Notes on June 19, 1991 Review and Evaluation of Clinical Data, Original NDA 0-31, Paroxetine (Aropax) Safety Review

In 1991, Martin Brecher, M.D. conducted a SKB-sponsored review of data from trials to determine the safety of paroxetine and prepared a report dated June 19, 1991. The conclusions from this review were important because Paxil (paroxetine) was approved for use for depression in adults in December, 1992 based on them.

Later, when controversy erupted over Study 329 for use of the same drug in adolescents, nobody questioned whether or not the drug had truly been proven safe and effective for adults. This was unfortunate because, in fact, what the data actually show is that paroxetine was not really effective, and was associated with significantly more suicidal events. Other behavioural disturbances were not investigated, and the clear evidence that the drug was associated with a greater incidence of suicidal behaviour was hidden through strategies, explained below.

The data from Dr Brecher's review is shown as it appears in the report in the table below:

Data Table from Paroxetine trials reported June 19, 1991			
	Paroxetine N = 2,963 1008 P.E.Y.[1]	Placebo N = 554 72 P.E.Y.	Active Control[2] N = 1,151 218 P.E.Y.
Completed Suicides No. (%) No./P.E.Y.	5 (0.17) 0.005	2 (0.36) 0.028	3 (0.26) 0.014
Attempted Suicides No. (%) No./P.E.Y.	40 (1.3) 0.040	6 (1.1) 0.083	12 (1.0) 0.055
Suicidality Reported as an adverse event No. (%) No./P.E.Y.	13 (0.4) 0.013	2 (0.4) 0.028	5 (0.4) 0.023
[1] P.E.Y. = patient exposure years [2] The active control group comprised foreign studies of various antidepressants, including paroxetine and tricylics			

This data purports to show a lower rate of completed suicides, suicide attempts and suicidal ideation than placebo, and lower that the "active control" group, which included paroxetine, other antidepressants, and placebo. Taking only the percentages at face value, one would have to conclude that there was no evidence to flag safety concerns with paroxetine.

A closer inspection of the data reveals some odd observations, some of which were subsequently investigated by independent experts.

One 55-year old woman was murdered while on paroxetine. Had the investigator been interested in actually understand the impact of paroxetine on behaviour, they might have been interested in the circumstances related to this violent event.

The review describes 59 "additional" suicide attempts, clearly not ascribed to treatment. Of these 14 were U.S patients, i.e. in the drug trial. Of these, 12 were on paroxetine. The other 45 cases were from the active control trials in Europe. "The 45 foreign suicide attempts include 30 paroxetine patients, 13 patients who received an active control and 2 placebo patients."

No Valid Control Group

In experiments that seek to isolate the effect of one variable, such as the effect of taking paroxetine on suicidality, the use of a control group is common. The control group is typically matched with the treatment group on all possible variables except the one of interest. In this study, the active control group was meant to represent other antidepressants, since there was also a placebo group. The fact that a significant percent of the "active control" was on the same drug as the treatment under study was highly questionable methodology, further compounded by the fact that patients in the studies used as active control were also receiving "active controls" within the comparison studies, and this review does not specify which drugs those people were taking.

For this reason, a reader cannot legitimately take comfort from noting that the high number of suicidal acts in the paroxetine group seems to match the "control" and thus may be due to some factor other than the drug, such as depression. The active control group, and most of the subjects who committed suicidal acts within that group, were under the influence of paroxetine. Therefore, the active control group is not a control at all and comparison with it is not meaningful.

Counting Suicide Attempts during Washout Period as Placebo

According to Dr David Healy, "trial data from submissions to the U.S. Food and Drug Administration for agents licensed as antidepressants during the 1990s, have been adapted from Khan, Warner, and Brown (2000). The data have been modified in the light of reports obtained under freedom of information provisions (Brecher 1991; Lee 1990; 1991), which indicate that **more than 50% of the suicidal acts categorized as occurring while a patient was on placebo during trials of** sertraline and **paroxetine** in fact occurred during the placebo washout period."[1] (bolding added)

"Manipulation of data

Although data submitted to the FDA show an excess of suicides with every antidepressant licensed since 1987 compared with placebo, this simple but crucial finding continues to be obscured. When presenting

[1] Are Concerns about the Ethics of Placebos a Stalking Horse for Other Issues? By David Healy, The American Journal of Bioethics 2.2 (Spring, 2002) 17-19

data on fluoxetine, sertraline, **and paroxetine** to both regulators and journals, the manufacturers included a series of suicidal acts that happened in the run-in phase before patients were randomised, presenting these as a post-randomisation placebo group."[2] (bolding added)

Denominator Adjustment

This was not the only way that the data was manipulated. In order to further disguise the higher rate of attempted suicides in the paroxetine group, the data was measured in "patient observation years". Under this scheme, suicide attempts become a rate over time, with the inclusion of high-risk, low risk and no risk periods considered together. That is, the longer a subject was observed the lower the "rate" to which any suicidal act would contribute. By observing the paroxetine group longer than the placebo group, the study pulled down the "rate" in terms of observations years for the paroxetine group to be lower than that of the placebo group.

Dr Healy commented about this strategy with respect to the 1991 review of sertraline (Zoloft). His comments relate to another study but are applicable to Dr Brecher's review of paroxetine:

"These data can be analyzed by absolute numbers or patient exposure years. If analyzed by absolute numbers there is a statistically significant increase in the number of all suicidal acts on paroxetine compared to placebo and a statistically significant increase in suicides and suicidal acts on all investigational agents as a group compared to all acts on placebo as a group. If washout data are amalgamated with placebo data, the denominator must be adjusted accordingly, and this yields a statistically significantly greater risk on sertraline compared to "placebo." "[3]

Even reading the study and the methodology, it is clear that something is very wrong with concluding that paroxetine is not associated with a higher rate of suicide. However, to see this clearly requires only that the manipulations noted above be corrected, and then the true results examined.

Note: In the REVISED table below, the following 3 adjustments were made:

1. Suicides (2) and attempts (3) during run-in phase later attributed to placebo group have been removed.
2. The 14 "additional" suicide attempts, 12 of which occurred in subjects taking paroxetine (1 on placebo) but which were not counted were added into the data. It is not clear why these attempts were not counted; perhaps for the same reason as the 15 additional completed suicides in the active control group, which appear not to have been included because "none of the deaths were attributable to overdosage of paroxetine."
3. The column with comparison to "active control" does not represent a real control, as explained above, and so has been eliminated.

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[2] Did regulators fail over selective serotonin reuptake inhibitors? BMJ 2006; 333; 92-95, by David Healy, July 8, 2006

[3] Are Concerns about the Ethics of Placebos a Stalking Horse for Other Issues? By David Healy, The American Journal of Bioethics 2.2 (Spring, 2002) 17-19

REVISED Data Table from Paroxetine trials reported June 19, 1991, Including Adjustments (see Note)		
	Paroxetine N = 2,974	Placebo N = 551
Completed Suicides		
Number	5	0
Percent	0.17%	0.00%
Attempted Suicides		
Number	52	4
Percent	1.85%	0.73%
Total Suicidal Acts		
Number	57	4
Percent	1.92%	0.73%
Rate	1 in 52	1 in 138
Suicidality Reported as an adverse event		
Number	13	2
Percent	0.4%	0.4%

From this table it is readily apparent that the true rate of suicidal acts is just over 2.5 times as high in the paroxetine group as the placebo group, in a sample large enough that this difference would be considered very significant by any standard.

Brecher concluded that "Together the safety and efficacy data allow for the conclusion that paroxetine is safe and efficacious and approvable for marketing."

The FDA response by Tom Laughren notes that: "The safety and efficacy findings for paroxetine were presented to the PDAC[4] on this date (10-5-92) and they unanimously agreed that Paroxetine has been demonstrated to be safe and effective."

[4] Psychopharmacologic Drugs Advisory Committee of the FDA