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Dear Dr Jamieson/ Ms Macnab

Ms Mcnab has asked me to comment on a section of a report prepared in the Toran Henry case by Dr Sabina Dosani, which purports to represent my position on the merits and risks of fluoxetine (Prozac). I have not been briefed on the details of Toran Henry's clinical state or the sequence of events in his clinical care, aside from knowing his age, and will not be commenting on these.

Qualifications

I am a Professor of Psychiatry at Cardiff University in Britain. In addition to being a medical doctor, specialized in psychiatry, I have a post-doctoral degree in psychopharmacology that centred on the role of the serotonin system in mood disorders and the effects of antidepressant drugs on this system. I am a former secretary of the British Association for Psychopharmacology, one of the largest national psychopharmacology associations in the world.

I have authored 20 books on physical treatments in psychiatry, over 150 peer reviewed articles, a further 180 academic pieces, and 50 book chapters. I have presented extensively on aspects of the history of psychiatry, pharmaceutical marketing and psychopharmacology at international meetings on all continents. A large number of these presentations have been in legal or medico-legal forums, and a large number have dealt with the topic of suicidality on antidepressants. I have written the standard history of the antidepressant group of drugs, published by Harvard University Press, and the only history of the SSRI group of drugs published by New York University Press. A curriculum vitae is attached.

I have testified in approximately 20 cases in which (SSRI) serotonin reuptake inhibiting antidepressants, including Prozac (fluoxetine) have been involved in cases of suicide or homicide, generally but not exclusively testifying that the drugs have been implicated. These have been cases in Australia, North America and Britain. I have been approached in perhaps a further hundred cases in which I have thought that the drug in question has not been involved or could not be shown to have been involved.

I have written reports in approximately 10 inquests in both Britain and North America; these reports have not aimed at offering a view as to whether the drug was involved in a particular case but rather alerting the Court to the potential that the drug might be involved and the implications of such an involvement for a possible verdict of suicide.

I realise that my first duty is to the Court. In this case, I have no involvement with the Henry family or their legal team, but have simply as noted above been asked to comment on a report by another witness in this case.

Dr Dosani's Report

Dr Dosani's report takes one article I have written on the topic of SSRI (selective serotonin reuptake inhibitor) antidepressants, of which Prozac (fluoxetine) is one, from among 22 peer reviewed articles specifically on this topic, and many other articles and somewhere over 50 presentations at international meetings also specifically on this topic, all of which make clear that my view is that SSRIs (and other) antidepressants can cause suicide. Dr Dosani's report based on a selective quotation from one article suggests that my view is that these drugs simply lead to suicidal acts and not to completed suicide. This is not my view.

The antidepressant group of drugs came into clinical use in the late 1950s. Within a year or two of first use, there was an emerging consensus that these drugs, while clinical very useful, could in some patients increase the risk of completed suicide (1).

When the SSRIs were launched controlled trials had become an important method of evaluating their clinical effects. Had these trials been meta-analyzed for suicidal acts, it is now clear, as I have shown in the paper Dr Dosani cites, that as of 1988 they would have shown a doubling of the risk of suicidal acts on SSRIs, compared with placebo (2). This rather than the message Dr Dosani offers is perhaps the key point to take from this particular paper.

Against this background, a series of articles between 1990 and 1992 describing an early onset dose-related emergence of suicidality on fluoxetine that cleared on discontinuation and reemerged on reexposure was not surprising (3). Using all standard causality algorithms, these studies of fluoxetine demonstrated a convincing causal link between treatment and adverse effect. The original article

described 6 nonfatal cases but omitted a death by suicide in a person aged 14 years with obsessive–compulsive disorder (4). King et al (5) described identical effects in children to those in adults.

While claiming that there was no significant difference in suicidal act rates between active treatment and placebo, all meta-analyses of clinical trial data from 1991 to 2005, in fact reported an excess of suicidal acts on active treatment[6]. The excess would have been greater but for the fact that these analyses included, under the heading of placebo, acts that happened during the pre- and (or) post-randomization phase of the trials analyzed (6).

The companies making Prozac, Aropax and Zoloft in other words have systematically sought to conceal the risks linked to treatment by manoeuvres that have no scientific justification – as reference 6 cited above makes clear.

In addition to company efforts to conceal the problems, there has been a clinical bias against recognizing that treatment might cause problems. A 2003 analysis of placebo controlled trials of antidepressants in anxiety concluded—on the basis of 11 suicides in 12914 patients on active treatment, compared with 0 suicides in 3875 patients on placebo—that anxiety was a risk factor for suicide (7). This conclusion points to a profound clinical bias against recognizing the risks stemming from treatment.

In 2004, the suicide risk of antidepressants came to the fore as linked to possible inefficacy of these agents in children, providing evidence for widespread failure to report trials and ghostwriting of those published. The US regulator, the Food and Drugs Administration (FDA) analysed the data from clinical trials in minors and confirmed a doubling of the risk of suicidal behaviours on active treatment, compared with placebo.

Randomized controlled trials (RCTs) offer some protection against the risks of confounding inherent in data from large uncontrolled cohorts. No antidepressant RCTs have been designed to look at treatment-induced suicidality. This means that unintended outcomes, such as suicidality, have in general not been properly monitored or recorded in these trials. Given this, deaths by suicide offer the least ambiguous outcome, suicidal acts a less certain outcome, and suicidal ideation a more ambiguous outcome.

The data from the review of suicidal behaviours in these trials posted by the British regulator in 2004 shows of a 2.62-fold increase in completed suicides (95% CI 0.89 to 7.81) and 2.4-fold (95% CI 1.63 to 3.63) increased relative risk in suicides and suicidal acts combined on active agents, compared with placebo (Table 1).

Table 1:
Suicides and Suicidal Acts in Adult Placebo Controlled Trials of Antidepressants

	Active Drug Suicides/ No. Subjects	Placebo Suicides/ No. Subjects	Active Drug Suicidal Acts/ No. Subjects	Placebo Suicidal Acts /No. Subjects
Citalopram	1/1320	1/0622	11/1320	5/0622
Escitalopram	0/2648	1/2088	06/2648	1/2088
Fluvoxamine	2/4186	2/3396	24/4186	10/3396
Mirtazapine	5/2618	0/0388	09/2349	3/0388
Sertraline	4/7169	0/5108	20/7169	8/5108
Venlafaxine	4/6153	0/2962	25/6153	8/2962
Paroxetine	1/8172	0/5391	16/8172	4/5391
Total	17/32,267	4/19,955	118/32,267	30/19,955

Data for all except paroxetine from Expert Working Group on the Safety of Selective Serotonin Reuptake Antidepressants 2004. www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1391&noSaveAs=1&Rendition=WEB (accessed 13 May 2006).
Data for paroxetine for adult depression trials (minus intermittent brief depression). Update April 5th 2006, Paroxetine Adult Suidality Analysis. gsk.com/media/paroxetine/briefing_doc.pdf (accessed 8th August 2007).

In 2006, FDA undertook a further analysis of the data from RCTs conducted in adults. Data from FDA's 2006 review of adult placebo controlled trials of antidepressants (Table 2) shows a 1.6-fold (95% CI 0.68 to 13.9) increased relative risk of death by suicide in people aged 18 to 64 years, compared with placebo. There was a 2.3-fold increased rate of suicidal behaviours in people aged 18 to 24 years, a 0.9-fold relative risk of suicidal behaviours in people aged 25 to 44 years, and a 1.75 relative risk of suicidal behaviours in people aged 45 to 64 years, compared with placebo.

Table 2:
Suicides in Adult Placebo Controlled Trials of Antidepressants
from FDA Review

	All Antidepressants Suicides/ No. Subjects	Placebo Suicides/ No. Subjects
18-24 Yr Olds	5/5,128	0/2,831
25-64 Yr Olds	3/53,133	2/29,854
Total	8/58,261	2/32,685

Stone M, Jones L (2006). Clinical Review: Relationship between antidepressant drugs and adult suicidality. Table 16 (p 26) & 18 (p 30). http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-index.htm,

It is sometimes claimed that there were no suicides in paediatric trials of antidepressants – that there were only suicidal acts or ideation. In fact it is more accurate to state that no suicides have been recorded. A large number of patients in these trials dropped out because of adverse events and were lost to follow-up and it is just not known if they went on to commit suicide or not.

It can be noted from table 2, that there was a marked excess of suicides in the FDA data for 18 to 24 year olds (which does not include all adolescent deaths by suicides from placebo controlled trials) compared with placebo. It would be imprudent therefore to discard the possibility that there were in fact suicides in the paediatric trials.

Another claim made about these data is that they reflect a reporting bias. Patients who become suicidal on antidepressants report their concerns to their doctors where patients on placebo do not. The data on suicides and suicidal acts in the tables above, which point to an increased risk of completed suicides and of suicidal acts, where there was no such increase in suicidal ideation in these same trials, suggest that this problem does not stem from a reporting bias and that to the contrary there is a bias against reporting SSRI induced suicidality.

Fluoxetine Risks & Benefits

In the course of clinical trials done in the 1980s to get fluoxetine on the market for adults, the trials undertaken by Lilly, the makers of Prozac, give the following figures for suicidal acts on fluoxetine compared to placebo.

Table 3
Suicidal Acts in placebo controlled trials of Fluoxetine

Study	Indication	Fluoxetine			Placebo	
		N	Suicide	Attempts	N	Attempts
1	DEP	55		0	56	0
2	DEP	45		0	45	0
3	DEP	21		0	19	0
4	DEP	639		1	107	0
5	DEP	285		0	78	0
6	DEP	247		2	248	0
7	DEP	30		0	30	0
8	DEP	76		2	62	0
	Total	1398		5	645	0

These data are in the public domain. They are laid out in an article authored by Charles Beasley and colleagues of Eli Lilly published in the British Medical

Journal in 1991. The data presented here have been adjusted in one respect in light of information from Brickler exhibit 1 in Fentress v Lilly that indicates that the 1 suicidal act coded by Lilly under the heading of placebo in the their 1991 paper in fact occurred during the washout phase of the clinical trials rather than on placebo. Its inclusion in the 1991 BMJ paper contravenes all pharmaceutical regulations, and good scientific practice.

If we analyse the data as presented here it will be obvious to all members of the Court, even those without statistical or mathematical expertise that the risk is significantly greater on Fluoxetine than on placebo. Infinitely greater.

If we include one suicide in the placebo group as Lilly did in their Beasley article, then analysing the results yields an increased relative risk of a suicidal act on Prozac compared to placebo of 2.31. The 95% confidence interval for this figure is 0.27 to 19.71. What this means is that while the data indicate that it is possible that Fluoxetine does not cause a problem, the scientific data as altered by Lilly to favour them, is consistent with a 19.7 fold increase in risk. And the scientific data – as altered by Lilly – also makes clear that the most probable relative risk is a 2.31 times increase.

The responsibility for clarifying whether or not a risk existed in 1991 lay with Lilly, who on the basis of these figures should have investigated this issue further. They chose not to do so.

The relevance of these figures to the current case is that they make clear that recent concerns about a suicide risk in juveniles are not something new. Fifteen years ago or more, there was clear clinical trial evidence of an increase in risk, along with the clinical reports noted above to show there was a risk in children.

In response to the argument that Prozac poses risks in susceptible individuals, it can be claimed that it has been approved for use in children and that therefore it offers benefits also.

The history of Prozac's approval for children runs as follows. The first key step was that in 1997 the FDA offered companies 6 months patent extension, worth over a billion dollars for submission of paediatric clinical trial data. This put a premium on undertaking trials in children and submitting them to the regulator. Companies have to submit 2 "positive" trials in order to be granted a license for use in children or for particular conditions.

There were two key Prozac trials. In clinical trials, it is customary to specify a primary outcome measure and if the drug fails to beat another drug or placebo on this measure the trial is negative. On this basis, the first study was a negative study noted as such by its FDA reviewer but almost everyone passes this off as a positive study (8).

The second study was even more surprising; in this, after the first week of the study, all children that had a bad reaction to Prozac were excluded (9). It is common in drug trials for a company to load the dice in their favour by excluding anyone who appears to do well during a placebo run-in before the study starts. But excluding anyone who was reacting poorly to Prozac during the first week of exposure was a novel development then – but one being copied since.

The drug was licensed for children on the basis of these two studies. Paxil, Zoloft and other SSRIs were not licensed shortly afterwards even though the data for these two drugs was quite comparable to the Prozac data. The difference was that by the time the regulators came to consider the data on these latter two drugs concerns about the risk that all SSRIs might trigger suicide had come into the public domain.

It was not readily possible for the regulator to go back on a prior judgment and remove approval from Prozac and this has created an incorrect impression that Prozac is in some way different to or better than other SSRIs for children. It is not.

Both the data from these trials and my personal clinical experience indicate that in some instances Prozac and other SSRIs may be helpful to children, but the likelihood of benefit is small and the risks considerable. When used, there should be close monitoring of their use and both subjects and their carers should be informed of the possible dangers and advised accordingly.

Conflict of Interest

Dr Dosani in her report, somewhat inexplicably, notes my conflict of interest statement at the bottom of the article of mine to which she refers. She fails to note that the other authors have no such conflicts of interest. It is highly unlikely that they would change their views of what the data in the paper show based on the possible conflicting interests of a single co-author.

She also fails to note that my conflicts include speaking engagements for, consultancies with and clinical trial work for most of the major pharmaceutical companies, all of which would presumably bias me in favour of these companies and their drugs.

Finally if she had hunted a little further she would have readily been able to find conflict of interest statements that include the fact that I have written reports for approximately 10 inquests and that these have all been done on a pro bono basis – as is this report.

Summary

There is a compelling case that Prozac (fluoxetine) can trigger suicide in susceptible individuals. There is little evidence that it is likely to be of benefit in

patients in Toran Henry's age bracket, and even less evidence that it is likely to be of benefit to males (this issue is not covered in the brief report above).

This is not to say that it has in fact caused suicide in this case. A determination of whether it has contributed substantially to a particular suicide, depends on the details of that case, including issues of duration on treatment, apparent response leading up to the suicidal event, dose of the drug, prior exposure to the drug or a history of familial responses. There may be contributory factors in which case the issue will be one of determining whether these were likely to have caused the suicide without the operation of any other factor.

If it is thought the drug contributed, a traditional verdict of suicide in the United Kingdom, which hinges on the ability of the person to form an intent to commit suicide in the normal fashion, would be correspondingly more difficult to sustain. I am not aware of New Zealand law or custom on this issue.

I would be happy to respond to any queries from the Court that this report occasions.

Yours faithfully

Professor David Healy MD FRCPsych

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