SPECIAL REPORT

Court Filing Makes Public My Previously Suppressed Analysis of Paxil's Effects

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In late 1999 I was asked by attorney Don Farber to be the medical expert in a product liability case brought by the family of Reynaldo Lacuzong against the drug company Glaxo SmithKline (GSK) in California. Mr. Lacuzong was a machine operator with no prior history of serious mental illness, violence, or suicidality before he was prescribed a relatively small dose of 10 mg of Paxil (paroxetine). Almost immediately after starting the Prozac-like selective serotonin reuptake inhibitor (SSRI) antidepressant, he developed akathisia—an inner agitation accompanied by a compulsive hyperactivity—as well as other manic-like signs of irritability and anxiety. Antidepressant-induced akathisia is known to be associated with violence, suicide, psychosis, and an overall mental deterioration (American Psychiatric Association, 2000, pp. 800–802). Depression with drug-induced agitation can produce similar results. On the third day of taking Paxil, Mr. Lacuzong drowned himself and his two small children in a bathtub.

As a medical expert, I was empowered by the court to examine hundreds of cartons of drug company files contained in GSK's sealed record room. These files included Food and Drug Administration (FDA) correspondence and all of the company's worldwide clinical trials and adverse drug reports for Paxil.

On July 21, 2001, my report in the form of an affidavit was sent to the judicial arbitrator in the case. It addressed GSK's practices in the development and marketing of Paxil, and in particular its alleged withholding or manipulation of information about the drug's dangerousness. Based on GSK's proprietary files that have to this day never been made public, my report examined many factors, including (a) how quickly after the first dose can Paxil cause severe adverse reactions; (b) the actual rates of akathisia; (c) the actual risk of overstimulation causing agitation, irritability, and manic-like symptoms; (d) the actual rates of suicidality in adults; and (e) promotional claims made for the drug.

The case against GSK was eventually "resolved" to the satisfaction of GSK and the Lacuzong family. GSK denied and continues to deny all of the allegations of negligence in developing and marketing Paxil. My impression is that a substantial amount of money was involved in the resolution of the case, although the amount was not disclosed. GSK at that time refused to unseal its records or to allow me to make public my findings, regardless of their significance for the FDA, medical profession, and public health.

On June 23, 2005, my report in the Lacuzong case was filed as a part of a motion in another Paxil case, *Moffett v. Glaxo SmithKline*, in the United States District Court for the Southern District of Mississippi. Because it was filed in the public record, my report is now

available to the public, and I am able to comment on the details. The complete version appears on my website *www.breggin.com*. The report should prove useful to the FDA, health practitioners, scientists, researchers, attorneys, consumers, and anyone concerned about how drug companies function in the development and marketing of their products.

In the meanwhile, the FDA has recently acknowledged many of my original observations about the stimulating effects of all of the SSRIs like Paxil and Prozac, as well as other new antidepressants such as Effexor. I first warned about these effects in *Toxic Psychiatry* (Breggin, 1991) and then in subsequent peer-reviewed articles and books (see for example, Breggin, 1997, 2001, 2003). As of 2005, the FDA now requires the drug manufacturers to place elaborate warnings on their labels concerning the potential of these drugs to cause stimulating effects, including agitation, anxiety, irritability, emotional lability, aggression, hostility, and mania. The labels must also include a warning about increased suicidality in children. Without coming to a scientific conclusion, the FDA has also warned about and begun to investigate the problem of antidepressant suicidality in adults. Among other things, my report in Lacuzong deals in detail with antidepressant-induced suicidality in adults and how the drug company handled that data.

The following excerpts include Sections XI–XIV of the report that can be found in its entirety on *www.breggin.com*. These excerpted sections focus on Paxil-induced suicidality in adults—the subject of a current FDA investigation. Other sections deal with numerous issues including FDA correspondence criticizing the company, advertising and promotion, the drug label, rates of adverse psychiatric effects after only a few doses, akathisia, and the stimulant or activation continuum. A lengthy, detailed summary and conclusion can be found in the complete report.

EXCERPTS FROM THE REPORT AND AFFIDAVIT OF PETER R. BREGGIN, MD, IN THE CASE OF *LACUZONG V. GLAXO SMITHKLINE*

XI. Evaluating Errors in the Compilation of Suicide Data

1. Suicide Attempts: U.S. Clinical Trials. A total of 14 suicide attempts were reported in the U.S. clinical trials. None were completed suicides. An overview is presented in Table 1 (PAR Safety Summary 20-Nov-1989, p. 203, stamped p. 297).

Note that the rate for suicide attempts on paroxetine approaches 1%, which the FDA considers "frequent." Also note that the rate for suicide attempts on paroxetine is 3.8 times higher than for placebo and 3.6 times higher than for the comparison antidepressants (tricyclics). Furthermore, the suicide attempt on imipramine is listed as a "possible suicide" (p. 211, stamped 306).

In regard to the onset of suicide attempts, one patient (117A-004, p. 200, stamped 291) cut himself on the third day of Paxil: "One day 3 this patient attempted to slash his wrists and abdomen and was withdrawn from the study." Also note that case 647 002 (above) made attempts on days 1, 8, and 15.

This all-important United States data is not presented in the text of SKB's (now Glaxo SmithKline or GSK) April 29, 1991, report for the FDA, "Suicidal Ideation and Behavior: Analysis of the Paroxetine Worldwide Clinical Database." To hide the U.S. data within worldwide data was extremely misleading.

TABLE 1. Overview of Attempted Suicide: U.S. Data[a]

	Paroxetine *N* = 1,562	Placebo *N* = 497	Other AD[b] *N* = 464
Drug overdose (imipramine)	9	0	1
Defenestration	2	0	0
Self-inflicted injury	1	0	0
Suffocation	0	1	0
Totals	12 (0.77%)	1 (0.20%)	1 (0.21%)

[a]Table numeration added. [b]AD = antidepressant (imipramine).

2. Leaving Out Two Non-U.S. Suicide Attempts. There is evidence that some suicide attempts were omitted from the calculations sent to the FDA. In the report "Adverse experiences which occurred during active treatment. Non-US Phase II-III studies" (Appendix V.1), I located two patients that appear to have been left out of the summaries of non-U.S. suicide attempts. Case 647 002 (Volume 420, p. 157) made three suicide attempts on days 1, 8, and finally on day 15, when the drug was stopped. The first two were considered "related" and the third "possibly related." Also, case 1 113 120 (Volume 420, p. 157) was considered "definitely drug related." These two attempted suicides do not appear in the complete list of 40 in the April 29, 1991, suicide report (pp. 17–18), or in any other source that we have located. This brings the total of non-U.S. suicide attempts to 32.

3. Leaving Out Two Non-U.S. Completed Paxil Suicides. Two non-U.S. *completed* suicides appear to have been left out of all official reports, including the April 29, 1991, suicide report. The missing two are found in Appendix 5.4.2—Summary of Deaths Occurring in Paroxetine-Treated Patients (unnumbered page, SB 0000044). See Table 2 for the seven cases with their complete descriptions under the heading of "Cause of Death and Comments."

TABLE 2. Seven Suicides Listed Under "Cause of Death and Comments"[a]

Case Number	Duration, days	Cause of Death and Comments
DFG124/12*	?	Suicide: Method—Overdose with doxepin
HDUK13/26*	144	Suicide: Method—Hanging
29060/149*	18	Suicide: Method—Overdose . . . 6 days after discontinuing paroxetine
HP-82-47/3*	47	Suicide: Method—Drowning
058/022**	?	Suicide: Method—Unknown
083.003.1090**	8	Suicide: Method—Hanging
2206.005/605*	150	Suicide: Hanging

[a]Table numeration and heading added.

Since only five non-U.S. suicides are listed in any of the tables or reports, it is apparent that there are two missing. *Two more should be added to the suicide completed counts (see below)*. I cross-checked these numbers and have found that five are included (see single asterisk [*]) in the official lists of suicides. We need to obtain the two missing cases (see double asterisk [**]).

Appendix 5.4.2 appears to be based on the Summary Basis of Approval data (SBA), which draws from the NDA. It was part of a list of 15 deaths described in an August 25, 1992, memo entitled "Miscellaneous Requests" from Thomas P. Laughren, MD, of the FDA to Thomas Donnelly, Jr., PhD, of SKB. He notes he is adding one, 083.003.1090, from the safety update, which is also a part of the original NDA.

We need to inquire about any further correspondence or corrections concerning this list.

4. Adding Two Placebo Run-In Completed Suicides to the Non-U.S. Studies. In the suicide report the following two suicide cases are listed: 7119.062 and 7119.009. However, both of these occurred during the placebo run-in (also called placebo wash-out) phase. The cases can be found summarized in the PAR Safety Summary 20-Nov-1989 (7119.062 on p. 202c, stamped p. 296, SB 0000544; 7119.009 on p. 202b, stamped p. 295, SB 0000543).

There is no question that placebo run-in is a euphemism for placebo wash-out. In the April 29, 1991, suicide report a footnote states, "Suicides were committed during the placebo wash-out phase of an active control study. These two acts were committed 2 days and 7 days prior to the baseline evaluation, i.e., -2 and -7 days."

Adverse drug effects are never reported from the placebo wash-out phase. Indeed, suicide and suicide attempts are probably the only supposed adverse drug effects reported from the placebo wash-out. The placebo wash-out period is not a part of the controlled clinical trials. It occurs before the randomization. All patients are lumped into them. Furthermore, many of the patients are very likely suffering from withdrawal from other drugs they were previously taking for depression.

The inclusion of these suicides into the placebo comparison group was misleading to the extreme. They must be removed from calculations pertaining to a comparison between suicides on Paxil and on placebo.

5. Including Two Placebo Run-In Suicide Attempts in Non-U.S. Studies. The worldwide data for suicide attempts also include placebo run-in data. This is confirmed in Table XI.21, Attempted Suicides and Overdoses—Worldwide Data (PAR Safety Summary 10-Nov-1989, p. 206, stamped page 300, SB 0000548). Exactly as in the case of including completed suicides from the placebo wash-out phase, the inclusion of two placebo run-in patients in the non-U.S. suicide attempt category is misleading and fraudulent. The two placebo run-in patients must be excluded from the non-U.S. and worldwide data.

XII. Re-Analysis of the Suicide Data

1. Re-Analyzing Non-U.S. Completed Suicides. Various SKB documents, including the April 29, 1991, suicide report, only list five completed suicides. As described above, we have found an additional two for a total of seven. Therefore the completed suicide rate for Paxil is seven in a population of 1,401 patients for a rate of 0.499%.

As also described above, we found that two placebo wash-out completed suicides were wrongly counted in the suicide rate for placebo. The true occurrence for completed suicides

in the placebo group is 1 in 544 for a rate of 0.180%. The suicide rate on Paxil is therefore 2.7 times that on placebo.

2. Creating a New Category of Suicidal Behavior or Suicides, Attempted and Completed. The 5 completed Paxil suicides (acknowledged by SKB) must be added together with the 42 (from Table XI.21) attempted suicides to create the category of *Suicidal Behavior* or *Suicides, Attempted and Completed*. The category contains, at the least, 47 cases of suicidal behavior (42 + 5 = 47). SKB's analysis obscures and hides the actual rate of suicidal behavior by evaluating attempted and completed suicides as separate entities. We also need to know the overall rate of suicidal behavior.

Based on this analysis, the rate of suicidal behavior is 47 out of 2,963 for a rate of 1.58%. If we add the additional two completed suicides that seem to have been left out of the data, we now have 49 (47 + 2 = 49) suicidal behaviors out of 2,963 for a rate of 1.65%. Whether we use the 1.58% figure or the 1.65% figure, this combined category of suicidal behavior is far more meaningful than the split categories of suicide attempts and suicides completed. It was grossly misleading not to create a combined category.

The above calculations were based on the assumption that there were 42 suicide attempts as indicated in the original NDA. If we added the two suicide attempts that appear to have been left out of the data, there are at least 44 total suicide attempts. The corrected total for combined suicidal behavior on Paxil then becomes 51 (44 suicide attempts + 7 suicides = 51). Fifty-one out of 2,963 produces a rate of 1.72% for suicidal behavior on Paxil.

3. Re-Analysis of the Worldwide Comparisons for Suicide Attempts. We have already found that two attempted suicides on Paxil were apparently not included in the worldwide calculations. As described above, this raises the original NDA figure from 42 to 44 for attempted suicides out of 2,963 cases, for a rate of 1.48%. In addition to undercounting suicide attempts on Paxil, SKB overcounted placebo-related suicide attempts.

For placebo, three suicide attempts are listed. But as we have documented, the correct number for placebo suicides is only one for the worldwide group. The other two suicide attempts were placebo wash-out cases. That makes the placebo suicide attempt rate a mere 1 out of 554 for a rate of 0.18%.

Thus the corrected comparison indicates a 1.48% rate of suicide attempts on Paxil compared to a 0.18% rate of suicide attempts on placebo worldwide. Thus suicide on Paxil was 8.2 times higher than the rate of placebo.

4. Hiding the Frequency of Suicide Worldwide in the April 29, 1991, Suicide Report. In the "Discussion and Conclusions" of the April 29, 1991, report (SB 0000819, report pp. 12–13) states the following conclusion:

> The incidence of attempted suicides did not differ substantively among the three treatment groups (paroxetine, placebo, active controls).

However, the report never deals with the U.S. clinical trials as a separate entity. They show a significantly higher suicide attempt rate for Paxil than for the other antidepressants or placebo.

Furthermore, there is no overall category of Suicidal Behavior or Suicides, Attempted and Completed. Therefore, when counting suicide attempts, suicides completed are

excluded, badly misrepresenting the data. In addition, there appear to be two unreported suicide attempts and six unreported completed suicides worldwide.

Finally, as already noted, the worldwide figure is distorted by miscounts in both the Paxil and placebo categories.

The April 29, 1991, suicide report also contains different numbers from the NDA. We find that the total number of paroxetine suicide attempts has been inexplicably reduced from 42 in the NDA to 40 two years later, while the total number of placebo suicide attempts has been inexplicably increased from 3 to 6. These manipulations of course favor the interest of the drug company. The April 29, 1991, report in fact states that it has based itself on the original NDA data, that is, "using data which were submitted at the time of the New Drug Application for paroxetine" (p. 1, SB 0000003). But the NDA data differ to the disadvantage of SKB.

XIII. Follow-Up of U.S. Suicide Attempt Cases

I was able to track many but not all of the individual case numbers listed in the compilation of suicide attempts (Table XI.19 from PAR Safety Summary 20-Nov-1989, p. 203, stamped p. 297). The cases were found separately in a book-length document, "Narrative of US Patients with Potentially Clinically Significant Events" (Appendix I.1 of NDA 20031, 409, November 1989). They indicate that the suicide attempts often occur in a context of various other distressing adverse drug reactions but sometimes occur without any other serious adverse effect. This contrasts with the non-U.S. data on completed suicides which indicate that the five we could track were all related to central nervous system adverse drug reactions, including akathisia and stimulation.

(1) 02-04-089 (p. 37). This patient had been taking Paxil 20 mg for 40 days. "Adverse clinical experiences . . . were moderate dizziness and lack of energy (probably drug related), and moderate headaches (possibly drug related)."

(2) 04-01-009 (p. 192; SB 0000571). This patient elected to switch from a tricyclic to Paxil. After 193 days the patient was taking 50 mg and experienced the following adverse reactions:

"clenching of teeth," dry mouth, decreased libido, inability to achieve orgasm, nausea, diarrhea, urinary retention, "weakness in legs," "twitching of left cheek," lightheadedness, anxiety, "speedy feeling," dizziness, "tingling," lethargy, headache, and decreased concentration.

(3) 04-02-056 (Volume 409, p. 260). This patient was taking Paxil 40 mg and at 19–20 days made self-inflicted scratches. The patient was given ECT [so probably experienced a worsening of depression]. Other than dry mouth, no other ADRs were reported.

(4) 04-06-96. This patient was on 30 mg of Paxil for 116 days. The patient could not be located in the "Narrative of US Patients with Potentially Clinically Significant Events."

(5) 05-01A-030 (Volume 410, p. 65). This 23 year old patient was taking Paxil 50 mg and attempted suicide twice. The two attempts were counted only once. "The patient required hospitalization because of excessive ethanol use with violent and unpredictable behavior." She intentionally overdosed.

(6) 05-01A-075. This patient was a 37 year old female taking Paxil 40 mg for more than three years. She was not located in the "Narrative of US Patients with Potentially Clinically Significant Events."

(7) 05-02B-019 (Volume 410, p. 124). This patient was taking Paxil 50 mg for 57 days when the overdose occurred. "Adverse experiences reported during the study were

mild rash, diarrhea, 'shakiness' (possibly drug related), and an overdose." She took 20–50 unknown pills and was hospitalized.

(8) 05-02F-002 (Volume 410, p. 151). This patient was taking Paxil 40 mg for 38 days and attempted suicide. No other ADRs were reported.

(9) 07-01A-001. This person was taking Paxil 40 mg for 20 days. The case could not be located in the "Narrative of US Patients with Potentially Clinically Significant Events."

(10) 09-01A-005 (Volume 410, p. 196). This patient was taking Paxil 40 mg and overdosed at 7 days. She was experiencing "moderate drowsiness, tremulousness, severe nausea (probably drug related), and overdose." She overdosed for a second time 7–8 days later. There were therefore two overdoses, one during drug exposure, and one apparently within a week after withdrawal.

(11) 09-01E-260. This patient was taking Paxil 10 mg for 60 days. The patient could not be located in the "Narrative of US Patients with Potentially Clinically Significant Events."

(12) 09-01J-573 (Volume 410, p. 279). This patient was taking Paxil 10 mg according to the summary (p. 298) but taking 20 mg according to this case report. The drug exposure was listed as 26 days but appears to have been 30 days. The patient "jumped from second story window" and "received multiple fractures."

In addition to these 12 Paxil patients who attempted suicide (for a total of 14 attempts), there was one attempted suicide on imipramine and one on placebo. They follow:

(13) 04-06-088 (Volume 410, p. 50). This patient was taking imipramine 225 mg for 61 days. The patient was listed as a "possible suicide attempt." "He reportedly had taken an unknown quantity of 'pills' and was intoxicated." In fact, this is probably not a suicide attempt.

If this case is discarded, there are no other cases of suicide attempt on the comparison drug and the ratio becomes 12–14 to 0. It appears that the drug company attempted to cover up the higher rate of suicide attempts on Paxil by including this unlikely case of a suicide attempt.

(14) 02-01-009 (volume 410, p. 5). This patient was on placebo for 6 days. The case is described as "a suicide gesture by suffocation. Her husband prevented her suicide." Notice that this case is a "gesture." I found no "gestures" included in the Paxil group.

If this case is discarded, as well as the one imipramine case, then there were 12–14 suicide attempts among 12 patients on Paxil and none on placebo or on imipramine.

XIV. Increasing Evidence of Suicidality on Paxil

On 1.14.00 the FDA wrote a 3-page letter to Thomas Kline of SKB suggesting a label change. The FDA recommends a label change under "Overdosage/Human Experience." Since the introduction to the US, 342 spontaneous cases of deliberate or accidental overdose with paroxetine have been reported worldwide (circa 1999). Seventeen involved Paxil by itself. There were 48 fatalities.

This issue is even more serious than the FDA indicates, since there are obviously a large number of suicide attempts in this group.

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