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.

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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

Our Ref: DH/JT

8th April 2002

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