly have produced the attached response where you see they state frankly that they will not supply the data.

In an era when evidence based medicine is so trumpeted, it is difficult to know how to handle this lack of important evidence. I'm writing to ask you if you could clarify whether there is any obligation on companies to provide such data. If not I wonder whether you would feel it appropriate to inform clinicians around the UK generally that there may be significant data on all medications that is being withheld from them?

I would appreciate a response at your earliest convenience.

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine
(Honorary Consultant Psychiatrist)

CC Dr Keith Jones, MCA

Department of Health
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Director
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December 2001

Dear Dr Healy

RE: ADVERSE EFFECTS AND PRESCRIPTION ONLY STATUS

Thank you for your letter of 7 December to Alan Milburn raising issues relating to suicidal behaviour and Selective Serotonin Reuptake Inhibitors. It has been passed to the Medicines Control Agency for response. As you are aware, we are in the process of looking into points raised in your further letters of 17 December. A response covering all the points you have raised will be sent to you shortly.

Please do not hesitate to contact me should you have any questions.

Yours sincerely

Ms Sarah Wark
Post-Licensing Division

Copy: Dr K Jones MCA/Dir
Dr J Raine MCA/PL

SW/DH/07122001

Our Ref: DH/JT

17th December 2001

Miss Sarah Wark
Senior Scientific Assessor
Pharmacovigilance Group
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

Dear Miss Wark

Many thanks for your letter of the 7th of December. I am surprised, however, that it is taking so long to address the question of the evidence base for warnings about the increased risk of suicide with benzodiazepines. I await with interest any details on how you propose to resolve the quandary this delay suggests you are in.

On the issue of agitation and SSRIs, I am pleased to hear that agitation will be listed as one of the psychiatric reactions listed as an undesirable effect of SSRIs in the forthcoming SPC. But if this is the case, I fail to understand how you do not feel obliged to put a further warning about the likely consequences of agitation in patients who are ill to begin with. It baffles me that, at least in principle, you consider that agitation might not express itself in terms of suicidal ideation.

You raise the difficulty of distinguishing psychiatric effects of SSRIs from the underlying disease, but I cannot accept your point that this is difficult, given the background of healthy volunteer studies you have where agitation is clearly a consequence of SSRI intake. In fact you have had a study available since 1986 by Saletu et al, published in two different journals, showing a dose dependent induction of agitation in healthy volunteers with sertraline.

When it comes to reviewing the other healthy volunteer studies you have for evidence of agitation and related problems, I would hope your reviewers do not take the excruciatingly pedantic approach companies appear to take at a

Continued/..

time like this when they look simply for the term agitation as it is used to describe experiences of healthy volunteers. They do this even though different companies, and each company at different points in time, have used various mapping systems for a range of terms such as tension, irritability, akathisia and anxiety as well as agitation and have mapped these onto agitation. If your search of this evidence, in contrast to company searches, is disinterested, I believe that it will become clear that effects, which may be generically described as agitation, occur following SSRI intake in healthy volunteers at a much higher rate than they occur on placebo or spontaneously. There will be a problem if this is not the result you get, as there are a lot of internal company documents pointing to such a link.

As regards the CSM's difficulties in distinguishing increased suicidality on SSRIs stemming from the drugs rather than from the disease source, the evidence is now rather conclusive. I would like at this stage to supplement the report I sent you earlier with a later draft of an article detailing this evidence. From this draft article, in Tables 1A & 1B you will see that the evidence for an increased number of suicides on SSRIs versus placebo is statistically significantly greater as is the evidence for increased suicidal acts of any sort on SSRIs versus placebo. The overall relative risk of suicidal acts on SSRIs versus placebo is greater than 2.0. The excess of suicidal acts on SSRIs holds whether the data analysed in terms of patient years or absolute numbers of patients. A similar finding is reported by Dr Laughren of the FDA in an article in this month's European Psychiatry.

Investigational Drug,	**Patient No**	**Suicide No**	*Suicide Attempt No*
Sertraline hydrochloride	2053	2	7
Active comparator	595	0	1
Placebo	786	0	2
Placebo Washout		0	3
Paroxetine hydrochloride	2963	5	40
Active comparator	1151	3	12
Placebo	554	0	3
Placebo Washout		2	2

To make things crystal clear I have enclosed the figures above in this letter. In addition to the increase in suicidal acts, one of the interesting points about these figures that I have drawn to the attention of a number of scientific audiences and media sources is that companies have been categorising as placebo suicides and suicidal acts, suicides and suicidal acts that occurred during the washout period of trials or following the termination of the trial. I think there will be questions asked of these companies as to why they engaged in such practices. It is difficult to see how these questions will not rebound on you in the MCA. Were you aware this was happening? Did you condone it? What do you make of the correct figures?

Continued/..

Whatever way you analyse the data, either by adjusting the denominator to include washouts, or by excluding washouts, whether by analysing in terms of absolute numbers or by patient exposure years, there is an excess of suicidal acts on SSRIs and this is statistically significant. And, as you will find from the draft article, these findings are consistent with epidemiological data drawn from primary care in the United Kingdom. Indeed the degree of consistency is quite striking with the figures from RCTs closely overlapping with the figures thrown up by the Drug Safety Research Unit studies, whether these figures are expressed in terms of absolute numbers or patient exposure years.

As regards the issue of dependence on the SSRIs, a great deal hinges on your definition of dependence. I would accept that SSRIs are not addictive. By the statement that SSRIs are not addictive, however, I mean just like you that they do not cause craving and do not cause tolerance. If we all accept this definition, then the term dependence syndrome must mean something else. I don't believe that the MCA can have their cake and eat it on this one by then suggesting that a dependence syndrome is characterised by the production of cravings and tolerance.

If the presence of tolerance and craving characterises a dependence syndrome for you then I would respectfully suggest to you that based on comparator studies of the animal and human literature there is no more evidence that benzodiazepines cause a dependence syndrome than SSRIs do. If this is your position, then just as I have asked you to consider the apparent inconsistency between your views on benzodiazepines and SSRIs as regards suicidality etc, I would also ask you to consider the inconsistency in your views as regards dependence syndromes with benzodiazepines and SSRIs and remedy one or other of your positions.

You have talked about withdrawal reactions with SSRIs being relatively mild and lasting for the most part only a few days. This statement is at odds with both clinical experience and popular perceptions. I suspect the greater part of your data on SSRIs stems for the 60% of patients we know from research discontinue treatment with SSRIs within a month and I can accept that the characterisation of withdrawal reactions from SSRIs you outline might well apply to this group.

I do not believe, however, that you have data on patients who have been taking SSRIs for months or years and cannot then stop. It follows that I do not believe that you are in a position to properly characterise the problems faced by such patients. But even in the case of the milder withdrawal reactions that you concede occur, this would be evidence for most people in the street of a dependence syndromes.

Continued/..

As we correspond with each other Glaxo SmithKline and other companies are actively stating that their drugs do not cause dependence syndromes, or

stating that they are not habit forming, or stating a range of similar things that will mislead the public into believing that these drugs do not cause withdrawal reactions of a severity that means that the patient may be effectively unable to halt treatment. Do you condone company statements of this sort or do you think companies are just not saying these things?

As regards the question of any lack of transparency by pharmaceutical companies, I think you need to revisit the experts who have given you an input on psychiatric matters, since the SSRI controversies first blew up, and ask them to outline for you exactly what potentially conflicting interests they have had, and exactly when they acquired these other interests. You should also ask them for any reports they may have written for any of the companies involved on issues to do with suicidality or dependence, that have you might not have seen. You might also ask for any unpublished data they have pertinent to these issues.

Finally, as regards your review of the current evidence on SSRIs and suicidality, can I make the following suggestion? There is a risk of an ongoing correspondence, unless your experts have the opportunity to persuade me that I'm making an error of some sort in the points that I have been making on both scientific and public platforms. Effectively I would like to offer the MCA the chance to silence me (it would be a great relief to be able to withdraw from this issue). I suggest therefore a meeting and would be happy to travel to London at short notice. In the light of the serious nature of the problem, and the fact that this correspondence has now been running for the better part of two years, I suggest this meeting should be scheduled for sometime in the near future

Yours sincerely

David Healy MD FRCPsych
Director
North Wales Department of Psychological Medicine

Department of Health

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20 December 2001

Dear Dr Healy

Thank you for your letter of 17 December. We are considering the information you have provided and will get back to you as soon as possible.

Yours sincerely

Sarah Wark
Team Leader
Pharmacovigilance Group
Post Licensing Division

SW/DRHEALYACK-201201/EY

Department of Health

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Gwynedd LL57 2PW
25 February 2002

Dear Dr Healy

I am writing further to my letter of 20 December. I apologise for the delay in responding.

First, I would like to update you on our current position in relation to SSRIs and suicidal behaviour. We consulted the Committee on Safety of Medicines (CSM) on the 12 December 2001 on a possible association between SSRIs and suicidal behaviour. The CSM considered all the material that you have provided since June 2000, and data from volunteer studies provided by the marketing authorisation holders.

The Committee advised that these date did not provide evidence to alter their previous position that the evidence was not sufficient to confirm a causal association between SSRIs and suicidality, although an effect in a small high-risk population could not be ruled out. The Committee concluded that no amendment to SSRI produce information in relation to suicidal behaviour was required.

In you letter of 17 December you raised a number of points and I will answer them individually.

Agitation

On the issue of agitation and SSRIs, we consider agitation to be a recognised adverse effect of SSRIs and this is the reason for adding it to the product information. We also consider that agitation may be a feature of depression in some patients. The CSM has reviewed the evidence for an association between SSRI induced agitation or akathisia and suicidal behaviour and considers that such a link remains surmise at present.

Suicidal behaviour

You have asked for our views on the further data that you have provided in your letter. We have analysed this and consider that your analysis and interpretation of your results all overstate the evidence for an effect of SSRIs on suicide rate and suicide attempts. You claim a relative risk of 2.09, and although the arithmetic is correct and the result of analysing all the date in a single table gives a highly significant result (more significant than you imply), it is misleading to pool the date in this way. A correct analysis is only marginally significant, but should be based on the original trial data. It is likely that if the original date were subjected to a correct meta-analysis, taking into account the time that patients were exposed to the risk of suicide, then this evidence would be even weaker.

I would also draw your attention to a recent publication in the Journal Pharmacoepidemiology and Drug Safety (Carlsten et al, 2001; 10:525-530) where the authors found a significant reduction in suicide rates following the introduction of SSRIs an Sweden, corresponding to approximately 348 fewer suicides in the seven year period following the introduction. While these data have limitations, they do not support an increased risk of suicidal behaviour with SSRIs.

Withdrawal reactions and dependence

With regard to dependence and SSRIs you make two points:

1) Withdrawal reactions and dependence are synonymous:

For our assessment of this issue in 1998 we used the definition of a dependence syndrome from the World Health Organisation International Classification of Diseases (ICD-10) is as follows:

'A cluster of behavioural, cognitive, and psychological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use that to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.'

This definition of dependence is consistent with that in the America Psychiatric Association Diagnostic and Statistical Manual 4th Edition (DSM-IV).

It is generally accepted that withdrawal reactions on stopping a drug are not sufficient, or necessary, for a diagnosis of drug dependence. Other features such as tolerance (requiring increased doses of the drug to produce the same effect) and drug seeking behaviour are required for diagnosis.

2) There are data on patients who have been taking SSRIs for months or years and cannot stop.

The sources of information used for our review of SSRIs, withdrawal reactions and dependence in 1998 were: worldwide spontaneous ADR date; published literature; unpublished date; information from other regulatory authorities and usage date from the Prescribing Authority and the MediPlus database. Detailed review of these date revealed evidence that SSRIs cause withdrawal reactions, however the evidence did not suggest that SSRIs were drugs or dependence or that a large proportion of patients were taking SSRIs for months or years and were unable to stop. We would be very interested to receive any information that you may have in relation to such patient.

The product information for SSRIs warns that they can cause withdrawal reactions and contains appropriate warnings and advice on gradual discontinuation of treatment.

Interest of experts

As you have suggested in your letter we have written to our experts on psychiatric matters and asked them to outline their interests over the years.

Finally, thank you for your offer of a meeting. We would be happy to meet with you again. I will write again next week with a possible date.

Yours sincerely

Sarah Wark
Team Leader – Pharmacovigilance

Copy: Dr June Raine MCA/PL
Prof Stephen Evans MCA/PL
Dr Cheryl Key MCA/PL

Our Ref: DH/JT

8th March 2002

Miss Sarah Wark
Senior Scientific Assessor
Pharmacovigilance Group
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

Dear Sarah Wark

Many thanks for your letter of February 25th and the invitation to discuss the issues on the 25th of March. To facilitate such a meeting it seems helpful to outline some of the key questions to do with interactions between SSRIs and suicide on the one hand and SSRIs and dependence on the other.

Before proceeding, however, I note that the MCA haven't answered the questions I posed in my recent letters. I specifically asked for information on what the basis was for the MCA linking the benzodiazepines with aggression and suicide. I asked this because there appears to be a much greater evidence base for making these claims about the SSRIs. Given MCA/CSM reluctance to make comparable statements about the SSRIs, I suggested that in the absence of comparable evidence it would be appropriate either to revise the previous MCA statement about the benzodiazepines or to revise the current statements about the SSRIs – or else to make it clear what basis there is for distinctions between these drugs. I raised a similar question about dependence on the benzodiazepines. Both sets of questions remain unaddressed.

Agitation
The MCA now appears to concede that there is a great deal of evidence pointing to an excess of suicidal acts on SSRIs. This must be explained somehow. I

Continued/..

think the most likely explanation is that SSRIs induce what is often termed agitation in the US but is more often termed akathisia in Europe. You concede that SSRIs produce agitation. The SSRI market authorisation holders concede that their drugs produce agitation and akathisia.

There is abundant material from the clinical literature including material from scientists and other personnel working for the SSRI market authorisation holders that akathisia/agitation can lead to suicide. The most recent edition of DSM IVTR notes that akathisia can precipitate suicide. This points to a general consensus in the field that there is such a link. (Appendix 1 contains a history of this issue).

But in addition to this general consensus, there is such obvious face validity to the idea that akathisia/agitation would lead to suicide that I would hate to be facing Kirsty Wark trying to defend the position that giving a drug which has been demonstrated in a dose dependent way to produce agitation even in healthy volunteers (and suicidality in some of those reports), and that may have led to suicide in one, that such a drug was not remotely likely to make depressed patients suicidal.

Am I to understand that in our healthy volunteer study when two of our volunteers became agitated and suicidal that their suicidality had nothing to do with their agitation? Would the MCA like to interview our two healthy volunteers?

Am I to understand that in Pfizers' Hindmarch study where all volunteers taking sertraline appeared to become agitated/apprehensive that Pfizer discontinued the study without any concerns that this agitation/apprehension might lead on to something like suicide? Can anyone in the MCA tell me what kind of agitation would not lead to concerns that if prolonged or severe it could result in suicide?

Quite apart from suggesting something that flies in the face of common sense, am I to presume the MCA position has now become one of asking me or others to prove that agitation leads to suicidality? Perhaps the agency could suggest how this should be done? While we work this one out, I would note that in the case of reasonable suspicions about a potentially lethal side-effect, even where causality is not proven, the statutes of most regulatory authorities require warnings. Are you telling me that the MCA regulations are more lax than those of other countries?

You may be interested to know that I have talked on the platform of a market authorisation holders for new antipsychotics and with their encouragement have

Continued/..

said that because particular agents are less likely to cause akathisia than other antipsychotics they are less likely to lead to suicide. Perhaps you would like to charge me, or the market authorisation holder in question, with inappropriate promotion?

Another of the market authorisation holders of one of the newer antipsychotics has also claimed that their agent is less likely to be associated with suicides and suicide attempts than older antipsychotics and spokespersons for the market authorisation holder have indicated that this is probably likely to be so because it is less likely to be associated with akathisia. It turns out that this agent is associated with a significant rate of akathisia and that there is also apparently an excess of suicides on this agent than on older antipsychotics or placebo.

In a letter copied to the MCA, I have recently drawn Alan Milburn's attention to the fact that the market authorisation holder in question has withheld data on the number of suicide attempts in their clinical trials. My understanding is that prescription only status for medication exists in great part so that clinicians will be able to get data like this from companies. It is difficult to see how we could practise evidence-based medicine otherwise. But the company has flatly refused to provide it. In your letter you haven't addressed the many issues associated with this point, even though it is germane to our discussions about the SSRIs.

In addition to agitation, there are two other mechanisms that may bring about this excess of suicides, one being psychotic decompensation on SSRIs and the other being emotional indifference/lability on SSRIs. (I enclose evidence on both these mechanisms in Appendix 2).

Suicidal Behaviour

On the issue of suicidal behaviour, the MCA now appears to concede that the figures that I've provided produce a significant association between SSRIs and suicidal acts.

Some mysterious original trial data are then invoked to minimise this problem. We perhaps need to consult our respective notes on what the original trial data is. I have photocopies of a great deal of this – and I am not relying on company reports of what this data means, as the MCA appears to have done on previous issues. When I communicate with others I am limited to reports prepared by the FDA, which have their inaccuracies, or other public domain documents, but I only use these because I have access to the underlying data and can verify the point. I have also seen a considerably larger trial dataset than the material that I've presented the MCA with, and as far as I can see the larger the dataset gets, the more significant any associations become.

Continued/..

As I understand it, each of the SSRI market authorisation holders has in fact several hundred suicidal acts in clinical trials undertaken on tens of thousands of patients. It should, therefore, be entirely possible to settle the issue of suicidality for each of these drugs individually in a manner that would avoid the pitfalls of pooling data that your letter alludes to – if the MCA asked the market authorisation holders to provide the data. Has the MCA asked for the data, in the light of the data-pooling problems that have been mentioned? If not, in the light of the excess of suicidal acts on SSRIs that the MCA now concedes is present, why not?

While I can appreciate MCA concerns about the hazards of pooling data, I am perplexed about the fact that the data presented for paroxetine on its own are significant and these have seemingly been ignored. Can you explain to me, whether there is any basis – other than saving paroxetine's skin by invoking patient exposure years – that has stayed the MCA hand on the issue of putting warnings on paroxetine?

A) Patient Exposure

In raising the issue of patient exposure time, the MCA's consultants appear to have fallen into a simple trap and come to an erroneous conclusion. I am happy to concede that in the case of some side effects of drugs, making an assessment in terms of the length of exposure to the drug is appropriate. But in the case of SSRI-induced suicidality, which has been closely tied to the first few weeks of exposure to the drug, the use of patient exposure years becomes a means for market authorisation holders to dilute the apparent problem.

It will be obvious even to someone with no experience of the field how this happens. Patients, who become agitated or suicidal on the drug, drop out of the clinical trial in the course of the first few weeks – roughly 5% do this. This leaves patients in the trials who are suited to the drug. Calculating suicidal acts in terms of exposure, when patients doing well may be left on the drug for up to a year, becomes a means of minimising the problem. Whether this minimisation happens because of deceit or because of incompetence is less clear to me. Is there an alternative to either of these options?

It becomes harder to resist the deceit option when we consider the market authorisation holders categorisation of washout suicidal acts as placebo suicidal acts. In addition to this, I presume the MCA must be aware that in the course of handling their data for registration purposes in Germany and presumably also in Britain, Lilly against a background of approximately 8000 patients entered into their trials reported six suicides on placebo, of which one occurred during the

Continued/..

washout period, while four occurred weeks or months after the trial was over and
only one was actually on placebo. If you do not have the data on this, I can provide it. Can the MCA tell me why a company should do this? Can you tell me whether the MCA are prepared to let Lilly and other market authorisation holders get away with it – now that it has been brought to your attention?

Deceit or incompetence aside, I presume the MCA is bound by the International Committee for the Harmonisation of Regulatory Submissions which require the data to be presented both in terms of absolute numbers as well as in terms of exposure. Have the market authorisation holders presented the data to the MCA in both forms? As the MCA has now appeared to concede that there is problem when the data is calculated in the terms of absolute numbers, given that there is little justification for the use of patient years in this context, I find it very hard to see how the agency would not at least warn about risks - even if any warnings include statements to the effect that a causal association has not been conclusively demonstrated.

Sweden
Your letter then draws my attention to a publication by Carlsten et al in 2001, noting a significant reduction in suicide rates in Sweden following the introduction of the SSRIs. The key figure behind this data is Goran Isacsson. The MCA may be interested to know that I invited Dr Isacsson to a symposium I chaired for the British Association for Psychopharmacology two years ago where he presented this argument and essentially these data. I can tell you that the overwhelming view in the symposium seemed to be that Dr Isacsson's contention that the fall in suicide rates in Sweden was linked to SSRI use was improbable.

I could draw MCA attention to the fact that for example since the SSRIs were introduced suicide rates in Ireland have increased and there is more convincing data linking this increase to SSRIs, as in the article by Donovan et al 1999 (Archives of Suicide Research), which shows a statistically significant increase in suicides on SSRIs compared to non-SSRI antidepressants during this period, than there is linking any fall in suicide rates with SSRI use in Sweden. I could draw MCA attention to data from others countries, but lets stick with Sweden.

Now I am sure the MCA will be aware that Prozac – or Fontex as it is there - had difficulties getting a licence in Sweden owing to Swedish perceptions of an adverse risk benefit ratio, and that it has minimal sales there. That like Fontex, Zoloft only came onto the market there in 1996, and has had rather minimal sales. You probably also know that citalopram has accounted for something like 50% of SSRI market there. Someone within the MCA may also know that suicide

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rates began falling in Sweden before the introduction of SSRIs, and a host of factors such as immigration and educational campaigns about suicide, as well as simply a regression to the mean from an extraordinarily high level of suicides are likely to have something to do with this. It is in fact hard to see how SSRIs can have had much to do with falling suicide rates in Sweden, given that the suicide risk in depression stems from hospitalised depression and SSRIs have never been shown to work for these patients.

But let's assume SSRIs might have something to do with this fall. How could this happen? My contention has never been that suicide is an inherent hazard of SSRI drugs that cannot be managed by good clinical practice. My argument has always been that the appropriate level of warnings and education of clinicians can minimise these hazards.

What are the warnings like in Sweden? Well from the early 1990s, Swedish warnings have stressed that the risk of suicide may increase in the early stages of treatment. They explicitly warn that SSRIs may lead to psychotic decompensation and it is textbook knowledge that psychotic decompensation is linked to suicide.

But rather crucially, these warnings which were stronger than British warnings appeared against a general clinical understanding in Sweden that antidepressants as a group, and not just SSRIs, can provoke suicidality in the first weeks of treatment. The MCA may be interested to know that I have Arvid Carlsson the recent Nobel Prize Winner, and creator of the SSRIs, a Swede, on videotape stating categorically that it is well known that antidepressants can trigger suicidality in some people.

In my previous meeting and in correspondence with the MCA, I've also drawn attention to the fact that Ulrich Malt a professor of psychiatry from Oslo writing up an RCT with sertraline reported that: "One patient on sertraline committed suicide, and three others reported increasing suicidal ideation which prompted premature stop of the treatment, in contrast to just one case on mianserin and none on placebo. Since the introduction of the tricyclic antidepressants, it has been known by clinicians that TCA could increase suicidality in the first week. For this reason a close supervision of depressed patients given TCA was recommended". He went on to say that the new antidepressants (SSRIs) would it seemed also require monitoring during the early phases of treatment.

I think this MCA example of Sweden rather proves my point about the importance of creating an appropriate climate in which antidepressants are used if they are to be used safely.

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Page 7.

How Big a Problem?

I thought your letter struck a few odd notes when it mentioned that actually my figures might be even more significant than I had made them out to be. Does

the MCA think I am under some obligation to prove that these drugs cause suicide? I have to put it to the MCA, through you, that it is the market authorisation holders in the first instance who have a legal, moral and scientific duty to prove there is not a significant problem and it is the MCA's role to ensure that that a majority of disinterested assessments of the evidence would be likely to support such a claim.

My hunch is that most disinterested observers would agree there are grounds for concern – and that is all I need to establish. But let's push this point just a touch further. We are teetering on the brink of proving a general excess of suicidal acts on SSRIs compared to placebo. It had never been my intention to prove this, as there is a real risk that many disinterested observers would conclude that proof of this point should lead to the use of these drugs being restricted by more than warnings. I'm afraid that it is the response from both the MCA and the market authorisation holders that has pushed the argument in just this direction.

I think the MCA and its experts now have a real dilemma that the best statistical brains in the world can't rescue you from. It's this. I am happy to endorse the claims of the market authorisation holders that SSRIs can reduce suicidality in some patients, if not the impression these market authorisation holders give that there would be no more suicides in Britain if everyone just took SSRIs. I would imagine the MCA would endorse some limited claims in this area also. But if SSRIs reduce suicidality in some and we still end up with an excess of suicidal acts no matter what way the data is calculated – in terms of absolute numbers or patient exposure years – where does that leave the MCA in terms of its causal assessments?

Against this background, I would respectfully suggest to the MCA that no matter which way you massage the data, using patient exposure years or original trial data, you cannot establish that SSRIs are not likely to cause suicide. And if the MCA cannot do this, I have to ask why doesn't the MCA let people know that it cannot do this? Alternatively, please show me how you think you can do it.

The only way you could conceivably minimise the problem facing you is to deny that SSRIs save anyone from suicide. But the market authorisation holders of the SSRIs have sold these agents heavily on the back of claims that they will

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lower suicide rates. As the data from controlled trials now clearly indicates, while a smaller lucky subset of patients may be made less suicidal, reducing suicidality cannot be a general effect of these agents, what I would ask you does the MCA plan to do about what must now be categorised as inappropriate promotion – viz. claims that these agents will lower suicide risks?

Withdrawal & Dependence

I am happy to stand by my statements about withdrawal and dependence being synonymous. You can check my recent The Creation of Psychopharmacology from Harvard University Press, for a history of these terms and the social contexts in which they arose. The meanings behind these terms have changed so often that it would be possible to prolong a debate endlessly, by simply shifting from one set of definitions to another when the going gets sticky. Under the 1994 WHO definitions for example both the benzodiazepines and SSRIs cause dependence and WHO as of 1998 still talk about SSRIs causing withdrawal.

I suggest cutting to the chase. Lets accept the subset of definitions put out by WHO in 1998 or DSM IV that the MCA now seems comfortable with. My point was that using these definitions, the benzodiazepines do not produce dependence.

I don't mind whether the MCA re-categorises the benzodiazepines to non-dependence producing. But if the MCA is not prepared to do this, I would very much appreciate being informed of the basis on which the agency is distinguishing between the benzodiazepines and SSRIs. I cannot find any RCT or other systematic evidence to indicate that on any of the points outlined in your letter there is a difference between the benzodiazepines and SSRIs.

In recent months, paroxetine, sertraline and venlafaxine have all promoted themselves heavily for anxiety disorders with literature contrasting themselves to the dependence producing benzodiazepines. There is a clear implication, however one defines dependence, addiction or withdrawal, that the SSRIs are doing something different to the benzodiazepines. As the MCA has not provided me with any basis for distinguishing between the benzodiazepines and the SSRIs, I wonder could I ask the agency to indicate what it is prepared to do about these misleading claims currently being given by the market authorisation holders to patients and general practitioners up and down the country?

The likely reaction from most people in the street will be that we are playing with words here. The problem many patients face however is that many of them

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simply cannot stop the SSRI they have been put on. As the MCA concedes that withdrawal reactions happen on SSRIs, and that these can be severe, the agency must logically concede that there are some people that cannot stop treatment and others yet to begin who will not be able to stop treatment.

I don't care whether being unable to stop treatment is called addiction, dependence or something else but I do think that the MCA has a moral obligation to ensure that the labelling and the education of physicians as regards these drugs makes it clear to the patients about to start these drugs that some people may not ever be able to stop, once they start. I can't imagine that anyone thinks the British labelling of the SSRIs currently reflects this.

I can, however, imagine that the MCA response on this point will be that unless some group like the Royal College of Psychiatrists were to lobby to get a new set of words put into the labelling to specify whether patients can be guaranteed being able to stop a drug, that the agency would feel under no obligation to do anything. If this is the logic of the MCA position, could you tell me exactly what such a group would have to do to bring about such a change?

Your letter asks for evidence I have on the point of people being unable to stop treatment. There is abundant RCT evidence that has in some sense passed through the MCA of patients who have had serious problems halting SSRIs. On the basis of trial designs which involved a re-randomisation to placebo and an interpretation of the difficulties that these patients had as new illness episodes, the MCA authorised market authorisation holders to claim a benefit in the long term treatment of depression, even though the market authorisation holders had prior trial data, which indicated that the withdrawal symptoms even in healthy volunteers include anxiety, agitation, violent dreams and possibly even suicide.

As long as 6 years ago, one of the market authorisation holders, fearing the competition of another, was paying psychiatrists like me significant fees to sample our opinions on withdrawal problems from antidepressants. It would appear that at least in part on the basis of these surveys, this market authorisation holder then ran an advertising campaign about problems with withdrawal from antidepressants confident that clinicians would know which SSRI antidepressants were being referred to – despite advice from me at least that this would be a bad idea. How much evidence do you need?

The Credibility of the MCA

The position of the MCA is now so much at odds with both the facts on the

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ground and the clinical data, that I have to ask whether the agency makes any assessment as to whether handling issues in this manner is likely to lead to an erosion of the public trust in Government with the consequences we now perhaps see in the MMR case?

If the MCA is not worried about this issue, I am. Consider the sequence of events. I write about healthy volunteer data, the MCA responds with studies you call epidemiological that a secondary school student could have told you were not epidemiological studies. I seek clarification of the healthy volunteer issues, the MCA responds by giving me the assessment the market authorisation holders have made of their own studies. I draw attention to further data, and the MCA responds by selectively citing data from Sweden that few people other than the market authorisation holders cite, data that are necessarily by their very nature inconclusive.

I count 25 questions in this letter to add to the unanswered questions from the previous letter. I would appreciate if this letter along with the enclosed revised copy of the draft paper I sent you earlier could be forwarded to the members of the CSM: Professor AM Breckenridge, Professor I Weller, Dr M Armitage, Professor T Barnes; Professor J Caldwell, Dr R Calvert, Dr T Chambers, Professor J Chipman, Professor J Darbyshire, Dr M Donaghy, Dr J Forfar, Professor M Langman, Dr A Mackay, Professor J Midgley, Professor K Woodhouse, Dr P Wilkie, Dr P Wright.

Yours sincerely

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Director
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15 March 2002

Dear Dr Healy

Thank you for your letter of 8 March. Given the issues you raise in this letter, we would like to postpone the meeting at the MCA that was planned for 25 March. In place of this meeting, we propose a meeting with relevant experts from the Committee on Safety of Medicines and MCA staff to take place as soon as it is possible to arrange.

The assessment report on suicidal behaviour, which you have requested, will be sent to you in the next couple of weeks.

I hope that postponing our meeting at short notice does not inconvenience you. I will contact you as soon as I have a date for the expert meeting.

Yours sincerely

Miss S Wark
Senior Scientific Assessor
Pharmacovigilance Group
Post Licensing Division

Copy: Dr June Raine
Prof Stephen Evans
Dr Cheryl Key

Our Ref: DH/JT

21st March 2002

Miss Sarah Wark
Senior Scientific Assessor
Pharmacovigilance Group
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

Dear Sarah Wark

Many thanks for your letter of the 15th March. On first reading I was uncertain as to what you were actually proposing. A follow-up phone call from Ken Woodhouse has indicated that what you appear to have in mind is a meeting that would involve me being able to present a case or at least interact with members of the CSM/MCA. I'd be very happy to attend such a meeting.

I would go into such a meeting prepared to have my mind changed on the issues, and to have this change of mind recorded as part of the public record. Ken Woodhouse intimated that the CSM/MCA have a similarly open mind. Given this openness on both sides and given the possibility of an intermediate outcome, were the issues appear to be too complex to admit of a complete resolution, it would be best from my point of view if it were feasible to record the exchanges, either by actually tape recording the proceedings or else by having someone there with court reporter level typing or shorthand skills.

I cannot see that such a request would pose problems from a confidentiality point of view. I am at least as hamstrung by confidentiality constraints, as any of the MCA/CSM experts will be. My request has to do with covering what I interpret will be a scientific debate. I would be happy for you to review the draft and

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propose deletions should there be any problems.

Clearly there may be CSM deliberations afterwards in which I play no part and I am not proposing that any of this should be recorded in any way other than the way you record these things normally.

A possible benefit to the CSM of this arrangement is that experts who could not attend – Professor Woodhouse was uncertain whether he would be able to attend – could have a reference point afterwards.

Finally given what I interpret as the scientific debate nature of the meeting I wonder would it be possible to bring a colleague with me to the meeting. At this point in time I have no one in mind, I'm simply trying to establish whether in principle this would be acceptable or not.

I look forward to hearing from you and will try to do everything I can to facilitate such a meeting – if that is I'm supposed to be included.

Yours sincerely

David Healy MD FRCPsych

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Our Ref: DH/JT

8th April 2002

Alan Milburn
Secretary of State for Health
Department of Health
Richmond House
Whitehall
LONDON
SW1

Dear Mr Milburn

It is almost four months since I wrote to you on the question of missing suicidal act data from trials of olanzapine, an antipsychotic widely used in this country.

There are a number of factors that deepen my concern at your lack of response. Several days ago a copy of Parliamentary Health Magazine came in my post. This appears to have been edited by one of your colleagues Dr Ian Gibson and appears to have been heavily sponsored by some of the major pharmaceutical companies producing antipsychotics, notably Lilly, who produce olanzapine. The magazine attempts to capitalise on the publicity for the movie "A Beautiful Mind" and features a Lilly advertisement with Russell Crowe/John Nash in one of the archetypal scenes from the movie. Interestingly although in the movie Crowe/Nash says that he was doing rather well because of the new drugs, it now seems clear that Nash never had the new drugs and possibly didn't have any of the older drugs for the last 20 or 30 years.

One of the other adverts in this piece is for the Janssen Pharmaceutical Company features a child. For anyone who has any knowledge in the field, this image links up with a large scale series of clinical trials that Janssen and Lilly have been doing in children with their respective antipsychotics risperidone and olanzapine – children who don't in fact have schizophrenia.

My first question for you is whether there are any centres participating in any studies of olanzapine in either children or adults in the UK? If there are any centres, it seems abundantly clear, based on the scenario I outlined to you in my previous letter, that none of the subjects entering these studies could be giving informed consent to entry into the studies. Can I ask whether you think

it is within your brief to determine whether there are studies taking place in this country in which investigators may have been mislead by the company and as a result are not in a position to elicit informed consent from subjects they enrol into studies? The fact that some ethics committee may have approved such a study and the consent form that came with it would of course not be an adequate response to this new situation. Should ethics committees have this critical piece of missing data brought to their attention?

Part of my concern on this issue stems from possibility that such studies are being conducted in children. Six years ago I chaired a Roundtable Meeting for the British Association for Psychopharmacology on the issue of the use of psychotropic drugs in children. I wrote the recommendations from this meeting up and these were published. I still have the transcripts of the meeting. This was a meeting in which senior regulators from the United States and Europe were involved as well as professors of child psychiatry from a number of European countries, the United States, Canada and leading figures here in the UK. My concern in promoting this meeting was to ensure that children who could benefit from psychotropic drug treatment would be enabled to gain access to treatment. Only six years ago the climate of the times were such that children were at a real risk of not getting effective drug treatment for their conditions.

If you read the proceedings from this meeting it will become clear to you that there is in principle no need for any drug studies in children for either antipsychotics or for treatments for OCD for example. Research that is conducted in children or adolescents with such conditions will only produce a situation in which a drug company gains a license to vigorously promote their treatment for these conditions. It will not produce a situation in which clinicians then become able to use these drugs. There are only two things that clinicians could conceivably learn from such studies. First, that paradoxically a treatment, which works in adults doesn't work in children. Second, that there are particular toxicities in children that need to be factored in to any risk benefit assessment as regards treatment in children. In return for this right to create the conditions in which children who may well not need the treatments are more likely to end up on drug treatment, the very least market authorisation holders could be expected to do would be to make available critical safety data that arise from such studies.

Against this background, consider the studies conducted several years ago by Pfizer in children who had Obsessive Compulsive Disorder which were the basis for Pfizer applying for and receiving a license to market sertraline for OCD in children in this country. In these studies there were 248 subjects enrolled altogether, 187 in one OCD arms of the studies and 61 in an allied mixed depression/OCD arm.

If you chase the scientific literature in which these studies were reported you will only find reference to one suicidal act on sertraline versus none becoming suicidal on placebo. However Pfizer's expert report, submitted to the FDA in response to FDA questioning about rates of suicidal acts in these trials, makes it clear that there were in fact at least six children who became suicidal on sertraline.

Pfizer go to great efforts to justify these six suicidal acts. First they claim that four of these occurred in the 44 children who were apparently depressed. This however gives a 1 in 11 rate of suicidal acts on sertraline in children who were depressed, which is a 20-fold higher rate of suicidal acts than appear in the published adult literature of depressed patients being treated with sertraline. I would imagine few, if any, clinicians giving sertraline in this country to children who have either OCD or depression are aware that the only studies submitted to regulators contain such a high rate of suicidal acts. It is almost certainly not therefore the practice of clinicians in this country to inform the parents of patients that they've put on this drug that there is such a hazard.

Pfizer attempt to justify the frequency with which this is happening saying that suicidal acts are common in children who are depressed anyway. They are not this common. Furthermore there is a dose response relationship evident in these studies as well as a very clearly defined interval between dose escalation and the onset of the problem. In addition, if suicidal acts were this common in depressed teenagers, a conundrum arises. One of the justifications that Pfizer offer for treatment is that treatment will reduce suicide rates but if there are any cases of suicidal acts averted by treatment with sertraline, given the figures for suicidal acts that come out of these trials, there would must logically have been an even higher rate of suicide provocation that is initially apparent from the data.

In the OCD arm of the trial, two children apparently made suicidal acts on sertraline versus one on placebo. In the case of the adult studies with sertraline it is clear that 50% of the reported suicidal acts apparently occurring on placebo in fact occurred during the washout period of clinical trials and were not true placebo suicidal acts. There appear to be at least a 50% chance that the same applied in this particular study, which would give no suicidal acts on placebo.

Against this background can I ask you whether there are any studies being conducted with SSRIs in children in the country? Can I also ask you to determine whether the investigators conducting these studies are informed as to the rates of suicidal acts recorded in the only other studies submitted to regulators? If these investigators are not so informed, can I ask you what you intend to do about the situation?

One of the methods for investigators to keep themselves informed is of course to submit a Freedom of Information request to the FDA. Few clinicians in the UK are probably aware that it may be necessary for them to regularly access this invaluable mechanism for safeguarding the health and interests of British patients. Can I ask whether you think it would be timely, in the light of the studies outlined in this letter and this missing data from these studies, to inform UK clinicians about the procedures by which they might make FOI requests? Can I ask whether your department has ever given any consideration to the issue of who should fund such requests?

However, to return to the olanzapine studies, in the case of the studies lodged with the FDA, it is not possible to access the relevant data, as FDA reviews of this drug do not contain the data. The scientific literature furthermore is no

use to anyone in this area, raising the questions to whether it justifies being termed a scientific literature. The “science” is no use in the case of olanzapine because all the authors on the studies involving Lilly drugs are typically Lilly personnel. It is of little use in the case of risperidone or other novel antipsychotics as for example the lead investigator in many of these studies has since been jailed for a series of practices related to the recruitment of subjects to these very trials, regarding which it is so hard to get information.

My question, which remains unanswered from my previous letter to you, is whether you think this situation is in fact legally incompatible with prescription only arrangements? As no request for data or proprietary information of any sort was put forward in the previous letter I did not cover the letter with a request to have the question it raised under the Code of Practice. Given the lack of response, however, I would like you to regard this question and the other questions posed in this letter as matters to be answered under the Code of Practice.

As regards Parliamentary Health Magazine it was extremely depressing to see a new magazine like this launched as an apparent mouthpiece for pharmaceutical companies. Can I ask you where the idea for this magazine came from? What is the level of pharmaceutical company sponsorship of the magazine? Are any public monies being put into this magazine? What fees do Dr Gibson or other members of the editorial board get for a role in fronting the exercise? What fees do contributors get for writing the pieces? Who exactly writes the pieces - by writes I mean what the person in the street would regard as writing - that is who writes the first draft of the pieces, especially the pieces appearing in the Lilly supplement to this magazine.

Yours sincerely

David Healy MD FRCPsych

Department of Health

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30 April 2002

Dear Dr Healy

Thank you for your letter of 21 March 2002in relation to the proposed meeting of CSM experts to which you would be invited. I apologise if my letter of 15 March was unclear as to what was being suggested.

We have considered your proposal to record the meeting. As you say in your letter, the proposed meeting is to take the from of a scientific debate leading to an improved understanding of the available data and the respective positions of yourself and the CSM. As this is not a regulatory procedure we do consider that verbatim recording would be appropriate. We would be happy to share detailed minutes of the discussion.

We would be happy for you to bring a professional colleague and would be grateful if you would give us details of who you intend to bring in advance of the meeting.

I intend to arrange the meeting towards the end of June. I will confirm a date with you as soon as possible.

Further to your request for a copy of the paper considered by CSM, please find enclosed an edited version of this paper. As you will see, the paper has been edited under the exemptions outlined in the Code of Practice on Access to Government Information which place certain restrictions on the disclosure of information. I enclose a copy of the Code for your reference.

If you have a query about this letter, please contact me. If you are unhappy with our decision, you may ask for it to be reviewed. A senior member of the Agency who has not so far been involved with you request will undertake that internal review. If you wish to ask for a review, you should write to Dr June Raine, at the above address, in the first instance. If you remain dissatisfied, you may as a Member of Parliament to make a complaint on your behalf to the Ombudsman (known officially as the Parliamentary Commissioner for Administration) who may decide to conduct his own investigation.

Yours sincerely

Miss Sarah Wark
Senior Scientific Assessor
Pharmacolvigilance Group
Post Licensing Division

Copy: Dr June Raine
Dr Cheryl Key