DAVID HEALY – JULY 30TH

Appendix2:
Data on Suicides and Homicides

There had been concerns about the risk of suicide and homicide on antidepressants drugs from the initial marketing of Prozac (fluoxetine) in the late 1980s. These concerns were based on convincing cases of challenge-dechallenge and rechallenge reported in the academic literature from 1990 onwards.

The history of these concerns is laid out in Let Them Eat Prozac. The development of the issues as they related to violence is laid out in Healy, Herxheimer and Menkes (appendix 7).

Renewed concern about the risk of suicide and homicide on antidepressant drugs was triggered by a BBC Panorama program in October 2002. This and a follow-up program led to an Expert Working Group set up by the UK regulator, the Medical & HealthCare Devices Regulatory Agency (MHRA) – the British equivalent of FDA.

The MHRA effectively banned the use of Paxil and Zoloft in children. This triggered a series of FDA hearings in February and September 2004 and December 2006 that led to Black Box warnings on antidepressants for anyone under the age of 25.

Both the FDA and MHRA reviews led to an accumulation of data on the risks of suicide and homicide along with the efficacy of antidepressants. I have used the FDA data in the Appendix on the Efficacy of Zoloft.

I use the MHRA data here because it gives a better insight on the risks linked to homicide and to the withdrawal period. The MHRA review was triggered by concerns about Paxil, a sister SSRI to Zoloft and the GlaxoSmithKline's submission to the regulator was accordingly more comprehensive than for other drugs and includes data on violence. There is no reason however to believe that the findings on Paxil do not apply equally to Zoloft.

The data on suicide is pertinent to the risk of homicide linked to taking SSRI drugs because the same mechanisms – akathisia, emotional blunting and psychotic decompensation – give rise to both. In one case the violence is directed inwards and in the other outwards.

As it transpires James Holmes appears to have had a personality type (an obsessive personality) that made homicide rather than suicide more likely.

Regulatory DATA on Suicides and Suicidal Acts

In 2003, the United Kingdom regulator asked companies for all data on suicides and suicidal acts. This initiative produced the data below. Lilly initially refused to offer data on Prozac.

The figures in Table 1 give a relative risk of completed suicides of 2.62 where the 90% Confidence Interval (C.I.) is 1.05, 6.54, and the 95% CI 0.88, 7.79

The relative risk for completed suicides and suicidal acts combined is 2.80 with a 90% C.I of 2.10, 3.90, and 95% C.I. of 1.88, 4.15

Table 1:

United Kingdom Expert Working Group Suicides & Suicidal Acts
Data on Paroxetine from GSK May 06 analysis

Drug	Suicides / No Patients	Placebo Suicides	Suicidal Acts / No Patients	Placebo Suicidal Acts
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	1/8058	0/5266	17/8059	4/5266
Suicide Total	17/32,153	4/19,830	119/32153	30/19,830
Suicide & Act Total			136/32,153	30/19,830

These figures do not stand in isolation. They come supplemented with convincing clinical reports of individuals becoming suicidal on these drugs, where the problem clears up when the drug is discontinued, and reappears when the original drug or a related drug is introduced.

There are a greater number of clinical reports of this type for Prozac than there is for Zoloft (sertraline) but this is likely to be an artefact of the sequence in which these drugs were introduced to clinical practice and the fact that sertraline was used less frequently than Prozac.

The combination of these clinical reports and the figures above show that, pretty well beyond a shadow of doubt, antidepressant drugs including sertraline have the capacity to lead patients to commit suicide or a suicidal act who would not have done so had they not been on treatment. Treatment appears to have the capacity to disturb the balance of an individuals mind and this raises the question as to whether the disturbance was such that it makes a verdict of suicide inappropriate.

As noted above, a further point is that in clinical trials of healthy volunteers with these agents healthy volunteers who can be presumed to be at no risk of suicide have become suicidal on SSRIs. This is particularly true of sertraline (See Appendix HV).

This crisis in 2003 and 2004 was triggered by Study 329, a study conducted of Paroxetine in adolescents who were depressed. Because of this the submission from GlaxoSmithKline (GSK) to the regulator was particularly detailed and most of this submission in due course entered the public domain.

This body of data for one of the SSRI drugs is the most comprehensive we have. It includes data on “hostile” acts in addition to suicidal acts and also includes data on the 30 days withdrawal period after treatment is stopped. Both of these factors are of importance in this case.

Having analyzed the data, the FDA had the view that the SSRIs could be treated as a group – that is that the data for Paxil were likely to apply to Zoloft and vice versa.

The data on Paxil is laid out in Tables 2 – 9.

Table 2:
Incidence of suicide-related events by treatment:
adult placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio (95% C.I)
Overall	26/8481 0.307%	8/5808 0.138%	2.22 (1.0, 4.91)
Depression	16/3421 0.467%	3/2117 0.142%	3.29
Non-Depression	10/5060 0.198%	5/3691 0.135%	1.466

Table 3:
Incidence of suicide-related events by treatment:
pediatric placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	7/738 0.95%	0/647	Infinity (1.65, Inf)
Depression	6/348 1.72%	0/285	Infinity
Non-Depression	1/390 0.26%	0/362	Infinity

Table 4:
Incidence of suicide-related events by treatment:
all placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	33/9219 0.36%	8/6455 0.124%	2.90 (1.34, 6.25)
Depression	22/3769 0.584%	3/2402 0.125%	4.67
Non-Depression	11/5450 0.201%	5/4053 0.123%	1.63

Table 5:
Incidence of hostility related events by treatment:
Adult placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	9/8481 0.106%	0/5808 0.0%	Inf (1.76, Inf)
Depression	1/3421 0.029%	0/2117 0.0%	Inf
Non-Depression	8/5060 0.158%	0/3691 0.0%	Inf

Table 6:
Incidence of suicide-related & hostility events by treatment:
all placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	43/9219 0.456%	8/6455 0.124%	3.68 (1.73, 7.82)
Depression	24/3769* 0.637%	3/2402 0.142%	4.45
Non-Depression	19/5450 0.349%	5/4053 0.135%	2.56

* Plus one pediatric hostility event in 30 days post taper.

The true figure is likely to be higher as events in the 30 post taper phase were not recorded systematically in early trials. It is also the case that events in real life may be quite a bit higher than this as subjects are stopped or stop abruptly from a 20 mg dose or higher, because no-one has warned them about the potentially lethal risks from withdrawal.

Table 7:
Hostility Events in Adult & Pediatric Placebo Controlled Trials

	Paroxetine	Placebo	Odds ratio	
Overall	51/9219 0.586%	20/6455 0.310%	1.89	
Depression	18/3799 0.474%	8/2402 0.333%	1.42	
OCD	19/737 2.580%	5/470 1.064%	2.43	
Anxiety	12/3823 0.314%	7/3404 0.206%	1.52	
PMDD	2/760 0.3%	0/379 0.0%	Inf	

Table 8:
Hostility Events in Adult & Pediatric Placebo Controlled Trials
on Therapy & in Withdrawal Phase

	Paroxetine	Placebo	Odds ratio	
Overall	60/9219 0.651%	20/6455 0.310%	2.10	
Depression	20/3799 0.527%	8/2402 0.333%	1.58	
OCD	19/737 2.580%	5/470 1.064%	2.43	
Anxiety	16/3823 0.419%	7/3404 0.206%	2.03	

These events occur in both depression and non-depression trials and therefore cannot be put down to any one disorder.

The evidence for violence (hostile events) seems clearer in trials for non-depressive indications, suggesting that these later primarily anxious patients when activated or otherwise altered by treatment may act out and injure others rather than themselves.

Combining suicide related and hostile events suggests that the overall numbers of events that can be linked to treatment induced disturbance is broadly comparable across indications but it seems clear that non-depressive conditions such as OCD give rise to hostile events where depressive conditions give rise to suicidal events. In the former case the drug induced violence is directed out while in the latter case it is directed inwards.