United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

February 6, 2008

**Via Electronic Transmission**

Mr. Christopher Viehbacher
President
U.S. Pharmaceuticals
GlaxoSmithKline
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Viehbacher:

As the Ranking Member of the United States Senate Committee on Finance (Committee), I have an obligation to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices. This includes the responsibility to conduct oversight of the medical and pharmaceutical industries that provide products and services to Medicare and Medicaid beneficiaries.

As reported today in *New Scientist*, several documents were unsealed on January 18, 2008, in the case of *O'Neal v. SmithKline Beecham d/b/a GlaxoSmithKline*. Several of these documents and transcripts suggest that GSK knew as far back as 1989 that Paxil is associated with an increased risk of suicide. However, the American public was never adequately informed of this risk until May 2006 in a "Dear Healthcare Professional" letter that reported a "higher frequency of suicidal behavior" associated with Paxil as compared to placebo.

Specifically, Dr. Joseph Glenmullen, a Clinical Instructor in Psychiatry at Harvard Medical School, prepared an expert report based on a review of internal GSK documents. Dr. Glenmullen's report suggests that GSK ensured that suicides and suicidal attempts were systematically included in the placebo arm of GSK's study, which had the effect of making it more difficult to detect suicide risks associated with Paxil. This information was then submitted to the FDA.

Dr. Glenmullen concluded in his report:

> Analyses of GlaxoSmithKline's data demonstrate a causal link between the antidepressant and suicidal behavior. This has been true since 1989 although the "bad" Paxil numbers obscured the risk for a decade-and-a-half.

It is my understanding that 9 pages of Dr. Glenmullen's report are not available publicly. Accordingly, please respond to the following questions and request for information. Please repeat each enumerated question and follow it with your response.

1. When did GSK first learn that Paxil was associated with an increased suicide risk?

2. When did GSK first report to FDA that Paxil was associated with an increased suicide risk?

3. When did GSK first notify patients and doctors that Paxil was associated with an increased suicide risk? Please provide all pertinent documents and communications.

4. Please provide the Committee with the complete, unredacted version of Dr. Glenmullen's report. Along with that report, please provide the appendix and all documents that are referred to in the report, in the order that they are referenced.

5. Please provide the Committee with the accompanying children and adolescents report. Along with this report, please provide the appendix and all documents that are noted in the report, in the order that they are referenced.

Thank you again for your continued assistance in this matter. Because I understand that these documents are already available in electronic format, I would appreciate receiving the documents and information requested by no later than February 14, 2008. If you have any questions, please feel free to contact Paul Thacker of my Committee at (202) 224-4515. All formal correspondence should be sent electronically in PDF format to Brian_Downey@finance-rep.senate.gov or via facsimile to (202) 228-2131.

Sincerely,

Charles E. Grassley
Ranking Member

Attachment

# EXHIBIT 1

## Filed Under Seal

JOSEPH GLENMULLEN, MD
1563 Massachusetts Ave.
Cambridge, MA 02138

June 29, 2007

Ms. Karen Barth Menzies
Baum Hedlund
12100 Wilshire Boulevard, Suite 920
Los Angeles, CA 90025

Dear Ms. Menzies:

It is my opinion, based on a reasonable degree of medical probability and based on my education, training, and clinical experience, as well as my review of the material referenced in this report and listed in the attached appendices, that Paxil increases the risk of suicidality in adults. In addition, GlaxoSmithKline was aware of this risk, but hid it. This is a companion to the accompanying report relating to children and adolescents and a Specific Causation Report in the case of Benjamin Bratt.

According to GlaxoSmithKline, when evaluating whether or not Paxil causes a side effect one should consider several sources of information: statistical analyses of the Paxil database, GlaxoSmithKline's researchers' assessments of whether or not Paxil caused the side effect in particular patients, and the published medical literature.[1] In this report, I use this GlaxoSmithKline methodology to evaluate whether or not the evidence indicates a causal link between Paxil and suicidal behavior. As we will see, the Paxil data, GlaxoSmithKline's researchers' casuality assessments, and the published medical literature all support a causal link between Paxil and suicidal behavior.

GlaxoSmithKline's Paxil data in its earliest reports to the FDA in 1989 show a statistically significant, greater-than-eight-fold increased risk of suicidal behavior—suicide and suicide attempts—for patients put on Paxil when compared to patients put on placebo (dummy) pills. Unfortunately, this demonstration of a causal link between Paxil and suicidal behavior was obscured by GlaxoSmithKline's improperly reporting the data to the FDA, doctors, patients, and the public for over fifteen years. The significant Paxil risk was only

acknowledged by GlaxoSmithKline this past year in 2006. In May 2006 GlaxoSmithKline reported in a "Dear Doctor" letter that the company's most recent analysis showed Paxil caused a statistically significant, six-fold increase in suicidal behavior in patients with major depressive disorder.[2] On this basis, GlaxoSmithKline changed its official prescribing guidelines on Paxil to warn doctors and patients of this significant risk. This is exactly what GlaxoSmithKline should have done a decade-and-a-half ago when Paxil was first approved by the FDA: GlaxoSmithKline should have warned of the significant, increased risk when it first introduced Paxil to this country since the original 1989 data showed a greater than eightfold increased risk. It is my opinion to a reasonable degree of medical probability that if GlaxoSmithKline had provided a warning all these years, Benjamin Bratt would still be alive today.

This report is based on the GlaxoSmithKline internal company documents listed in Appendix A and on the medical literature and other documents cited in the end notes. The report is divided into three parts:

- Part 1 discusses statistical analyses of GlaxoSmithKline's Paxil data and the history of how the company handled the data.
- Part 2 examines GlaxoSmithKline's researchers' assessments of whether or not Paxil caused suicidal behavior in individual patients in the company's studies.
- Part 3 discusses the published medical literature on antidepressant-induced suicidality and self-harm.

## Part 1. Statistical Analyses of GlaxoSmithKline's Paxil Data and the History of How the Company Has Handled the Data

In 1989, GlaxoSmithKline submitted its New Drug Application for Paxil to the FDA. The Paxil New Drug Application is an enormous submission totaling tens of thousands of pages. One critical part of the New Drug Application is GlaxoSmithKline's safety report, entitled "Integrated Summary of Safety—Paxil Clinical Trials Program, November 10, 1989."[3] By 1989, GlaxoSmithKline's Paxil studies included 2,963 patients who were given the drug and 554 patients who were given a placebo. In the safety report, Table XI.21 summarizes suicide attempts in the worldwide Paxil database. An important context for this data is that in GlaxoSmithKline's Paxil studies up to that point in time, seriously suicidal patients were excluded from the studies.[4] So, anyone who became seriously suicidal during the studies only became so after being given Paxil or a placebo.

Table 1 below is a photocopy of the data on suicide attempts in patients on Paxil versus placebo that GlaxoSmithKline submitted in Table XI.21 of its 1989 safety report. "Paroxetine" in the table is the chemical name for Paxil.[5] GlaxoSmithKline reported that 42 of 2963 patients on Paxil attempted suicide while only three of 554 patients on placebo made suicide attempts.

Table 1

**GlaxoSmithKline 1989 NDA**

Table XI.21

Attempted Suicides and Overdoses - Worldwide Data

| | WORLDWIDE | |
|---|---|---|
| | Paroxetine | Placebo |
| | N=2963 | N=554 |
| Attempted Suicides (%) | 42(1.4%) | 3* |

* 2 overdoses during placebo run-in period

GlaxoSmithKline presented the data on suicides in another table in which it reported all deaths, not just suicides. Table 2 below is a photocopy of the data on deaths in patients on Paxil versus placebo. This was originally Table XI.17 in GlaxoSmithKline's safety report. The text explained that of the twelve patients who died on Paxil, five committed suicide and that the two deaths reported for placebo were suicides. Thus, according to GlaxoSmithKline, five of 2,963 patients on Paxil committed suicide while two of 554 patients on placebo committed suicide.

*In 1990, Reports of Prozac Making Patients Suicidal Raise New Concerns About Paxil*

While GlaxoSmithKline was waiting for the FDA to approve Paxil, in 1990 startling news broke that Prozac—the first, and at that time only, SSRI on the market—was making patients suicidal. Two prominent psychiatrists at Harvard Medical School—Drs. Martin Teicher and Jonathan Cole—reported on the phenomenon in the *American Journal of Psychiatry*, igniting a firestorm of publicity.[9] The Harvard psychiatrists' report and other reports in academic journals lent credibility to sensational cases in the media including the suicide of rock star Del Shannon and the mass murder-suicide of Joe Wesbecker in Louisville, Kentucky who killed twelve people and wounded eight others before taking his own life.[10] The intense publicity prompted the FDA to announce it would investigate the problem.

*On October 3, 1990 the FDA Asks GlaxoSmithKline for a Report on It's Paxil Suicide and Suicide Attempt Data*

For its investigation, the FDA asked GlaxoSmithKline and other pharmaceutical companies to submit reports on completed and attempted suicides in their studies of new SSRI-type antidepressants. An October 3, 1990 internal GlaxoSmithKline memo documents the FDA's request.[11] The "FDA Conversation Record" details a telephone call from Dr. Martin Brecher, the medical officer at the FDA responsible for reviewing Paxil's safety, to Dr. Thomas Donnelly, GlaxoSmithKline's director of FDA affairs. According to the memo:

> [Dr. Brecher] said he was calling to inform us of a concern that has arisen about Prozac and he is formally requesting a response to the same issues. He said that the public press has been widely discussing the relationship between Prozac and violence-ideation and suicide-ideation [thoughts]. Although the [psychiatric drugs] Division [of the FDA] does not see it as a real issue, but rather as a public relations problem, Lilly [Prozac's manufacturer] has been asked to submit a detailed response to the public's concern. He therefore is requesting that we do the same since we have a drug with a similar mechanism of action. He said his request is not based on any concern that has developed from his review of Paxil, but simply that it is an issue that must be addressed with this group of drugs.

GlaxoSmithKline's 1991 report to the FDA went through several drafts. The evolution of the drafts is interesting in itself. The first draft, dated February 15, 1991, was written by Dr. Geoffrey Dunbar, Director and Vice-President of GlaxoSmithKline's division of central nervous system drugs.[17] This first draft included the five wash-out suicide attempts counted as though they occurred in the placebo group. But, this draft did not report that any completed suicides occurred in patients on placebo. The two wash-out suicides counted as though they happened in the placebo group were added in the next draft.

The first draft also contains an analysis of the "time course of suicide attempts." The analysis showed that when patients on Paxil attempted suicide:

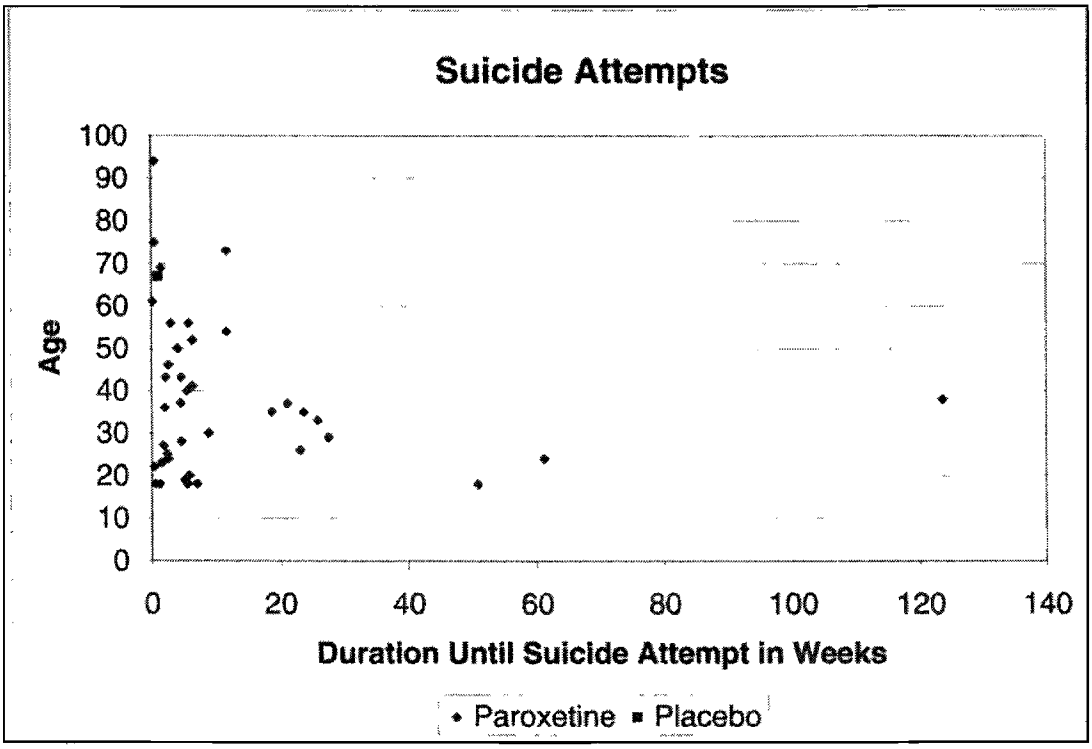
> most suicide attempts occurred early, especially during the first week of therapy.

The report stated that:

> Since the advent of effective antidepressant pharmacotherapy in the 1950s, clinicians have realized the increased risk of suicide early in treatment.

Thus, the Paxil data provided scientific evidence of what clinicians had observed for decades with earlier classes of antidepressants. But, GlaxoSmithKline deleted this crucial section from the final draft of the report. The final draft of the report includes an appendix listing all the patients who attempted suicide on Paxil. The list includes additional patients not included in the earlier draft. The list includes data on how many days the patients had been on Paxil, although in many cases the data are inaccurate when checked against the original clinical data reports. The correct data are plotted in Graph 2. As seen in Graph 2, this side effect is not evenly distributed over time; more than 60% of suicide attempts in patients on Paxil occurred in the first six weeks.

**Graph 2**




Both drafts and the final version of GlaxoSmithKline's 1991 report to the FDA insist that depression, not Paxil, causes suicide. GlaxoSmithKline maintained this position for over fifteen years, while relying on the "bad" Paxil numbers. Says the final, April 29, 1991 version of the report:[18]

> Suicidal ideation is a universally recognized accompaniment to the symptom complex of *depression* and, when acted upon by the patient, is the ultimate expression of the illness. Suicide ranks eighth among all causes of death in the United States and accounts for about 15% of deaths in patients with *mood disorders* [emphasis added].

Remarkably, the final draft of GlaxoSmithKline's report acknowledges that antidepressants can cause "intensification of suicidal thoughts and behavior" but claims that the company's data shows Paxil does not cause this phenomenon:

> In summary, suicidal ideation and behavior is an inherent risk when treating patients with major depressive disorder. Moreover, it is now recognized that *intensification of suicidal thoughts and behavior can occur in depressed patients undergoing* active treatment, including *antidepressant pharmacotherapy*. Nevertheless, analyses of our prospective, clinical trials for depression show that patients who were *randomized to Paxil* therapy were at no greater risk for suicidal ideation or behavior than were patients *randomized to placebo* or other active control therapies [emphasis added].

In addition to incorrect data on suicides and suicide attempts, the data GlaxoSmithKline submitted to the FDA had numerous other problems, some of which are discussed in my earlier report in this case. Below are brief descriptions of some of the additional problems:

- When GlaxoSmithKline coded suicidal behavior in its computerized database, most of the suicides and suicide attempts were coded as "emotional lability," a technical term for rapid mood swings, for example from crying to laughing.[19] FDA memos have since described Paxil suicides and suicide attempts as being "hidden," or "obscured," by GlaxoSmithKline's "inappropriate terminology" and "coding maneuvers."[20]

- GlaxoSmithKline often points to the small number of patients who attempted or committed suicide during the Paxil studies.[21] But the numbers are relatively small because suicide and suicide attempts are uncommon events, especially in studies where seriously suicidal patients were excluded. Moreover, the way in which GlaxoSmithKline collected its side effects data often does not reflect the true incidence. During the Paxil studies, at each follow-up visit, GlaxoSmithKline only let its researchers ask patients a general, open-ended question about potential side effects such as: "Do you feel different in any way since starting the new treatment [or] since the last assessment?"[22] Such general, open-ended questions are known to yield low rates of side effects. In the case of another Paxil side effect, Paxil withdrawal, GlaxoSmithKline originally reported that withdrawal reactions are "rare" in patients stopping Paxil.[23] The pharmaceutical industry officially defines rare side effects as occurring in less than one patient in a thousand, or 0.01 percent.[24] But when researchers at Harvard Medical School later developed sensitive

measures of antidepressant withdrawal, their systematic studies revealed withdrawal reactions in 66% of patients stopping Paxil.[25] The example of Paxil withdrawal reactions demonstrates how much insensitive, unsystematic, open-ended questions can underestimate antidepressant side effects.

- Sensitive scales for systematically evaluating treatment-emergent suicidality are available. But, GlaxoSmithKline chose not to introduce them into most of its Paxil studies despite the concern about Paxil-induced suicidality dating to before the drug was approved and marketed in this country. GlaxoSmithKline defends its insensitive, unsystematic, open-ended question about potential side effects as "non-leading."[26] But GlaxoSmithKline uses systematic checklists to diagnose and monitor patients' depressions. GlaxoSmithKline does not worry about "leading questions" when diagnosing psychiatric conditions, only when diagnosing side effects.

- In its 1991 report, GlaxoSmithKline added another statistical calculation that was not included in its original 1989 New Drug Application safety report. In GlaxoSmithKline's Table 6 and Table 7 on page 11, note the addition of P.E.Y., which refers to patient exposure years. This is not just the absolute count of how many patients on Paxil versus placebo attempted or committed suicide. Rather, this is another count factoring in how long patients were on Paxil or placebo. GlaxoSmithKline's patient exposure years calculations are based on the "bad" Paxil numbers. Still worse, counting side effects per patient exposure years is only appropriate statistically when the risk of the side effect is evenly distributed over time. The risk of antidepressant-induced suicidality is not evenly distributed over time.[27] GlaxoSmithKline's own data showed that the majority of suicide attempts in Paxil-treated patients occurred during the first six weeks of treatment, according to a graph in the company's original draft of the report as described above. *But, GlaxoSmithKline deleted that section of the report in the final draft.* Since the risk of antidepressant-induced suicidality is not evenly distributed over time, GlaxoSmithKline counting this side effect over patient exposure years was once again inappropriate.

*On June 19, 1991 the FDA Concludes Paxil Is Safe*
*Based on GlaxoSmithKline's "Bad" Numbers*

Dr. Martin Brecher was the medical reviewer at the FDA responsible for evaluating Paxil's safety based on the data GlaxoSmithKline provided him. Based on his review, Dr. Brecher issued a June 19, 1991 report entitled "Review and Evaluation of Clinical Data Original NDA [New Drug Application] 20-031 Paxil Safety Review."[28] As part of reviewing Paxil's safety, Dr. Brecher highlighted the data on "significant" side effects, including suicidality. Specific sections of Dr. Brecher's report are devoted to suicide, suicide attempts, and an "overview of suicidality," combining the data on suicides and suicide attempts.

Table 11 below is a photocopy of the table in Dr. Brecher's 1991 report listing suicides and suicide attempts in patients on Paxil versus placebo. In the table, one can see that Dr. Brecher relied on GlaxoSmithKline's "bad" Paxil numbers to evaluate whether or not Paxil made patients suicidal. The numbers in Dr. Brecher's table match the "bad" numbers in GlaxoSmithKline's April 29, 1991 report shown in Tables 6 and 7 on page 11, submitted to the FDA a little over a month before Dr. Brecher's June 19, 1991 report.

Table 11
**FDA (Brecher's) 1991 Paxil Safety Review**

TABLE 13
Suicidality in Paroxetine Clinical Trials

| | Paroxetine N=2963 1008 P.E.Y.* | Placebo N=554 72 P.E.Y. |
|---|---|---|
| Completed Suicides | | |
| No. (%) | 5 (0.17) | 2 (0.36) |
| No./P.E.Y. | 0.005 | 0.028 |
| Attempted Suicides | | |
| No. (%) | 40 (1.3) | 6 (1.1) |
| No./(P.E.Y.) | 0.040 | 0.083 |

* P.E.Y. stands for Patient Exposure Years

Note that in addition to the "bad" Paxil numbers, Dr. Brecher reproduced GlaxoSmithKline's patient exposure years calculations. As described earlier, per patient exposure years calculations are only appropriate when a side effect is evenly distributed over time. The original draft of GlaxoSmithKline's 1991 report

included a section showing that Paxil-induced suicidality is not evenly distributed over time and instead occurs early in treatment. But GlaxoSmithKline deleted this section in the final draft submitted to the FDA. So, Dr. Brecher did not know that GlaxoSmithKline's per patient exposure years calculations were inappropriate.

Based on GlaxoSmithKline's "bad" numbers, Dr. Brecher concluded:

> Although the instruments available may not be ideal to capture the elusive clinical events reported by Teicher..., there is no [statistical] signal in this large data base that Paxil exposes a subset of depressed patients to additional risk for suicide, suicide attempts or suicidal ideation [thoughts].

Note that the phenomenon of antidepressants making patients suicidal was very much on Dr. Brecher's mind as he reviewed Paxil's safety in the spring of 1991. Teicher and Cole reported the phenomenon with SSRIs the previous year in 1990, precipitating a furor. In the spring of 1991, the FDA was in the middle of evaluating the issue. In just a few months, in September 1991, the FDA would hold a hearing on the matter. In fact, as we have seen, the accurate data showed patients on Paxil had a statistically significant eight-fold increase in suicides and suicide attempts. The correct data would have confirmed Teicher's report.

*The FDA Schedules a Hearing on Whether or Not Antidepressants Make Patients Suicidal for September 20, 1991*

Responding to public and professional fear that this new class of SSRI-type antidepressants was making patients suicidal, the FDA held a day-long hearing on the subject on September 20, 1991. The hearing was eagerly awaited for over a year. For the hearing, the FDA appointed a nine-member advisory panel comprised of physicians and scientists outside the FDA to evaluate the evidence. The advisory panel has since been heavily criticized because five of the nine members had such serious conflicts of interest—close ties to the pharmaceutical industry—that the FDA had to waive its own standards for conflicts of interest. The FDA had to waive its standards for consultants to the advisory panel as well. As we will see, two of the psychiatrists for whom the FDA had to waive its standards later played crucial roles in GlaxoSmithKline publishing its "bad" numbers: Dr. David Dunner of the Department of Psychiatry and Behavioral Sciences at the University of Washington in Seattle had done research on Prozac

for Eli Lilly.[29] So, too, had Dr. Stuart Montgomery of the Department of Psychiatry, Saint Mary's Hospital Medical School in London, England.[30] Both Dunner and Montgomery played crucial roles in the Paxil story, as we will see.

*For the 1991 FDA Hearing, GlaxoSmithKline Explicitly Denies Paxil Induced-Suicidality*

On September 19, 1991, the day before the FDA hearing, GlaxoSmithKline distributed a memo to over twenty senior staff.[31] The memo reads:

> Here are approved statements that Bruce Wallin [the head of GlaxoSmithKline's U.S. division of central nervous system drugs] will use to respond to questions [regarding] Paxil during the FDA special Advisory Committee meeting tomorrow on suicide. These statements will be used by Corporate Affairs in the U.K. and U.S. to respond to any media/financial analyst inquiries.

Note the reference to financial analysts. GlaxoSmithKline was concerned about the potential financial impact of the FDA hearing on Paxil and therefore GlaxoSmithKline. The prepared "Statement to be used to respond to inquiries re Paxil/Suicide" claims explicitly that during GlaxoSmithKline's studies:

> the incidence of suicide was *lower* among patients receiving Paxil than among those receiving placebo [emphasis added].

As we've seen, five patients in the Paxil group committed suicide while no patients in the placebo group did.

*Lacking Accurate Data on Paxil-Induced Suicidality, the FDA Was Without Crucial Information That Could Have Led to a Warning in 1991*

At the September 20, 1991 FDA hearings, the committee was forced to examine incomplete and insensitive data. The transcript of the FDA's 1991 hearing is available through the Freedom of Information Act. In the transcript, one can see the committee members and other speakers repeatedly comment on the poor quality of the data available to them and the need for more research:

The Hamilton [Depression Scale] item itself is not a great fine screen for suicide; it is a very coarse instrument. That may be a problem in really interpreting these data.[32]

I am not completely convinced that those are all the data we need [to resolve the issue].[33]

I don't feel I have all the data.[34]

I want to endorse the need for better data sets to operate from.[35]

I am not convinced that all of the appropriate data and analyses have been done…the responses to this end up always being with that caveat…[36]

Given what we have, what do we recommend to the agency [i.e. the FDA] that they should do?[37]

I sense that my answer [from the] presentation this morning is that, yes, there is a signal there. The problem is… this issue is not yet fully answered to our satisfaction.[38]

I think it is more likely to be a class [i.e. the whole class of SSRI-type antidepressants] issue than a specific drug issue, [but] I do not think we have adequate information on the other antidepressants beside Prozac [i.e. Paxil and the other SSRIs]….[39]

It needs to be studied further.[40]

We really do need to obtain more data….[41]

It is a fairly sorry state where we are picking one item from the Hamilton Depression Scale [a coarse, insensitive measure for evaluating suicidality]….[42]

[What can be done about] the question of the discomfort that the committee has felt about the data availability.[43]
Given our uncertainty, given the lack of knowledge, just what do we say?[44]

As seen in the quotes from the transcript, the committee suspected a "signal" in the data suggesting SSRI-type antidepressants were making patients suicidal. The committee felt the need for more data, especially on the other SSRI antidepressants, like Paxil. Unbeknownst to the committee, the data already existed, in GlaxoSmithKline's files. The correct data showed patients on Paxil had a statistically significant increased risk of becoming suicidal.

Despite the poor quality of the data available to the committee and despite the committee members' many conflicts of interest, one third of the committee members voted for a warning in 1991. In 2003, when the issue of Paxil-induced suicidality exploded in the media as discussed later in this report, the *New York Times* interviewed members of the FDA's 1991 advisory committee who said they would have voted for a warning back in 1991 had the data been available to them.[45] Instead we had to wait for new hearings in 2004 before the FDA issued its first warning.[46]

*After the FDA Hearing, a September 30, 1991 GlaxoSmithKline Memo Acknowledges the Likelihood of Antidepressant-Induced Suicidality*

A week-and-a-half after the 1991 hearing, Dr. Thomas Donnelly, GlaxoSmithKline's head of FDA affairs, reported on the hearing in a September 30, 1991 internal GlaxoSmithKline memo.[47] Discussing the "possible implications for Paxil," Dr. Donnelly states:

> The Advisory Committee, based on scientific data presented to its members, voted that there was *no causal relationship* between marketed antidepressants and suicide attempts, suicide ideation and violent behavior. By extension, they also *voted it was not necessary for the Agency to take any action* against antidepressants in general, a class of antidepressants or any particular agent [emphasis added].

However, Dr. Donnelly acknowledged that there appeared to be a risk of antidepressant-induced suicidality in a small, vulnerable subpopulation of patients:

> The Committee was obviously moved by the anecdotal reports from the public. It was generally agreed that there appears to be some problems with antidepressant use and suicidality and/or

> violent behavior in a small subgroup of patients; *however the data at this point only provide clues to the identity of that subgroup and no solid scientific evidence that it exists* [emphasis added].

But solid scientific evidence of a significant increased risk did exist, in GlaxoSmithKline's files. With the threat of the hearing behind them, GlaxoSmithKline was still waiting for the FDA to approve Paxil. The company continued to promulgate the "bad" Paxil numbers and its claims that Paxil is safe.

### *In December 1991, GlaxoSmithKline Presents Its "Bad" Paxil Numbers to the American College of Neuropsychopharmacology*

In December 1991 the American College of Neuropsychopharmacology(ACNP) met in San Juan, Puerto Rico. The ACNP's members are prominent academic psychiatrists who specialize in psychopharmacology, that is, prescribing psychiatric drugs. The ACNP has issued influential position papers on antidepressant-induced suicidality. Naturally, GlaxoSmithKline would want to influence the College's views on Paxil.

At the San Juan meeting, two psychiatrists presented GlaxoSmithKline's Paxil data. Dr. Geoffrey Dunbar was Director and Vice President of GlaxoSmithKline's division of central nervous system drugs. Dr. David Dunner is a psychiatrist in the Department of Psychiatry and Behavioral Sciences at the University of Washington in Seattle. Recall that Dunbar wrote the first draft of GlaxoSmithKline's 1991 safety report to the FDA in which the "bad" Paxil numbers appeared. Dunner was one of the psychiatrists on the Advisory Committee at the FDA hearing two months earlier in September 1991. Indeed, Dunner was one of the committee members whose conflicts of interest—his work for the pharmaceutical industry—were so extensive that the FDA had to waive its own standards for conflict of interest. In fact, in his conflict of interest statement Dunner did not even divulge all his conflicts of interest to the FDA.[48] In December 1991, Dunner and Dunbar presented the "bad" Paxil numbers to the American College of Neuropsychopharmacology meeting. GlaxoSmithKline later produced an annotated bibliography summarizing presentations and published articles on Paxil.[49] According to GlaxoSmithKline, Dunner and Dunbar told the American College of Neuropsychopharmacology that during GlaxoSmithKline's Paxil studies:

> Suicides and suicide attempts occurred *less frequently with Paxil* than with either placebo or active controls [comparison older antidepressants][emphasis added].

On March 2, 1992 the ACNP issued a Consensus Statement on the issue of whether or not antidepressants increase suicidal behavior. The ACNP's Consensus Statement was later published in the journal *Neuropsychopharmacology* in 1993.[50] In the Consensus Statement, the ACNP cites "data supplied by the manufacturer of Paxil," i.e. GlaxoSmithKline. The data replicates GlaxoSmithKline's "bad" Paxil numbers. Misled by GlaxoSmithKline's "bad" Paxil numbers, like the FDA, the influential ACNP took the position that antidepressants do not increase the risk of suicidal behavior.

Dr. John Mann was one of the four members of the ACNP task force that wrote the Consensus Statement and was the lead author when it was published in the journal *Neuropsychopharmacology*.[51] Mann is a professor of psychiatry at Columbia University Medical Center. GlaxoSmithKline later hired Mann as an expert witness in lawsuits over Paxil-induced suicides. In sworn testimony in a Paxil murder-suicide case, Mann was asked whether GlaxoSmithKline gave the ACNP the raw data to analyze or summary tables with the "bad" Paxil numbers:[52]

> Q. Doctor, if I might, I would like to turn your attention now to the—what we've abbreviated as the ACNP task force that you served on....What was the mission or purpose of that task force, sir?
>
> A. The task force—well, the ACNP regarded itself as the—as *an important opinion former in the scientific and medical community* and wanted to follow up and supplement the findings that the FDA committee [the 1991 FDA hearing]....By obtaining additional information and data that had been unpublished by pharmaceutical companies on *[SSRI antidepressants] that were in the pipeline* because thousands of patients had been studied in order to determine the safety and efficacy of these...SSRIs. Thousands of patients had been studied in the United States and overseas under controlled clinical trial conditions, where the patient and the doctor didn't know which medication the patient was receiving so nobody was biased, looking at the safety and efficacy of these other drugs. *So the question is we've got all this other information. The question is really important. How safe and how effective are these*

*medications? Let's tap into this additional information and find out. And that's what the committee did. We spent quite a bit of time gathering data from various drug companies and formulating it into the publication of the committee's findings.*

Q. Did you obtain information from SmithKline on Paxil?
A. We did.

Q. And did this task force look at the medical literature again?
A. Yes. The report reviewed both the so-called case reports, including the Teicher report, and as well as information from controlled clinical studies, randomized controlled, double-blind clinical studies.

Q. How long did the task force work together before issuing its report, sir?
A. Well, it took us, I think, about *five months*.

Q. And what conclusion did the statement make as to whether or not SSRIs cause suicides or suicidal ideation?
A. The conclusion was that....[I'm] just going to look at my copy....In fact, it says here, "There is no evidence that antidepressants such as selective serotonin reuptake inhibitors...trigger emergent suicidal ideation over and above the rates that may be associated with depression."

Q. Dr. Mann, let me ask you this. I know there were four members of your task force. Did you have access to all of the data, all of the unpublished data, or were you provided with summaries or statistical summaries of the data from SmithKline?
A. To be perfectly honest, I can't recall how much of the statistical raw data we received at the time that we put these numbers together...No, I think we all went through the tables of data that were provided at the time [emphasis added].

In other words, GlaxoSmithKline apparently just supplied the ACNP with the tables presenting the "bad" Paxil numbers.

*On December 29, 1992 the FDA Approves Paxil*
*Based on GlaxoSmithKline's "Bad" Paxil Numbers*

Just before approving a new antidepressant, the FDA often appoints an advisory committee of psychiatrists and scientists to evaluate the data on the new antidepressant and recommend whether or not the FDA should approve the new drug. The Paxil advisory committee met on October 5, 1992 to review the data. Dr. Geoffrey Dunbar, Director and Vice-President of GlaxoSmithKline's division of central nervous system drugs, presented the Paxil efficacy data. Dr. David Wheadon, Senior Vice President of U.S. Regulatory Affairs, presented GlaxoSmithKline's safety analysis. The transcript of the hearing is available through the Freedom of Information Act.[53] Using GlaxoSmithKline's "bad" Paxil data, Dr. Wheadon told the FDA committee "there is a very favorable comparison" of Paxil to placebo for both suicides and suicide attempts. Based on the "bad" Paxil numbers, the committee voted in favor of the FDA approving Paxil.

On December 29, 1992, the FDA approved Paxil based on GlaxoSmithKline's "bad" Paxil numbers. Table 12 is a photocopy of Table 55 in the FDA's "Summary Basis of Approval" for Paxil, summarizing the "incidence of suicides and suicidal acts in the pooled worldwide dataset" for Paxil and placebo.[54]

Table 12
**FDA Summary Basis of Approval**

TABLE 55

Incidence of Suicides and Suicidal Acts
Pooled Worldwide Dataset

| | Paroxetine (n=2963) 1008 PEY | Placebo (n=554) 72 PEY |
|---|---|---|
| Suicides | | |
| No. (%) | 5 (0.17) | 2 (0.36) |
| No./PEY | 0.005 | 0.028 |
| Total Attempted Suicides (Overdose and Other Methods) | | |
| No. (%) | 40 (1.3) | 6 (1.1) |
| No./PEY | 0.040 | 0.083 |

PEY = Patient Exposure Years

As one can see, these are the same "bad" Paxil numbers that GlaxoSmithKline reported to the FDA the previous year in 1991. FDA's Summary Basis of Approval states that suicides occurred in

> 2 (0.36%) [of] patients *randomized* to placebo [emphasis added].

But, as we have seen over and over again, this is simply not true. None of the patients randomized to placebo committed suicide. The two suicides GlaxoSmithKline counted as occurring in the placebo group actually occurred during the wash-out period. The FDA's Summary Basis of Approval goes on to say:

> A total of 40 (1.4%) Paxil-treated patients attempted suicide. In comparison, 6 (1.1%) placebo-treated…patients also attempted suicide.

Again, this is not true. Only one patient in the placebo group attempted suicide. The other 5 suicide attempts GlaxoSmithKline counted as occurring in the placebo group actually occurred during the wash-out period before the randomized study. Based on GlaxoSmithKline's "bad" Paxil numbers, the FDA concluded:

> These analyses show that patients *randomized* to Paxil were at no greater risk for suicidal ideation or behavior than patients *randomized* to placebo…[emphasis added].

Thus, GlaxoSmithKline's "bad" Paxil data again misled the FDA, causing the agency to arrive at the wrong conclusion. Again, the key word is randomized. GlaxoSmithKline's "bad" Paxil data made it *look as if* patients randomized to Paxil were no more likely to become seriously suicidal when, in fact, the correct data shows patients on Paxil were *eight times* more likely to commit or attempt suicide. Once again , GlaxoSmithKline's "bad" Paxil numbers carried the day: The FDA approved Paxil on December 29, 1992 with no warning for doctors or patients of the significant increased risk of suicidal behavior.

*GlaxoSmithKline Uses Its "Bad" Paxil Numbers in a May 1994 Researchers' Brochure*

Throughout the 1990s, GlaxoSmithKline continued to present the "bad" Paxil numbers to doctors, patients, and the public. In May 1994 GlaxoSmithKline produced a brochure for researchers doing its Paxil studies.[55] By 1994, more patients had been enrolled in Paxil studies. GlaxoSmithKline's original Paxil studies only included depressed patients. But GlaxoSmithKline began testing and ultimately applying for FDA approval for Paxil for other conditions including obsessive compulsive disorder, panic disorder, generalized anxiety disorder, social anxiety disorder, and post traumatic stress disorder. Indeed, GlaxoSmithKline has gotten Paxil approved by the FDA for more psychiatric conditions than any other antidepressant in history.

By 1994, GlaxoSmithKline's researchers' brochure reported that 4,126 patients had taken Paxil in its growing studies and 625 patients had taken placebo. This is an increase from the 2,963 and 554 patients reported in the data that we have examined so far from the original studies of depressed patients. GlaxoSmithKline reports that among patients on Paxil: "6 deaths were due to suicide." This is an increase of one from the previously reported five Paxil suicides, apparently because one of the patients in the new studies had committed suicide on Paxil. GlaxoSmithKline again reported two wash-out suicides as though they occurred in the placebo group. On the basis of these new "bad" Paxil numbers, GlaxoSmithKline again blamed depression and reassured its researchers:

> Suicides and overdoses are to be expected in a depressed population. The evidence to date suggests that treatment with Paxil is not associated with an increased risk of such events.

Below Table 13 is a photocopy of Table 27 from GlaxoSmithKline's 1994 researchers' brochure providing the data on suicide attempts in patients on Paxil versus placebo. The number of Paxil patients who attempted suicide has increased from 40 in 1991 to 49 in 1994. But, because of the number of patients studied on Paxil has also increased, the *rate* goes down from 1.3% in 1991 to 1.2% in 1994. None of the additional placebo patients had attempted suicide. The same six patients reported in 1991 are reported in 1994. As we have seen, only one of these six patients was actually in the placebo group; the other five were taken from the wash-out period.

Table 13
**GlaxoSmithKline 1994 Researchers' Brochure**

Table 27
Attempted suicide
Worldwide clinical trials programme

| | Paroxetine (n=4126) | Placebo (n=625) |
|---|---|---|
| No. (%) | 49 (1.2%) | 6 (1.0%) |

Note that once again, GlaxoSmithKline's 1994 "bad" numbers make the rate of suicide attempts in patients on Paxil and patients on placebo look virtually the same, 1.2% versus 1.0%. Once again, in the 1994 researchers' brochure, GlaxoSmithKline makes the inaccurate claim:

> the data shows there was a similar incidence of attempted suicide in the Paxil *group* as compared to the placebo and active control *groups* [emphasis added].

Here the operative word is "group." Five of the six suicide attempts GlaxoSmithKline alleged happened in the placebo group, in fact, occurred during the wash-out period. GlaxoSmithKline was making the same inaccurate claims using updated "bad" Paxil numbers.

Below are tables comparing GlaxoSmithKline's "bad" 1994 data with the correct data now acknowledged by the company.[56] Note that once again GlaxoSmithKline's incorrect numbers make Paxil look roughly equal to or better than placebo, and obscure a statistically significant increase in the risk of suicidal behavior for patients put on the drug.

Table 14
**GlaxoSmithKline's 1994 Data**
Suicide Attempts -- Worldwide data

| Paxil 4126 patients | Placebo 625 patients | Odds Ratio Paxil/ Placebo | Statistically Significant? |
|---|---|---|---|
| 49<br>1.2% | 6*<br>0.96% | 1.2 | No<br>p = 0.84 |
| 49<br>1.2% | 1<br>0.16% | 7.5 | Yes<br>p = 0.01 |

**GSK's "bad" 1994 numbers** in its researchers' brochure. *Includes 5 wash-out suicide attempts counted as though they occurred in the placebo group.

**The correct data** now acknowledged by GSK, in which the wash-out suicide attempts are removed.

Table 15
**GlaxoSmithKline's 1994 Data**
Suicides -- Worldwide data

| Paxil 4126 patients | Placebo 625 patients | Odds Ratio Paxil/ Placebo | Statistically Significant? |
|---|---|---|---|
| 6<br>0.15% | 2*<br>0.32% | 0.45 | No<br>p = 0.28 |
| 6<br>0.15% | 0<br>0% | | All suicides occurred on Paxil; none on placebo. |

**GSK's "bad" 1994 numbers** in its researchers' brochure. *Included 2 wash-out suicides counted as though they occurred in the placebo group.

**The correct data** now acknowledged by GSK, in which the wash-out suicides are removed.

Table 16
**GlaxoSmithKline's 1994 Data**
Combined Suicidal Behavior
(Suicides and Suicide Attempts)
Worldwide data

| Paxil 4126 patients | Placebo 625 patients | Odds Ratio Paxil/ Placebo | Statistically Significant? |
|---|---|---|---|
| 55<br>1.3% | 8*<br>1.3% | 1.0 | No<br>p = 1.0 |
| 55<br>1.3% | 1<br>0.16% | 8.4 | Yes<br>p = 0.008 |

**GSK's "bad" 1994 numbers** in its researchers' brochure. Includes 7 wash-out suicides and suicide attempts counted as though they occurred in the placebo group.

**The correct data** now acknowledged by GSK, in which the wash-out suicides and suicide attempts are removed.

*GlaxoSmithKline Uses Its "Bad" Paxil Numbers to Claim a Potential Market Advantage in the Journal* European Neuropsychopharmacology

In 1995, GlaxoSmithKline, published the "bad" Paxil numbers and suggested that Paxil has an *advantage* over other antidepressants that might be more likely to increase the risk of suicidality.[57] The "bad" Paxil numbers were published in a 1995 article entitled "Reduction of Suicidal Thoughts with Paxil in Comparison with Reference Antidepressants and Placebo" in the journal *European Neuropsychopharmacology*.[58] The authors of the article were Dr. Stuart Montgomery, a psychiatrist at St. Mary's Hospital Medical School in London; Dr. David Dunner, a psychiatrist at the University of Washington Medical Center in Seattle; and in-house GlaxoSmithKline psychiatrist Dr. Geoffrey Dunbar. Recall that these three psychiatrists have already played central roles in the debate over antidepressant-induced suicidality. Dr. Montgomery was a consultant at the FDA's 1991 hearing on antidepressant-induced suicidality. To appoint Dr. Montgomery, the FDA had to waive its own standards for conflicts of interest because of his extensive ties to the pharmaceutical industry. Dr. Dunner was a voting member of the Advisory Committee at the FDA's 1991 hearing. The FDA also had to waive its standards for conflicts of interest to appoint Dr. Dunner. In

fact, Dr. Dunner left the hearing early not even bothering to listen to all of the discussion of the evidence. Dr. Dunner left a proxy to vote against the warnings for him.[59] And, Dr. Dunbar is the in-house GlaxoSmithKline psychiatrist who wrote the first draft of the company's April 29, 1991 safety report to the FDA in which the "bad" Paxil numbers appeared. Dr. Dunbar presented the Paxil efficacy data at the October 5, 1991 FDA hearing to win Paxil approval. Together, Dr. Dunbar and Dr. Dunner presented the "bad" Paxil numbers to the American College of Neuropsychopharmacology in December 1991.

Table 17 below reproduces Table 8 in Montgomery, Dunner, and Dunbar's article in *European Neuropsychopharmacology* showing the data on suicides and suicide attempts in patients on Paxil versus placebo. This is GlaxoSmithKline's 1991 "bad" Paxil data including the "bad" patient exposure years calculations.

Table 17
**GlaxoSmithKline's 1995 Paper**
**in *European Neuropsychopharmacology***

Table 8
Suicides and suicide attempts; intention-to-treat sample; worldwide open and controlled trial data base

| | Paroxetine n = 2963 1008 PEY | Placebo n = 554 72 PEY |
|---|---|---|
| Suicides n (%) | 5 (0.17) | 2 (0.36) |
| n/PEY | 0.005 | 0.028 |
| Attempted suicides n (%) | 40 (1.3) | 6 (1.1) |
| n/PEY | 0.040 | 0.083 |

Based on the "bad" Paxil numbers, Drs. Montgomery, Dunner, and Dunbar asserted:

> It has sometimes been assumed that vigorous treatment of depression with effective antidepressants will necessarily reduce the risk of a suicide attempt but this assumption may not be well founded. *There is evidence to suggest that some antidepressants, rather than having a positive or neutral effect on suicidality, may even provoke suicide attempts*....Differing inherent toxicity of the various antidepressants cannot adequately explain the disproportionately

> high rates of death from overdose with some antidepressants, e.g. desipramine, amitriptyline, dothiepin....*Suicide provocation by an antidepressant* is suggested by a large placebo-controlled study of long-term treatment with maprotiline....Consistent reduction in suicides, attempted suicides, and suicidal thoughts, and protection against emergent suicidal thoughts suggest that *Paxil has advantages in treating the potentially suicidal patient* [emphasis added].

Thus, GlaxoSmithKline used the "bad" Paxil numbers to claim a market advantage over other antidepressants that might "provoke" suicidal behavior.

Dr. Dunner has been deposed in ongoing Paxil litigation. Dr. Dunner was asked if GlaxoSmithKline provided him with the raw data to analyze for the 1995 paper in *European Neuropsychopharmacology* or just summary tables with the "bad" Paxil numbers. Dr. Dunner responded:[60]

> A. I didn't see the raw data in the case report forms. I did see the tables. I work with the tables. The tables came before any draft, as I recall. We—we created the paper from the tables.
>
> Q. And—and you never questioned, did you, or did you not question the validity of the data in Table 8?
> A. No.

This apparently was the pattern: That GlaxoSmithKline provided the tables with the "bad" Paxil numbers to doctors and the public.

### *GlaxoSmithKline Reassures Doctors with the* European Neuropsychopharmacology *Paper with the "Bad" Paxil Numbers*

On July 5, 1995, GlaxoSmithKline's marketing department issued a memo to its sales force trumpeting the *European Neuropsychopharmacology* paper with the "bad" Paxil numbers.[61] The memo urged the sales force to use the Montgomery-Dunner-Dunbar paper to reassure doctors concerned about Paxil-induced suicidality. According to GlaxoSmithKline:

> This paper adds to the burden of proof that Paxil is a safe and effective antidepressant and may be used with physicians to

alleviate any concerns they may have regarding suicidal ideation [thoughts].

*On April 2, 1999 the FDA Makes Another Request for Information About Paxil Suicides*

In the late 1990s, the FDA was debating the ethics of treating patients in drug studies with placebo if their medical condition is potentially life threatening. In the case of depression, for example, do patients given a placebo have statistically significant *higher* rates of committing suicide? If so, then doing placebo controlled studies of depression might be unethical. As we have seen, the correct Paxil data shows quite the opposite: Patients exposed to Paxil have a statistically significant increased risk of committing or attempting suicide compared to patients put on placebo.

To address the question, the FDA asked pharmaceutical companies for the data on deaths—in the case of antidepressants, especially suicides—in their drug studies. The FDA's request to GlaxoSmithKline is dated April 2, 1999.[62] This new request from the FDA was independent of the debate over antidepressants making patients suicidal. But, it was a request for the same type of data.

*GlaxoSmithKline Submits New "Bad" Paxil Data to the FDA in 1999*

GlaxoSmithKline submitted its report to the FDA on July 13, 1999. The report states that GlaxoSmithKline included suicides "with the cut-off date prior to 17 June 1999...."[63] Table 18 reproduces GlaxoSmithKline's table in the July 13, 1999 report to the FDA. By 1999, the number of patients who had taken Paxil in depression studies now totaled 7,225, while the number who had taken placebo had increased to 1,607. According to GlaxoSmithKline's 1999 table, twelve patients on Paxil had committed suicide while only one patient on placebo had.

Table 18
**GlaxoSmithKline's New 1999 "Bad" Paxil Data**

**Paroxetine IR: 7225**
**Placebo: 1607**

| Treatment | Non-Suicides | Suicides | Unknown Cause | Total |
|---|---|---|---|---|
| Paroxetine IR | 28 | 12 | 4 | 44 |
| Placebo | 3 | 1 | 0 | 4 |
| | | | **Grand Total:** | **48*** |

*Grand total does not include 10 cases undergoing further investigation.

Note that the count for patients on placebo who committed suicide no longer includes the two wash-out suicides that were previously improperly counted against the placebo group. But, the one *new* suicide counted against placebo also is improper. Examination of the individual case report shows that the patient was on an older antidepressant, mianserin, and therefore cannot be properly counted as a placebo suicide.[64] Thus, the new, 1999 Paxil numbers are once again "bad." I have not analyzed this "bad" data set because GlaxoSmithKline subsequently revised the report and submitted a new one.

On November 18, 1999 GlaxoSmithKline's David Burnham wrote an email to seven of his colleagues expressing concern that the July 13th report made no mention of the two wash-out suicides which had previously been reported to the FDA as if they occurred in the placebo group.[65] What if the FDA inquired why the placebo suicide count had gone *down* from two to one in the decade from 1989 to 1999? Burnham sent a new draft of the 1999 report to his colleagues, saying:

> The two suicides among the 544 placebo patients [originally reported in 1989]…actually occurred during single-blind placebo run-in, not double-blind placebo…. Because patients undergo usually 1 week of single-blind run-in *before* randomization, these 2 suicides on placebo are not comparable to deaths occurring after randomization….*Bottom line: We must mention the placebo run-in [wash-out] deaths to reconcile the overall incidence figures….However, we cannot combine these placebo run-in deaths with the randomized placebo death rate…. Thus, we are left with a 0.1% suicide rate on Paroxetine IR and a 0% rate on placebo.* [emphasis added].

Three weeks later, one of the colleagues Burnham emailed, Thomas Kline called Dr. Michael Seika, a medical reviewer at the FDA.[66] Kline documented the call in a GlaxoSmithKline December 8, 1999 memo. Kline wrote:

> Specifically, I asked [Dr. Seika at the FDA] if a patient were to die during a placebo run-in [wash-out], i.e. prior to randomization, should that patient be included in the calculation for placebo deaths. He clearly stated that such a patient should not be counted in our analyses, since such a patient would not comprise the "controlled" portion of a trial.

On December 16, 1999 GlaxoSmithKline submitted a revised version of the report to the FDA.[67] As Burnham suggested in his email, this time the report mentioned the wash-out deaths in the event that they needed to be reconciled with the earlier figures. As in the July 13th version of the report, they were not counted against the placebo group. However, the December 16th report still improperly counted the mianserin suicide as though it occurred in the placebo group. What is more, in the December 16th version, GlaxoSmithKline reported that it could not provide a full, accurate count of the number of patients who had taken Paxil, making it impossible to fully analyze the data. Thus, GlaxoSmithKline's second 1999 report contained still another, new set of "bad" Paxil numbers.

*On June 6, 2001 a Wyoming Jury Awards $6.4 Million in a Paxil-Induced Murder-Suicide*

By the late 1990s, several lawsuits had been filed against GlaxoSmithKline over Paxil-induced suicides and murder-suicides. One of the best-known Paxil suicide cases is the so-called Tobin case, which went to trial in May 2001 in the United States District Court in Cheyenne, Wyoming. The case involved a sixty-year-old man, Donald Schell, who shortly after starting Paxil killed his beloved wife Rita, daughter Marie, and granddaughter Alyssa before committing suicide. The lawsuit was brought by the only surviving member of the family, Schell's son-in-law Tim Tobin who had been married to Marie and was the father of Alyssa.

On June 6, 2001 the jury of eight men and women found Paxil responsible for the gruesome murder-suicide, based on medical experts testifying about scientific evidence and internal GlaxoSmithKline documents.[68] The jury awarded $6.4 million in the case.

*On August 24, 2001, a Group of Plaintiffs File a Class Action Lawsuit Against GlaxoSmithKline Over Severe Withdrawal Reactions Including Suicides*

On August 24, 2001 a group of plaintiffs filed a class action lawsuit against GlaxoSmithKline over severe Paxil withdrawal reactions including suicides. Paxil withdrawal reactions occur when the drug is stopped abruptly or tapered too quickly. Episodes of Paxil withdrawal are one of the high-risk periods for Paxil-induced suicidality.[69] The group ultimately included over 3,000 patients who suffered severe withdrawal. The symptoms of Paxil withdrawal are divided into two main groups: physical symptoms and psychiatric symptoms.[70] The physical symptoms can include dizziness, flu-like aches and pains, nausea, headaches, tremors, and sensory abnormalities like electric zap-like sensations in the brain. The psychiatric symptoms can include crying spells, depressed mood, anxiety, insomnia, irritability, impulsivity, confusion, and suicidality. Severe Paxil withdrawal can be incapacitating and force patients to taper off the drug painstakingly slowly over months. A large-scale, systematic study of Paxil withdrawal conducted at Harvard Medical School found that 66% of patients abruptly stopping the antidepressant experienced withdrawal reactions.[71] In another Paxil study conducted by the British equivalent of the FDA, 21% of Paxil withdrawal reactions were mild, 58% were moderately severe, and 21% were severe.[72] In a catch-22, when patients and doctors are not well informed about Paxil withdrawal, the psychiatric symptoms can be mistaken for relapse, a return of the patient's original psychiatric condition.[73]

Although originally filed as a class action, the individuals in the Paxil withdrawal lawsuit ultimately became part of a multi-district litigation. The attorneys conducted extensive discovery and deposed GlaxoSmithKline executives. The ongoing litigation over Paxil withdrawal and Paxil-induced suicides put pressure on GlaxoSmithKline as attorneys and medical experts became aware of the company's inappropriate reporting of side effects including counting wash-out suicides and suicide attempts as though they occurred in the placebo group.[74] The Paxil withdrawal lawsuits were ultimately resolved to the plaintiff's satisfaction before going to trial.

*FDA Officials Testify that GlaxoSmithKline Should Not Have Counted Wash-Out Suicides and Suicide Attempts Against the Placebo Group*

FDA officials have also been deposed in the ongoing Paxil litigation. Dr. Robert Temple is the Director of the Office of Medical Policy and Acting Director of the Office of Drug Evaluation at the FDA. In his deposition, Dr. Temple was shown some of GlaxoSmithKline's table:[75]

Q Do you see where it says two of the five placebo suicides occurred during run in [another name for the wash-out period]. Do you see that?
A Yeah. You shouldn't count those as part of the placebo rate.

Dr. Martin Brecher was the FDA's medical officer who reviewed Paxil's safety. As discussed earlier, Dr. Brecher's report on Paxil's safety relied upon and reproduced GlaxoSmithKline's "bad" Paxil numbers. In his deposition, Dr. Brecher was asked:[76]

Q Is it scientifically legitimate to count a suicidal act occurring during wash-out and run-in to the placebo count?...
A No, because everybody got placebo.
Q So it's [a] scientifically illegitimate way to count, correct?
A Yeah.

*GlaxoSmithKline's CEO Testifies that the Company Should Not Have Counted Wash-Out Suicides and Suicide Attempts Against the Placebo Group*

GlaxoSmithKline's Chief Executive Officer, Dr. Jean-Pierre Garnier, has also been deposed in the ongoing Paxil litigation.[77] Garnier was asked when pharmaceutical companies should begin counting side effects in drug studies:

Q. Now, in terms of the clinical trials, there is a term called wash-out or run-in phase; are you familiar with those terms?
A Yes.

Q. Okay. And that in terms of when you are looking at a clinical trial, adverse events [side effects], you don't start counting them until the randomization period; is that correct?
A. Until the randomization period, yeah, that is correct.

Thus, GlaxoSmithKline's own Chief Executive Officer acknowledged that side effects should only be counted after the washout phase is complete and the official study has begun, when patients are randomly assigned to either be on placebo or the drug.

*On May 2, 2002, GlaxoSmithKline Discloses to the FDA Counting Wash-Out Suicide Attempts Against Placebo*

By the spring of 2002, GlaxoSmithKline decided it needed to disclose to the FDA that it had counted wash-out suicide attempts as though they occurred in the placebo group. On April 10, 2002 Dr. David Wheadon, GlaxoSmithKline's Senior Vice President of U.S. Regulatory Affairs, called Dr. Thomas Laughren, a senior medical officer at the FDA. According to an April 10, 2002 GlaxoSmithKline memo Wheadon wrote about the phone conversation:[78]

> I explained to Dr. Laughren that, subsequent to ongoing defense of Paxil cases, the issue of attempts in patients on placebo during placebo run-in had been debated and a decision had been made to reanalyze the original NDA [New Drug Application] data on suicide attempts....

Note that Dr. Wheadon specifically attributed GlaxoSmithKline's need to disclose the inaccuracy to "ongoing defense of Paxil cases." In other words, it was the diligent efforts of plaintiff's attorneys that forced GlaxoSmithKline to divulge the inaccurate counting method to the FDA. Note that Dr. Wheadon told Dr. Laughren GlaxoSmithKline had decided to "reanalyze the original NDA [New Drug Application] data on suicide attempts." Just a few weeks later, on May 2, 2002, GlaxoSmithKline submitted a report on the reanalysis discussed below in more detail. However, Dr. Wheadon goes on to say in his memo:

> I assured him that this was only an issue in terms of attempts and the other analyses stood as submitted in the NDA and the 1991 report based on the NDA (specifically completed suicides and the HAM-D item 3 analyses.)

This is not true. Completed suicides that occurred in the wash-out phase were counted as though they occurred in the placebo group in the New Drug Application and the special 1991 report to the FDA. In other words, GlaxoSmithKline only disclosed half the problem—the improper suicide attempts counts and not the improper completed suicide counts—to the FDA. Moreover, GlaxoSmithKline presented the data in 2002 in a new and different way. Rather than provide aggregate data on all of the Paxil studies, as they had up until this point, instead GlaxoSmithKline divided the data up into smaller pieces—they disaggregated it. GlaxoSmithKline divided the data up into three separate groups, discussed in detail below when I discuss the report GlaxoSmithKline submitted to the FDA. The net result of the new way in which GlaxoSmithKline presented the data was that the problem was again obscured.

The way in which GlaxoSmithKline presented the data in 2002 was not how they presented the data in the November 10, 1989 New Drug Application's Summary of Safety; the April 29, 1991 special report on suicidality when the FDA was looking at the issue intensely after reports of Prozac-induced suicidality; the September 20, 1991 FDA hearing on antidepressant-induced suicidality; the October 5, 1992 hearing to win FDA approval for Paxil; the December 1991 presentation to the American College of Neuropsychopharmacology; the May 1994 researchers' brochure; the 1995 Montgomery-Dunner-Dunbar article in *European Neuropharmacology*; or the July 5, 1995 memo to their sales force instructing them to use the article in *European Neuropharmacology* "with physicians to alleviate any concerns they may have regarding [Paxil-induced] suicidal ideation [thoughts]."

After presenting the data one way for over a decade, when GlaxoSmithKline disclosed the improper data (really only half of the inaccurate data because they did not disclose the inaccurate data on completed suicides) the company presented the data in a new way that again obscured the problem. Proclaimed Dr. Wheadon in his April 20, 2002 GlaxoSmithKline memo recounting his telephone conversation with Dr. Laughren:

> He stated that he did not see this as a regulatory issue given the outcome of these [new] analyses—that is that *none of them showed a signal of Paxil having a statistically greater incidence of attempts* vs. the comparator groups (placebo or active control). He said we should file these new data to the NDA as information but *no further action would be required* [emphasis added].

If GlaxoSmithKline had presented its new analysis of the correct data on suicide attempts the same way it had presented the inaccurate data for years, the correct data would have shown that Paxil increases the risk of suicide and suicide attempts more than eight-fold, as we have seen. But GlaxoSmithKline's new way of presenting the data obscured the problem again.

GlaxoSmithKline's report is dated February 6, 2002 and was apparently completed before Dr. Wheadon's April 10, 2002 telephone conversation with the FDA.[79] The company submitted the report to the FDA on May 2, 2002.[80] Below are the key tables from the report. Table 19 presents the Paxil data only for placebo-controlled trials. Note that only five of the 40 suicide attempts in patients on Paxil occurred during the placebo-controlled studies. The remaining 35 Paxil suicide attempts occurred during studies in which the control was another antidepressant or the studies were uncontrolled. Paxil still caused more than double the rate of suicide attempts, 0.5% versus 0.2%, but the increase is not statistically significant, the p-value is 0.42.

Table 19
**GlaxoSmithKline's 2002 "Disclosure" to the FDA**

| | Paroxetine | Placebo | P-value |
|---|---|---|---|
| n/N (%) | 5/921 (0.5%) | 1/554 (0.2%) | 0.42 |
| PYE | 108 | 51 | |
| n/PYE (rate relative to exposure) | 0.05 | 0.02 | 0.43 |

† in both cases above, n refers to the number of patients with the event

Five patients with attempted suicide have been excluded from the figures above for the placebo group because they occurred during the placebo run-in phase (1 09 021, 1 46 010, 7119 011, 7119 071, 7119 118)

Note that GlaxoSmithKline's admission that only one patient on placebo attempted suicide and that *five* other suicide attempts previously counted against placebo have now been "excluded from the figures" only appears as a footnote to the table in the report. Note also that GlaxoSmithKline continues to report patient-years exposure (PYE) calculations, which as discussed earlier are inappropriate because the risk of Paxil-induced suicidality is not evenly distributed over time.

Table 20
**GlaxoSmithKline's 2002 "Disclosure" to the FDA**

| | Paroxetine |
|---|---|
| n/N (%) | 40/2963 (1.3%) |
| PYE | 1008 |
| n/PYE (rate relative to exposure) | 0.04 |

† in both cases above, n refers to the number of patients with the event

Table 20 reproduces the table in GlaxoSmithKline's 2002 report detailing the 40 suicide attempts that occurred in all patients given Paxil. But the table fails to compare the complete Paxil number to the placebo number. In 2002, GlaxoSmithKline failed to pool all the data in one, overall, complete analysis. Instead, the company disaggregated the data, breaking it up into smaller pieces that obscured the problem. Up until now, from 1989 to 2002, GlaxoSmithKline had pooled the data. Indeed, in its 1991 report to the FDA, GlaxoSmithKline specifically commented: "Rather than introducing a selection bias, the data from all the trials has been pooled." But in 2002, GlaxoSmithKline changed the way it presented the data.

Compare Table 20 above to all of the earlier GlaxoSmithKline tables in which the 40 Paxil suicide attempts appear beside the placebo suicide attempts. See, for example, Table 7 on page 11 from GlaxoSmithKline's 1991 report to the FDA. Had GlaxoSmithKline shown the data the way it always had in the past, it would have looked like Table 9 on page 12 with the correct data on suicide attempts. The 40 Paxil suicide attempts in 1991 would be the same in 2002, but the 6 placebo suicide attempts in 1991 would be down to 1 in 2002. The significant difference would be instantly recognizable: a Paxil suicide attempt rate of 1.3% versus a placebo rate of 0.18%, representing a statistically significant more than seven-fold increased risk of suicide attempts for patients on Paxil.

Finally, GlaxoSmithKline should have disclosed that completed suicides which occurred in the wash-out phase were also inappropriately counted against placebo. GlaxoSmithKline should have added the correct completed suicide numbers to the correct suicide attempt numbers, combining all suicidal behavior. And GlaxoSmithKline should have directly compared in a table the complete,

correct suicidal behavior counts for Paxil with the correct counts for placebo. As we have seen in the combined suicidal behavior Table 10 on page 13, the full tally is 45 Paxil suicides and suicide attempts to only one placebo suicide attempt. Had GlaxoSmithKline compared the complete, correct counts, the data would have shown that Paxil causes a statistically significant, greater-than-eight-fold increased risk of suicidal behavior for patients put on the drug. Instead, GlaxoSmithKline's new way of presenting the data again obscured the problem.

### *In 2002-2003 The BBC Runs a Pair of Hard-Hitting Exposés on Paxil-Induced Suicide and Suicide Attempts*

On October 13, 2002 the British Broadcasting Company (BBC) ran a powerful exposé entitled "The Secrets of Paxil" on Paxil-induced suicidality and withdrawal reactions.[81] The BBC received an overwhelming response: some 65,000 calls from viewers, 1,300 emails, and 120,000 website hits. As a result of the response, the BBC ran a follow-up exposé on May 11, 2003 entitled "Paxil: Emails from the Edge."[82] The BBC exposés put enormous pressure on the British equivalent of the FDA—the Medicines and Healthcare products Regulatory Agency (MHRA). The British MHRA formed an advisory committee to look into Paxil-induced suicidality. At the time, GlaxoSmithKline was waiting for the British to approve Paxil for children. But when the advisory committee examined the Paxil pediatric data, they concluded that Paxil was not effective for depressed children *and* made them suicidal.

### *The British Virtually Ban Paxil for Children and Adolescents in 2003*

In June 2003, the British virtually banned Paxil for children and adolescents under eighteen years of age.[83] Immediately following the British announcement, on June 10, 2003 GlaxoSmithKline issued a "Dear Doctor" letter to physicians in England saying Paxil should not be prescribed to children and adolescents because it "failed" to work any better than placebo and frequently caused "hostility, agitation, [and] emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts, and attempted suicide)."[84] Unfortunately, GlaxoSmithKline did not simultaneously issue the warning here in the United States.

*The British Virtually Banning Paxil for Children and Adolescents Puts Pressure on the FDA*

The international publicity over the British virtually banning Paxil for children and adolescents put tremendous pressure on the FDA to re-examine the issue of antidepressant-induced suicidality. By December 2003, the British had virtually banned almost all of the SSRI-type antidepressants for children and adolescents. The British later changed the virtual ban to a warning to be aligned with the position taken by the European-wide equivalent of the FDA.

*The FDA Holds Two Hearings in 2004 on Paxil and Other Antidepressants Making Children and Adolescents Suicidal*

In response to public pressure, the FDA held two hearings on antidepressants making children and adolescents suicidal. Following the first hearing on February 2, 2004, the FDA issued an historic warning alerting doctors and patients that antidepressants may make adult and pediatric patients suicidal over and above any underlying depression.[85] The FDA warning covers all antidepressants currently on the market, including Paxil. The FDA warning states that "patients who are started on [antidepressant] therapy should be observed clearly for clinical worsening, suicidality, or unusual changes in behavior."[86] The FDA warning specifies a number of antidepressant side effects that may cause new or worsen existing suicidality. According to the FDA, these antidepressant side effects are "anxiety, agitation, panic attacks, insomnia, irritability, hostility, akathisia (severe restlessness), hypomania, and mania."[87] All of these side effects are acknowledged in the GlaxoSmithKline's official prescribing guidelines for Paxil.[88] Experts describe them as "paradoxical" side effects of antidepressants because they can cause a worsening of the patient's condition.[89] At the February 2004 hearing the FDA announced its intention to scrutinize the pediatric and ultimately the adult data on antidepressant-induced suicidality even more closely.

*In June 2004, New York Attorney General Eliot Spitzer Sues GlaxoSmithKline for Fraud over Its Handling of the Paxil Pediatric Data*

After the initial, historic FDA warning, in June 2004 New York Attorney General Eliot Spitzer sued GlaxoSmithKline for fraud over its handling of the Paxil

pediatric data. The linchpin of Spitzer's case was a secret, internal GlaxoSmithKline report dating to October 1998 saying the studies showed Paxil "failed" to be more effective than placebo pills in depressed children.[90] The secret memorandum urged company executives to "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact" that might "undermine the profile" of Paxil. In other words, the position paper raised concerns that the damaging information might affect Paxil's global sales, which approached $5 billion a year. How did the report propose to "effectively manage" the potentially damaging results? By selectively publishing the few "positive data" that would appear to make Paxil look good.

To accomplish this goal, GlaxoSmithKline turned to the psychiatrists who originally conducted the studies for the company. Headed by Dr. Martin Keller, chairman of the Department of Psychiatry and Human Behavior at the Brown University School of Medicine, a group of more than twenty leading academic psychiatrists published the selected Paxil data in the July 2001 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*.[91] In stark contrast to the 1998 secret, internal GlaxoSmithKline memo, Keller and his colleagues used highly selected pieces of positive data to glowingly conclude in 2001: "Paxil is generally well tolerated and effective for major depression in adolescents."

After the British and FDA warnings, in April 2004 the prestigious medical journal *The Lancet* published a damning critique of Keller's and a number of other similar antidepressant studies.[92] In an accompanying editorial, *The Lancet* expressed outrage over the GlaxoSmithKline internal memo and Keller's misleading report.[93] *The Lancet* described the "selective reporting of favourable research" when side effects as serious as drug-induced suicide are at stake as a "catastrophe" that "should be unimaginable." *The Lancet* called the false reassurances of the pharmaceutical industry and the academic psychiatrists who work closely with the industry "an abuse of the trust patients place in their physicians." Calling the burgeoning antidepressant scandal "a disaster," *The Lancet* called for "legal powers" to force pharmaceutical companies to make unpublished data public.

Keller's misleading 2001 report in the *Journal of the American Academy of Child and Adolescent Psychiatry* was highly influential and widely used to promote prescribing Paxil to children. After its publication, the use of antidepressants for children skyrocketed.[94] But two years later, in June 2003, on the basis of the same data, the British introduced their virtual ban on Paxil for children. After the FDA issued its historic warning after its February 2004 hearing, Eliot Spitzer filed suit

against GlaxoSmithKline charging the company with "fraud" for misrepresenting its studies of Paxil in children.[95] GlaxoSmithKline quickly settled the lawsuit.[96]

*The FDA Issues a Black Box Warning that Paxil and Other Antidepressants Can Make Children and Adolescents Suicidal*

On September 13 and 14, 2004 the FDA held its second hearing at which the agency presented its data analysis showing that antidepressants more than double the risk of suicidal behavior in children and adolescents. The increased risk is statistically significant. Thus, the FDA's data analysis showed a causal link between antidepressants and suicidal behavior in children and adolescents.[97] As a result, the FDA strengthened the warning on antidepressants making children and adolescents suicidal to the highest level possible: a prominent black box warning.[98] The agency stated that it was in the process of re-examining the data on adults. In the meantime, the FDA did not elevate its warning on adults to the level of a black box. However, the FDA continued to release advisories that adults need to be monitored closely for this side affect.[99]

Throughout 2005 and 2006, the FDA was reanalyzing the data on adults becoming suicidal on antidepressants. During this time, the results of the FDA's re-analysis were eagerly awaited. Once again, the FDA turned to pharmaceutical companies asking for their data on antidepressant-induced suicidality in adults.

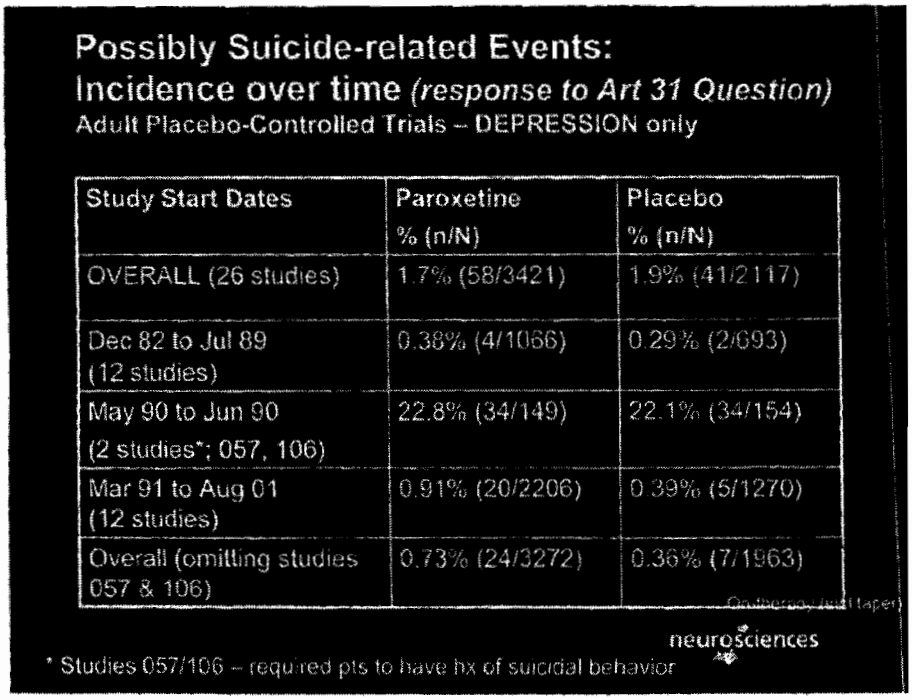
*The FDA Requests GlaxoSmithKline's Adult Paxil Data*

On December 24, 2004 the FDA requested that GlaxoSmithKline provide the agency with its adult Paxil data.[100] The FDA asked only for data from placebo-controlled studies of patients with major depressive disorder. The FDA's request excluded two Paxil studies that differed from other studies in an important way: These two studies—Studies 057 and 106—specifically recruited seriously suicidal patients, whereas other Paxil studies did not allow seriously suicidal patients. GlaxoSmithKline's protocol for Study 057 states that only adults "with a history of at least one episode of suicidal behavior and an episode of suicidal behavior within the last 10 days (index episode) were admitted" to the study.[101] Similarly, study 106 "specifically evaluated…patients [who] were at high-risk for suicidality…."[102]

Not surprisingly, a high rate of suicide attempts occurred in Studies 057 and 106. According to GlaxoSmithKline internal documents, "over 68% of patients with suicidality identified by means of an algorithmic analysis of verbatim adverse event [side effect] reports in placebo-controlled depression studies of Paxil in adults arose from studies 057 and 106, although 057 and 106 contributed only 5.5% of the patients in the adult placebo-controlled depression studies dataset."[103] In other words, some two-thirds of suicidal behavior occurred in these two relatively small studies, whose design—specifically studying **seriously** suicidal patients—was the opposite of GlaxoSmithKline's other studies, which specifically *excluded* seriously suicidal patients.[104] Because they were studies of a distinctly different patient population who had a high rate of suicide attempts, including the studies in the data analysis would confound the results and be inappropriate.

GlaxoSmithKline's global safety board met on January 24, 2005 to discuss the FDA's excluding the data from Studies 057 and 106.[105] Table 21 reproduces a slide prepared for the global safety board.[106] Note that all the other Paxil studies have relatively low rates of suicidal behavior ranging from 0.29% to 1.9% in the placebo or Paxil groups. Paroxetine in the table is the chemical name for Paxil. By contrast, Studies 057 and 106 in the middle of the table, in the third row, have a high rate of suicidal behavior: 22% of patients in the Paxil and placebo groups. Including in the high rates in Studies 057 and 106 would drown out the relatively small rates in the other studies, obscuring the differences between Paxil and placebo in the studies that excluded seriously suicidal patients.

**Table 21**
GlaxoSmithKline Global Safety Board Meeting
January 24, 2005



Possibly Suicide-related Events:
Incidence over time *(response to Art 31 Question)*
Adult Placebo-Controlled Trials – DEPRESSION only

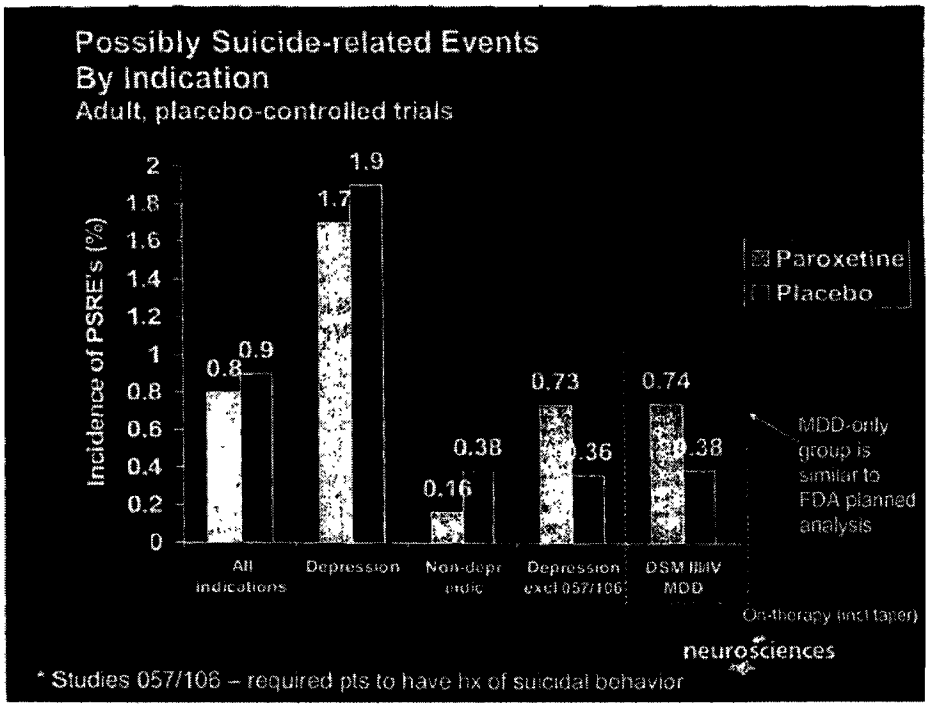
| Study Start Dates | Paroxetine % (n/N) | Placebo % (n/N) |
|---|---|---|
| OVERALL (26 studies) | 1.7% (58/3421) | 1.9% (41/2117) |
| Dec 82 to Jul 89 (12 studies) | 0.38% (4/1066) | 0.29% (2/693) |
| May 90 to Jun 90 (2 studies*; 057, 106) | 22.8% (34/149) | 22.1% (34/154) |
| Mar 91 to Aug 01 (12 studies) | 0.91% (20/2206) | 0.39% (5/1270) |
| Overall (omitting studies 057 & 106) | 0.73% (24/3272) | 0.36% (7/1963) |

neurosciences

* Studies 057/106 – required pts to have hx of suicidal behavior

Graph 3 reproduces another slide prepared for the global safety board.[107] The graph contains five pairs of bar graphs in which the white bars represent suicide-related events, or behavior, occurring in patients on Paxil while the black bars represent placebo. The first pair of bars presents the data on all Paxil studies including Studies 057 and 106; "all indications" on the x-axis means all diagnoses. More suicidal behavior occurred in patients on placebo than Paxil, although the two are nearly the same. The next pair of bars presents the data only for studies of depression, which still includes Studies 057 and 106. According to GlaxoSmithKline, the patients in Studies 057 and 106 were depressed and suicidal but not so depressed that they met the diagnostic criteria for major depressive disorder. Again, more suicidal behavior occurred in the patients on placebo, although Paxil and placebo are close to the same. The third pair of bars represents studies of diagnoses other than depression. The placebo rate is more than double the Paxil rate.

**Graph 3**
GlaxoSmithKline Global Safety Board Meeting
January 24, 2005




The last two pairs of bars in Graph 3 show what happens if one excludes the data from Studies 057 and 106, as the FDA planned to do. Note the dramatic difference: the rate of suicidal behavior in patients on Paxil is almost double the rate of suicidal behavior in patients on placebo. In other words, Studies 057 and 106 would indeed dilute the data, obscuring the problem of Paxil-induced suicidality. Removing Studies 057 and 106 reveals the problem. In the slide, an arrow explicitly points out that the last pair of bars represents the analysis the FDA "planned" on doing; an analysis of the studies of patients with major depressive disorder, which excluded Studies 057 and 106.

Another slide prepared for the global safety board meeting reported on a recent analysis of its adult data that GlaxoSmithKline conducted for the European Agency for the Evaluation of Medicinal Products, the European-wide equivalent for the FDA.[108] According to the slide, GlaxoSmithKline's analysis for the Europeans *included* the data from Studies 057 and 106. The analysis found:[109]

> Overall (i.e. across all indications [diagnoses]) the incidence of on-therapy possibly suicide-related events [behavior] was 0.8% in the Paxil treatment group and 0.9% in the placebo group. Although possibly-suicide related events occurred at a lower incidence in the Paxil group than in the placebo group this difference was not statistically significant (Paxil 66/8481 (0.8%), placebo 55/5808 (0.9%), OR 0.82, 95% Cl 0.57, 1.18, P=0.31).

The results of the analysis GlaxoSmithKline did for the Europeans are shown in the first pair of bars on the left in Graph 3. Because GlaxoSmithKline's analysis for the Europeans included the confounding data in Studies 057 and 106, it did not show an increased risk of Paxil-induced suicidality. By excluding the confounding data in Studies 057 and 106, the analysis the FDA planned would show the problem with Paxil.

Table 23 and Table 24 below further demonstrate how including Studies 057 and 106 mask the statistically significant difference in suicide attempts between Paxil and placebo in GlaxoSmithKline's studies. Table 22 reproduces Table 1 in an October 25, 2005 GlaxoSmithKline report on suicide attempts that included Studies 057 and 106. As seen in Table 22, when Studies 057 and 106 are included there is no statistically significant difference between the rate of suicide attempts in patients on Paxil versus placebo. As indicated by the arrows, this is true for both the overall data including patients with all diagnoses and for the data including only patients in GlaxoSmithKline's studies of depression. The p-values were not statistically significant: 0.51 and 0.61 respectively.

Table 22
**From a GlaxoSmithKline October 25, 2002 Analysis of Suicide Attempts in its Paxil Studies**

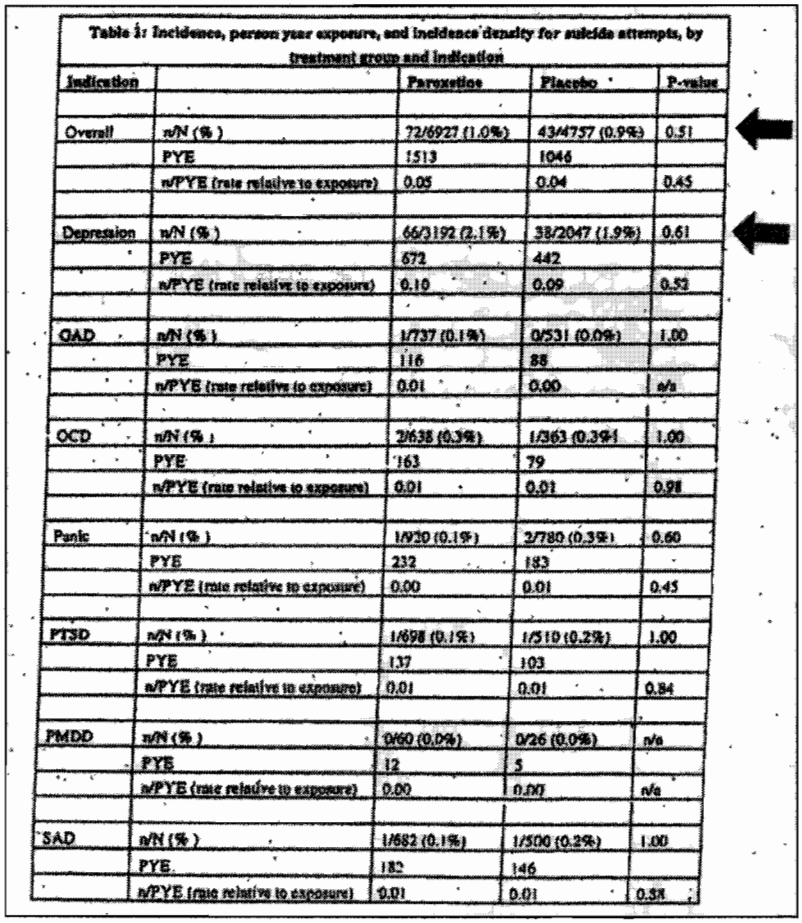


**Table 1: Incidence, person year exposure, and incidence density for suicide attempts, by treatment group and indication**

| Indication | | Paroxetine | Placebo | P-value |
|---|---|---|---|---|
| Overall | n/N (%) | 72/6927 (1.0%) | 43/4757 (0.9%) | 0.51 |
| | PYE | 1513 | 1046 | |
| | n/PYE (rate relative to exposure) | 0.05 | 0.04 | 0.45 |
| Depression | n/N (%) | 66/3192 (2.1%) | 38/2047 (1.9%) | 0.61 |
| | PYE | 672 | 442 | |
| | n/PYE (rate relative to exposure) | 0.10 | 0.09 | 0.52 |
| GAD | n/N (%) | 1/737 (0.1%) | 0/531 (0.0%) | 1.00 |
| | PYE | 116 | 88 | |
| | n/PYE (rate relative to exposure) | 0.01 | 0.00 | n/a |
| OCD | n/N (%) | 2/638 (0.3%) | 1/363 (0.3%) | 1.00 |
| | PYE | 163 | 79 | |
| | n/PYE (rate relative to exposure) | 0.01 | 0.01 | 0.98 |
| Panic | n/N (%) | 1/920 (0.1%) | 2/780 (0.3%) | 0.60 |
| | PYE | 232 | 183 | |
| | n/PYE (rate relative to exposure) | 0.00 | 0.01 | 0.45 |
| PTSD | n/N (%) | 1/698 (0.1%) | 1/510 (0.2%) | 1.00 |
| | PYE | 137 | 103 | |
| | n/PYE (rate relative to exposure) | 0.01 | 0.01 | 0.84 |
| PMDD | n/N (%) | 0/60 (0.0%) | 0/26 (0.0%) | n/a |
| | PYE | 12 | 5 | |
| | n/PYE (rate relative to exposure) | 0.00 | 0.00 | n/a |
| SAD | n/N (%) | 1/682 (0.1%) | 1/500 (0.2%) | 1.00 |
| | PYE | 182 | 146 | |
| | n/PYE (rate relative to exposure) | 0.01 | 0.01 | 0.58 |

As seen in Table 23, when the data from Studies 057 and 106 are excluded from the overall analysis of all diagnoses, patients on Paxil had a statistically significant increase in the risk of suicide attempts. The odds ratio was 2.8 and the p-value was 0.014. Similarly, as seen in Table 24, when the data from Studies 057 and 106 are excluded from the analysis of GlaxoSmithKline's depression studies, depressed patients on Paxil had a statistically significant greater-than-three-fold increased risk of suicide attempts when compared to depressed patients on placebo; the p-value was 0.0004. Diluting the data by including the two confounding Studies 057 and 106 *masks* this statistically significant difference. Yet this is precisely what GlaxoSmithKline sought to do.

Table 23
**GlaxoSmithKline 2002 Data**
Suicide Attempts – Worldwide data

| | Paxil 6927 patients | Placebo 4757 patients | Odds Ratio Paxil/ Placebo | Statistically Significant? |
|---|---|---|---|---|
| **Overall (i.e. all diagnoses)** | 72<br>1.0% | 43<br>0.9% | 1.15 | No<br>p = 0.51 |
| **Overall with the data from Studies 057 and 106 excluded** | 35<br>0.5% | 10<br>0.2% | 2.38 | Yes<br>p = 0.014 |

Table 24
**GlaxoSmithKline 2002 Data**
Suicides – Worldwide data

| | Paxil 3192 patients | Placebo 2047 patients | Odds Ratio Paxil/ Placebo | Statistically Significant? |
|---|---|---|---|---|
| **Depression Studies** | 66<br>2.1% | 38<br>1.9% | 1.12 | No<br>P = 0.61 |
| **Depression with the data from Studies 057 and 106 excluded** | 29<br>0.9% | 5<br>0.24% | 3.61 | Yes<br>P = 0.004 |

Two days after the GlaxoSmithKline global safety board meeting, on January 26, 2005, the company wrote to the FDA requesting "clarification with regard to some of the details of the analyses described in the [FDA's] December 24th [2004] letter" requesting the adult Paxil data.[110] In the letter, GlaxoSmithKline questioned the two obstacles that stood in the way of including Studies 057 and 106: the FDA originally requested only data on studies of patients with major depressive disorder and only studies lasting less than seventeen weeks. Studies 057 and 106 were not studies of patients with major depressive disorder. As described earlier, they were studies of patients with milder forms of depression but who were at high risk for suicidal behavior. And, Studies 057 and 106 both lasted longer than seventeen weeks; Study 106 lasted twenty-four weeks and patients could stay in Study 057 for up to 52 weeks.[111] In its January 26, 2005 letter, GlaxoSmithKline requested that the "FDA considers expanding the requested analyses to include studies conducted for other [psychiatric] conditions" and also questioned the "rationale" for "the criteria of limiting the studies analyzed to those 'up to 17 weeks.'" In other words, GlaxoSmithKline sought to remove both obstacles to including Studies 057 and 106.

Over the next twelve months, GlaxoSmithKline lobbied the FDA to include the two studies. In a March 18, 2005 email, the agency declined to broaden the scope of the analysis to diagnoses other than major depression because of limited resources.[112] The FDA expressed concerns about the longer-term Studies 057 and 106 because the patients were "clinically different" and could "dilute" the data from the other studies, thereby confounding the analysis.[113] In a May 12, 2005 letter, the FDA agreed to include other diagnoses besides major depressive disorder.[114] But the FDA requested that GlaxoSmithKline submit two separate datasets: one with only the data originally requested from studies of major depressive disorder and a second with the data from studies of other diagnoses.[115] A separate analysis of the major depressive disorder dataset would still exclude Studies 057 and 106. And, the other obstacle to including the two studies—the seventeen-week cut-off—also still remained.

GlaxoSmithKline's global safety board met again to discuss the matter on June 24, 2005. The GlaxoSmithKline executives expressed concern "that the analysis currently planned by the FDA" would "differ" from GlaxoSmithKline's earlier analyses.[116] An "Executive Summary" of the June 24, 2005 global safety board meeting states: "Thus, the team proposes sending a *second* response to FDA to ask that they *reconsider* the inclusion" of Studies 057 and 106 "in their evaluation [emphasis added]."[117]

Anticipating that the FDA analysis would produce a different result, the Paxil team also proposed "conducting an in-house analysis in parallel to FDA" according to the minutes of the June 24, 2005 meeting.[118] The global safety board approved the in-house analysis. GlaxoSmithKline went ahead and did an in-house analysis in parallel with the FDA. GlaxoSmithKline separately analyzed the data from the studies of patients with major depressive disorder, which excluded Studies 057 and 106, expecting the FDA to do the same.

GlaxoSmithKline sent another letter to the FDA on July 28, 2005 again requesting the agency include Studies 057 and 106.[119] The FDA responded with two emails dated August 26 and September 2, 2005.[120] The emails asked for additional information on the high-risk patients in Studies 057 and 106. The FDA also asked GlaxoSmithKline to respond to the agency's concern that "pooling high risk patients with lower risk patients" would dilute the data and "obscure findings" in the data analysis.

GlaxoSmithKline appealed to the FDA again on September 20, 2005.[121] The company acknowledged that the patients recruited into Studies 057 and 106 had a high risk of suicidal behavior, but still argued for including them in the analysis. Even though GlaxoSmithKline knew from its own preliminary analysis that including Studies 057 and 106 would dilute the data and obscure findings, the company only acknowledged that as a *possibility* and attempted to justify including the studies nonetheless.

In its efforts to lobby the FDA, in the fall of 2005 GlaxoSmithKline hired two consultants: Dr. John Mann is a professor of psychiatry at Columbia University Medical Center. Columbia's psychiatry department has been intimately involved in assisting the FDA evaluate the data on antidepressant-induced suicidality. The FDA hired the Columbia group to classify all the suicidal behavior in the pediatric studies of antidepressants for its analysis of the pediatric data. And GlaxoSmithKline hired the Columbia group to classify suicidal behavior in its adult studies before it submitted the data to the FDA.

On October 11, 2005, seven GlaxoSmithKline doctors and scientists met with Mann at Columbia. For the meeting, GlaxoSmithKline prepared a slideshow presenting its "rationale for including… Studies 057 and 106."[122] According to internal GlaxoSmithKline documents, after the meeting Mann "intends to discuss with Tom Laughren at FDA" including Studies 057 and 106.[123] Dr. Thomas Laughren is a senior medical officer at the FDA who has overseen the FDA's investigation of antidepressant-induced suicidality.[124] Laughren has been central

to the FDA's handling of the matter since 1990 when SSRI-induced suicidality first came to public and professional attention. In the fall of 2005, Laughren was the FDA official with whom GlaxoSmithKline was negotiating trying to include Studies 057 and 106.[125]

GlaxoSmithKline also consulted with Dr. Michael Thase, professor of psychiatry at the University of Pittsburgh Medical Center.[126] Like Mann, Thase is a prominent academic psychiatrist with close ties to the pharmaceutical industry. On October 21, 2005, six GlaxoSmithKline executives met with Thase.

Throughout this time, Dr. Pam Barrett was the leader of GlaxoSmithKline's Paxil team.[127] Barrett recently testified in a deposition that the company never heard back from the FDA with a final word on whether or not the agency would agree to including Studies 057 and 106. So, the company went ahead and did the two data analyses it expected the FDA to do: One analysis of just the major depression studies, which would excluded Studies 057 and 106, and a second analysis of the data from all diagnoses, in which GlaxoSmithKline included Studies 057 and 106.

*In May 2006, GlaxoSmithKline Releases Its Analysis of the Adult Paxil Data Showing the Risk that Has Always Been There*

GlaxoSmithKline's in-house analysis indeed showed that adults with major depressive disorder given Paxil have more than six times the rate of treatment-emergent suicidality when compared to patients given placebo.[128] This six-fold difference is statistically significant; the lower limit of the confidence interval is greater than one.[129] As GlaxoSmithKline suspected, excluding Studies 057 and 106 revealed the risk that has always been there. Recall that the correct, original 1989 Paxil data submitted to the FDA was also based on studies of adults with major depressive disorder and showed a greater-than-eight-fold, statistically significant increased risk of suicidal behavior for patients on Paxil. The difference in the magnitude of the increased risk—more than six-fold versus more than eight-fold—owes to the different points in time, patient populations, and methodologies.[130] The bottom line is that a statistically significant, substantially increased risk has always been there in GlaxoSmithKline's data.

In the fall and winter of 2005-2006, GlaxoSmithKline wrote several drafts of a report on its findings to the FDA.[131] The company submitted the report on March 8, 2006.[132] In **a cover** letter, GlaxoSmithKline acknowledged the need to revise its

official Paxil prescribing guidelines. At the time the Paxil prescribing guidelines described the risk for children and adolescents, since the FDA's black box warning, but said: "It is also unknown whether the suicidality risk extends to adults."[133] GlaxoSmithKline deleted that sentence and acknowledged the significant increased risk for adults.[134]

In May 2006, GlaxoSmithKline issued a "Dear Doctor" letter announcing the results of its new analysis and the changes in its official prescribing guidelines for Paxil.[135] The letter states:

> GlaxoSmithKline (GSK) would like to advise you of important changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section on the labels for PAXIL (paroxtine HCI) and PAXIL CR (paroxetine HCI Controlled-Release Tablets). These labeling changes relate to your adult patients....In the analysis of adults with MDD (all ages) [i.e. adults of all ages with depression], the frequency of suicidal behavior was higher in patients treated with paroxetine [Paxil] compared to placebo....This difference was statistically significant....

In the Briefing Document released along with the letter, GlaxoSmithKline stated:[136]

> Notably, the odds ratios for Definitive Suicidal Behavior for the MDD [depressed] population are 6.7....

That is, depressed adults on Paxil were 6.7 times more likely to exhibit suicidal behavior than patients on placebo in GlaxoSmithKline's studies. The dramatic increase in risk is not based on new data; this is merely a new analysis of its old Paxil data forced by the heightened attention to the issue and by the FDA's excluding the confounding data from Studies 057 and 106.

Once again, GlaxoSmithKline attempted to minimize the significance of Paxil's six-fold increase in treatment-emergent suicidality by claiming that the "absolute number and incidence of events [of suicidal behavior] are small."[137] But, as described earlier, the reported number of suicidal events is small because suicides and suicide attempts are uncommon events in studies where seriously suicidal patients are excluded. Moreover, GlaxoSmithKline collects side effects data using insensitive, unsystematic, open-ended questions that underestimate the true incidence of side effects.

*On December 13, 2006 the FDA Presents Its Analysis of GlaxoSmithKline's Adult Paxil Data Showing the Risk That Has Always Been There*

The FDA held its most recent hearing on antidepressant-induced suicidality on December 13, 2006. At the hearing, the FDA presented its latest data analysis of adults becoming suicidal on antidepressants.[138] Ironically, the FDA did their analysis the way GlaxoSmithKline had wanted the agency to: the FDA did not separately analyze the data for major depressive disorder by drug (or at least did not publicly announce the results) and the FDA lifted the seventeen-week cut-off. So, the FDA apparently included Studies 057 and 106. If GlaxoSmithKline had not separately analyzed the studies of patients with major depressive disorder because it *thought* the FDA was going to, the substantial increased Paxil risk would still not be known.

In addition to its overall analysis of all the antidepressants it studied, the FDA released its analysis on each of the specific antidepressants. According to the FDA, Paxil increases the risk of behavior in adults by a factor of 2.76.[139] That is, Paxil almost triples the risk of suicidal behavior in adults. The increased risk is statistically significant; the p-value is 0.02.[140] Thus, the most recent FDA analysis demonstrates a causal link between Paxil and suicidal behavior in adults as well as children and adolescents. The FDA's figure of Paxil more than doubling the risk of suicidal behavior differs from GlaxoSmithKline's most recent figure of Paxil increasing the risk by more than six-fold, in part, because the FDA's figure is based on adults with *all* psychiatric disorders while GlaxoSmithKline's figure is based on adults with major depressive disorder. The bottom line is that a statistically significant risk has always been there in GlaxoSmithKline's Paxil data for all age groups.

To date the FDA has limited itself to warnings that apply to all antidepressants on the market. Experts report that this is because of pressure from the pharmaceutical industry; in this way no one drug is singled out to have a market disadvantage. On the basis of its December 13, 2006 hearing, the FDA is extending the black box warning to adults under the age of twenty-five. So far, the standard the FDA has used for the black box warning is a statistically significant, two-fold-or-greater increase in the risk of suicidal behavior. If the FDA applied the same standard to individual antidepressants, in the case of Paxil the black box warning would apply to all age groups based on the FDA's own analysis of GlaxoSmithKline's data.

*GlaxoSmithKline's "Bad" Paxil Data Obscured the Risk of Paxil-Induced Suicidality for Over Fifteen Years*

The list below summarizes the chronology of GlaxoSmithKline's "bad" Paxil data obscuring the risk of Paxil-induced suicidal behavior from 1989 to 2006, more than a decade-and-a-half.

| | |
|---|---|
| • 1989 New Drug Application Summary of Safety | GlaxoSmithKline's Original "Bad" Paxil Numbers Obscured the True Risk |
| • 1991 Report to the FDA Scrutinizing the Issue | GlaxoSmithKline's New, More Egregious "Bad" Paxil Numbers Obscured the True Risk |
| • 1991 FDA Hearing | GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk Again |
| • 1991 Presentation to American College of Neuropsycho-pharmacology | GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk Again |
| • 1992 Hearing to Win FDA Approval for Paxil | GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk Again |
| • 1994 Researchers' Brochure | A New Version of GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk |
| • 1995 Montgomery-Dunner-Dunbar article in *European Neuropsychopharmacology* | GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk Again |

| | |
|---|---|
| • 1995 Instructions to Sales Force to Reassure Doctors | GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk Again |
| • 1999 Report to the FDA | Still Another Version of GlaxoSmithKline's "Bad" Paxil Numbers Obscured the True Risk |
| • 2002 "Disclosure" to the FDA that It Counted Wash-Out Events Against Placebo | GlaxoSmithKline "Discloses" Only Half the Problem and Presents the Data in a New Way That Again Obscures the True Risk |
| • 2003 British Virtually Ban Paxil for Children and Adolescents | GlaxoSmithKline Is Forced to Acknowledge the Risk for Children and Adolescents |
| • 2004 Eliot Spitzer Sues GlaxoSmithKline for Fraud over Its Handling of the Pediatric Data | GlaxoSmithKline Quickly Settles the Lawsuit |
| • 2006 GlaxoSmithKline's Report to the FDA on Adults | GlaxoSmithKline Acknowledges the Statistically Significant Risk for Adults But Only Those with Major Depression and Emphasizes Younger Adults |
| • 2006 FDA Analysis of the Paxil Adult Data | FDA's Analysis of GlaxoSmithKline's Paxil Data Shows the Risk Extends to Patients of All Ages and All Diagnoses |
| • The CORRECT, ORIGINAL 1989 Data | Shows the Risk Was Always There in GlaxoSmithKline's Data |

The above chronology indicates a pattern of GlaxoSmithKline's repeated "bad" Paxil numbers obscuring the true risk for over a decade-and-a-half.

Part 2: GlaxoSmithKline's Researchers' Assessments of Whether or Not Paxil Caused Suicidal Behavior in the Company's Studies

During its Paxil studies, when patients exhibited suicidal behavior, GlaxoSmithKline asked its researchers to assess whether or not the behavior was related to, or caused by, Paxil. These causality assessments are an important part of the Paxil database.

On May 9, 2006, GlaxoSmithKline's Chief Executive Officer Jean-Pierre Garnier was deposed. At the deposition, when Garnier was asked if the assessments are important for establishing whether or not Paxil causes suicidality, he responded:[141]

> A: It's another element to be considered.

Garnier was asked how many reports would constitute a critical number:

> Q: If 30 investigators [researchers] reported…that they thought that Paxil was causing suicide events…is that something that would be important to your company?
> A Important, yes. I'm sure this has been taken into consideration.

Garnier's testimony is supported by internal company documents describing causality assessments as an important component in GlaxoSmithKline's evaluating whether or not Paxil causes a particular side effect.[142]

In the protocol for its Paxil studies, GlaxoSmithKline gives the following instructions to its researchers for assessing the causality of potential Paxil side effects:[143]

> Every effort should be made by the investigator to explain each adverse experience [side effect] and assess its relationships, if any, to study drug treatment. Causality should be addressed using the following categories: unrelated, probably unrelated, possibly related, related.
>
> The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative cause, e.g. natural

history of the underlying diseases, concomitant therapy etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

a) Known pharmacology of the drug. [SSRIs like Paxil boost serotonin in the brain, causing a reflexive drop in dopamine, which has been linked to medication-induced suicidality for decades.[144]]

b) Reaction of similar nature being previously observed with this drug or class of drugs. [Antidepressant-induced suicidality was reported before Paxil was on the market.]

c) The experience having often been reported in literature for similar drug as drug related e.g. skin rashes, blood dyscrasia. [Again, antidepressant-induced suicidality was reported before Paxil was marketed.]

d) The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

GlaxoSmithKline defined related, possibly related, probably related, and unrelated as follows:[145]

RELATED: There is a *direct cause and effect* relationship between the adverse experience and the study drug

POSSIBLY RELATED: A *direct* cause and effect relationship between the drug and the adverse experience has not been demonstrated but *is possible* or likely

PROBABLY UNRELATED: Cause and effect relationship between the drug and the adverse experience has not been demonstrated, is improbable but not impossible

UNRELATED: The adverse experience is definitely not related to the rest drug [emphasis added]

In some studies GlaxoSmithKline used a slightly different, five-point scale: Definitely, probably, possibly, probably not, and definitely not. Rating suicidal behavior as definitely caused by Paxil required that the patient be dechallenged and rechallenged—that is, taken off Paxil and later put back on the drug. If the suicidal behavior disappeared when the patient was taken off Paxil and reappeared when the patient was put back on the drug, then GlaxoSmithKline instructed its researchers to assess the suicidal behavior as definitely related to Paxil.

GlaxoSmithKline received numerous reports of suicide attempts, worsening depression, or suicidal thoughts that its own researchers judged possibly, probably, or definitely related to Paxil. Below are some of the reports from GlaxoSmithKline's researchers:

> Patient number: 136.067.0403. This 51 year old Caucasian female was hospitalized on day 42 for severe depression and the following day she attempted suicide by ingesting 10 tablets of flunitrazepam [a sleeping pill/anti-anxiety agent] (20mg), reported as a severe adverse experience [side effect] of emotional lability [GlaxoSmithKline's code for suicidality]. She had been receiving 50mg Paxil daily which was discontinued on day 43. In the opinion of the investigator, the diagnosis of aggravated depression was probably related to study medication, and the suicide, *related.*
>
> Patient number: 059.005.0003. This 50 year old female…received Paxil 20mg on days 0 to 3 and Paxil 30mg on days 4 to 6….The patient displayed severe suicidal tendencies (preferred term: emotional lability), paranoid reaction and insomnia from day 5, which the investigator considered to be *probably related to treatment.* The patient was withdrawn on day 6 because of these adverse events [side effects] and a lack of [therapeutic] effect. After withdrawal the events were treated using levomepromazine [an antipsychotic] 125mg and amitriptyline [an older, tricyclic antidepressant] 50mg. The emotional lability [GlaxoSmithKline's code for suicidality] was considered to be serious as it was *incapacitating, life threatening and prolonged hospitalization.*
>
> Patient number: 059.003.0079. This 55 year [old] male patient….received Paxil 20mg on days 0 to 3 and Paxil 30mg for a further 10 days….The patient developed moderate agitation from

day 2 for four days. This had become severe by day 7 and continued for a further seven days. By day 12 the patient had developed severe suicidal tendencies (preferred term: emotional lability). The patient was withdrawn on day 13 because of these adverse events [side effects] and a lack of effect. All events were considered by the investigator to be *possibly related to study treatment*. The emotional lability [suicidality] was considered to be serious as it was *incapacitating*.

Patient document number: 000843. [A 29 year old] patient receiving Paxil in a Paxil study was hospitalized for suicidal ideation [thoughts]. The patient complained of worsening depression. He had a feeling of worthlessness and helplessness. Paxil was discontinued and Elavil [an older, tricyclic antidepressant] was administered. The patient was scheduled for group therapy and transferred to another psychiatric institution. Outcome: hospitalized. Investigator relationship: *related*.

Patient document number: 6664. [A 38 year old] patient receiving Paxil in a Paxil study developed a hypomanic episode with suicidal ideation and was found shoplifting. She was hospitalized and treated with lithium. Study medication was discontinued. Patient was discharged. Outcome: recovered. Investigator relationship: *related*.

Patient number: 149ei. The patient was a 46 year old caucasian male....On day 18, emotional lability *(suicide attempt)* regarded as a serious event was noted and *attributed to the drug* by the investigator. *This adverse event lasted 4 days and disappeared before the end of the study when the patient was withdrawn [from the study].*

Patient number: 349.XXX.1173. Increasing Suicidality....*Definitely related.*

Identification number: PRX920276U. A patient taking Paxil committed suicide. The reporting physician considers the event was *possibly drug related.*

Patient number: 349.XXX.2701. Severe psychomotoric restlessness [and] increase of suicide tendency....*Definitely related.*

> Patient number: 715.201.00106. On 25-Jan-2001 [a 10 year old boy] began therapy with study medication, Paxil. On 11-Mar-2001, 45 days after the patient began therapy with study medication, the patient ran away from home to his father's house, and was returned to his mother on 12-Mar-2001, the patient was reported to be "out of control" and was admitted to an emergency room for severe mania and suicidal ideation....The patient was withdrawn from the study and the study medication was stopped due to the events. The patient received 20mg of study medication at the time of the events, and had completed the dose-rising phase of the study from 10 mg to 30 mg (30 mg until 09-Mar-2001). The investigator clarified that the suicidal ideation was symptomatic of the severe mania. *The investigator reported that the severe mania and suicidal ideation were life-threatening, disabling/incapacitating, and possibly related to treatment with study medication.*
>
> A 34 year old male patient requested hospitalization due to increased depression. He was discharged to attend a relative's funeral and *committed suicide* (hanging) the next day. The investigator felt that the events *may have resulted from aggravation of the patients' primary disease or enhancement of irritated feeling by antidepressant during treatment.*
>
> Patient number: 05 01 A 030....Attempted overdose....Definitely related.

One list of Paxil side effects in GlaxoSmithKline's studies includes 29 reports of suicide attempts, suicide gestures, suicidal thoughts, and self-destructive urges that the company's researchers judged possibly, probably, or definitely related to Paxil.[146] The list has a cutoff date of January 16, 2006 but is apparently not complete since another thirteen individual case reports of suicidality attributed to Paxil—including some dating to before January 16, 2006—are not on the list. This is a total of at least 42 cases, well above the 30 cases that GlaxoSmithKline's CEO Jean-Pierre Garnier testified would be "important" to "take into consideration" when evaluating a potential causal link between Paxil and suicidal behavior.

GlaxoSmithKline also received numerous reports of akathisia and agitation-type reactions, the antidepressant side effect most closely linked to antidepressant-

induced suicidality. Akathisia is a form of drug-induced agitation, as explained in my earlier report. GlaxoSmithKline's researchers rated numerous agitation-type reactions as definitely, probably, or possibly related to, i.e. caused by, Paxil. Below are some of the reports from GlaxoSmithKline's researchers:

> Patient number: 116.007.0198. This 37-year-old caucasian male....on Day 1 of Paxil 20mg dose level, patient developed severe akathisia....Severe akathisia was treated with Inderal (propranolol hydrochloride) 20mg daily for one week followed by one month of treatment at 30mg daily. Akathisia...resolved about three weeks after study medication was discontinued....The investigator [researcher] reported the adverse events [side effects] as *probably related* to the study medication.[147]
>
> Patient number: 02H.007. [A 38 year old women experienced] agitation....Severe. Relationship: *Definite.*[148]
>
> Patient number: 4615. Patient [was a 53-year-old woman who] participated in drug monitoring study...from 27-Oct-92 to 7-Nov-92....On 30-Oct-92, the patient developed 'unrest and agitation.' The patient recovered. She received Paxil, 20 mg, daily, for 12 days. Physician relationship: *'Related.'*[149]
>
> Patient number: 349.XXX.0588. [Experienced] inner restlessness [and] psychomotoric restlessness. *Probably related.*[150]
>
> Patient number: 349.XXX.1665. [Experienced] restlessness, increase of impulsion. *Probably related.*[151]
>
> Patient number: 349.XXX.3534. [Experienced] increased restlessness. *Possibly related.*[152]
>
> Patient number: 4441. Patient [a 38-year-old woman on 20mg/day of Paxil] participated in drug monitoring study...starting on 22-Oct-92....On 22-Oct-92, she developed...anxiety and inner restlessness....Physician relationship: *'Related.'*[153]
>
> Patient number: 00263. This 56-year-old female patient experienced...increased restlessness...after starting Paxil. The events lasted for several days and led to the withdrawal of Paxil.

> The treating physician considered these events as *possibly related* to Paxil.[154]
>
> Patient number: 1714. [A] 59-year-old man participating in drug monitoring while under treatment with Paxil 20mg (from 20-Sep-92), experienced restlessness....Relationship per investigator [researcher]: *'probable.'*[155]
>
> Patient number: 239.204.9233. [A 27-year-old woman on 20mg/day of Paxil developed] mania...[and] psychomotor agitation....Investigator [researcher] Relationship: *Definitely related.*[156]

Part 3. The Published Medical Literature on Antidepressant-Induced Suicidality and Self-Harm

As described in my earlier report, an extensive medical literature dating back decades has reported on antidepressant- and, more specifically, SSRI-induced suicidality. In the attached Appendix A, Binder 10 is a bibliography of over fifty articles and studies published in medical journals including the *Journal of the American Medical Association, New England Journal of Medicine, Lancet, British Medical Journal, American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, European Psychiatry,* and *British Journal of Psychiatry.* Below are brief descriptions of a few of the published journal articles I have relied upon in forming my opinion, including studies of antidepressant-induced suicidality whose analyses achieve statistical significance.

1. **Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B. "Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials."** ***British Medical Journal.*** **2005 Feb 19; 330 (7488):396.**

This study utilized data from 702 clinical studies of selective serotonin reuptake inhibitor antidepressants (SSRIs, including Paxil) where the drugs were compared to placebo or an older, comparison antidepressant. A total of 87,650 patients were involved in the studies. The data analysis found "a more than two-fold increase in the rate of suicide attempts" in patients on SSRIs when compared to patients on placebo pills. The odds ratio of suicide attempts in patients on SSRIs versus patients on placebo was 2.28 with a p value of 0.02 and a 95% confidence ratio of 1.14 to 4.55.

2. **Donovan S, Clayton A, Beeharry M, Jones S, Kirk C, Waters K, Gardner D, Faulding J, Madeley R. "Deliberate self-harm and antidepressant drugs. Investigation of a possible link."** ***British Journal of Psychiatry.*** **2000 Dec; 177: 551-6.**

This prospective study collected data on 2,776 consecutive patients who came to a hospital emergency room after acts of deliberate self-harm (including overdoses, other forms of suicide attempts, or behavior like cutting oneself). The study compared the incidence of self-harm in patients on SSRIs versus older, tricyclic antidepressants. The study found that: "Significantly more DSH [deliberate self-harm] events occurred following the prescription of an SSRI than that of a TCA [tricyclic antidepressant]." The difference was statistically significant, with a p value of <0.001. Patients on Paxil were 4 times more likely to harm themselves than patients on an older, comparison antidepressant.

3. **Muller-Oerlinghausen B, Berghofer A. "Antidepressants and Suicide Risk."** ***Journal of Clinical Psychiatry*** **1999; 60 Suppl 2: 94-9.**

Had the Donovan study above been conducted in this country, a concern might be preferential prescribing practices, where doctors might be more likely to prescribe SSRIs to patients who were suicidal because they are safer in overdose than older, tricyclic antidepressants. But the opposite is true in Europe, where the Donovan study was conducted in England. Muller-Oerlinghausen and Berghofer are two psychiatrists in Germany who report in this article: "Several antidepressants including the selective serotonin reputable inhibitors (SSRIs) may increase suicidal behavior by energizing depressed patients to act along preexisting suicidal thoughts or by inducing akathisia with associated self-destructive impulses. For acutely suicidal patients, the use of more sedating [older, tricyclic] antidepressants is recommended....General textbook wisdom—at least in Europe—recommends preference of the more sedating antidepressants in suicidal patients because of the risk of activating preexisting thoughts...."

4. **Jick H, Kaye JA, Jick SS. "Antidepressants and the risk of suicidal behaviors."** ***Journal of the American Medical Association (JAMA).*** **2004 Jul 21; 292 (3):338-43.**

This study examined data on suicide attempts in 159,810 patients on four antidepressants (Prozac, Paxil, amitriptyline, or dothiepin). The study compared the rate of suicide attempts over time for patients on antidepressants to see if there was a greater risk shortly after starting the

drugs. (The new FDA warnings state that the greatest risk of antidepressant-induced suicidality is shortly after starting the drugs or changing the dose.) The study found: "The risk of suicidal behavior is increased in the first month after starting antidepressants, especially during the first 1 to 9 days." The increased risk was statistically significant: the risk of a suicide attempt in the first nine days on an antidepressant was 4.07 times the risk after being on the drugs more than 90 days with a 95% confidence interval of 2.89 to 5.74. The relative risk of a completed suicide in the first nine days after starting the drugs was 38 with a 95% confidence interval of 6.1 to 231. The study looked at both adults and children.

5. **Aursnes I, Ivete I, Gaasemyr J, Natvig B. "Suicide attempts in clinical trials with Paxil randomized against placebo."** ***BMC Medicine*****. 2005 August; 3:14.**

This paper analyzed suicide attempts in sixteen of GlaxoSmithKline's placebo controlled Paxil studies. Seven suicide attempts occurred in 916 patients given Paxil while only 1 suicide attempt occurred in 550 patients on placebo. The data analysis found that Paxil "is connected with an increased intensity of suicide attempts per year." The authors stated that the Paxil finding, together with published meta-analyses of antidepressant-induced suicidality, "make a strong case for the conclusion, at least with a short time perspective, that adults have an increased risk of suicide attempts."

6. **Fisher S, Bryant SG, Kent TA. "Postmarketing surveillance by patient self-monitoring: trazodone versus Prozac."** ***Journal of Clinical Psychopharmacology*****. 1993 Aug;13(4):235-42.**

In this study, patients taking Prozac or another antidepressant called trazadone agreed to report side effects to their pharmacy over a one month period after filling their prescription, which according to Fisher is a well-validated method for assessing drug side effects. The study analyzed data on 4,099 patients. The study found "a higher incidence of various psychologic/psychiatric adverse clinical events, including delusions and hallucinations, aggression, and suicidal ideation" with Prozac. Patients on Prozac were three times more likely to report new or unusual suicidal thoughts when compared to patients on trazadone. The relative risk was 3.11 with a p value of 0.0784.

7. **Fisher et al. "Postmarketing surveillance by patient self-monitoring: Preliminary data for Zoloft versus Prozac,"** ***Journal of Clinical Psychiatry*** **56, 1995;288-296.**

This follow-up to the above study utilized the same methodology to compare reports of side effects by patients on Zoloft, the second SSRI introduced to the U.S. market, with Prozac. Fisher found that even more patients on Zoloft reported side effects similar to those of Prozac: "almost 1 (31.4%) of every 3 Zoloft-treated patients called at least once to report one or more valid adverse clinical events compared with only about 1 (19.7%) of every 5 Prozac-treated patients...." The results were statistically significant; the p-value was less than 0.001. Fisher concluded: "These data indicate that many adverse reactions [side effects] known to be induced by Prozac are being reported with even greater frequency by Zoloft-treated patients." In other words, most of the side effects of SSRIs are class effects, induced by other SSRIs. With regard to suicidality, Fisher reported: "The groups so far do not differ on reports of suicidality...."

8. **Donovan S, Kelleher M, Lambourn J, Foster T. "The occurrence of suicide following the prescription of antidepressant drugs."** ***Archives of Suicide Research*****, 1999, vol. 5, no. 3, pp. 181-192(12).**

This study analyzed data on 222 suicides, examining suicides that occurred in the initial month after patients were on antidepressants. Suicide rates in patients on SSRI antidepressants were compared to the rates in patients on older, tricyclic antidepressants. The study concluded: "The overall occurrence of suicide by any method was lowest in patients prescribed TCAs [tricyclic antidepressants] and highest in those prescribed SSRIs. This difference was statistically significant ($p < 0.01$)."

9. **Jick SS, Dean AD, Jick H. "Antidepressants and suicide."** ***British Medical Journal.*** **1995 Jan 28; 310 (6974):215-8**

This study analyzed data on 172,598 patients taking antidepressants, 143 of whom committed suicide. Patients on Prozac had a statistically significant increased risk of committing suicide. The relative risk for patients on Prozac was 3.8 with a 95% confidence interval of 1.7 to 8.6 when compared to dothiepin, the reference antidepressant.

10. **Bonnet-Brilhault F, Thibault F, Leprieur A, Petir M. "A case of Paxil-induced akathisia and a review of SSRI-induced akathisia."** ***European Psychiatry*****, 1998, 13:109-11.**

In 1989, these four French psychiatrists reviewed the medical literature on SSRI-induced akathisia and suicidality. They also reported the case of a patient who developed severe akathisia when put on Paxil. The Paxil was discontinued and the patient's akathisia cleared after six days.

**11. Rothschild A. J. and Locke C. A., "Re-exposure to Prozac After Serious Suicide Attempts by Three Patients: The Role of Akathisia," *Journal of Clinical Psychiatry*, 1991(52): 491–93.**

Rothschild was a psychiatrist at Harvard Medical School and McLean Hospital. He published this study in 1991, the year after Teicher and Cole published their report of Prozac-induced suicidality. In this dechallenge-rechallenge study, Rothschild represcribed Prozac to three patients who had previously become suicidal on the drug to see if they would have the same reaction. All three patients "developed severe akathisia [the form of drug-induced agitation which is the SSRI side effect most closely linked to suicidality] during retreatment with Prozac and stated that the development of the akathisia made them feel suicidal and that it had precipitated their prior suicide attempts." When the first patient's Prozac was stopped, the akathisia and suicidality cleared within 72 hours. Recall that in GlaxoSmithKline's scale for causality assessments when side effect disappears on dechallenge (stopping Paxil) and reappears on rechallenge (resuming Paxil), Paxil is assessed as *definitely* causing the side effect. For the second and third patients, Rothschild prescribed the beta-blocker propranolol. In both these patients, once the propranolol treated the akathisia, the suicidality cleared. This phamacologic approach demonstrated that it was the akathisia and not the patients' underlying depressions that caused the suicidality.

**12. Wirshing W. C., Van Putten T., Rosenberg J., Marder S., Ames D., and Hicks-Gray T., "Prozac, Akathisia and Suicidality: Is There a Causal Connection?," *Archives of General Psychiatry*, 1992(49): 580–81.**

This group of psychiatrists at UCLA included Theodore Van Putten, one of the world's leading experts on akathisia. The UCLA group described a series of patients who developed Prozac-induced akathisia and suicidal urges. When the UCLA psychiatrists took their patients off Prozac or lowered their dose sufficiently, the agitation and suicidality cleared. When anti-anxiety agents were used to temper the agitation, the suicidality also improved. As in Rothschild's study, when one patient was rechallenged with a higher dose of the drug, she experienced a return of the side effects. The UCLA group concluded, "Our cases appear to confirm that certain subjects experience akathisia while taking Prozac and that this effect is dose-related in the individual patient. Further…the 'Prozac akathisia' can apparently be associated with suicidal ideation, sometimes of ruminative intensity."

**13. Hamilton M. S. and Opler L. A., "Akathisia, Suicidality, and Prozac," *Journal of Clinical Psychiatry*, 1992(53): 401–6.**

Hamilton and Opler are in the Department of Psychiatry at Columbia University College of Physicians and Surgeons in New York. Together they reviewed the many previously published cases and presented one of their own, a young woman who developed severe agitation and suicidality, a month after starting Prozac. Hamilton and Opler concluded that suicidality in association with SSRIs "is really a reaction to the side effect of akathisia [agitation] and not true suicidal ideation as is typically described by depressed patients experiencing suicidal ideation." They characterized it as an "extreme" version of the "behavioral toxicity" of the drugs.

**14. Lane R.M., "SSRI-Induced extrapyramidal side-effects and akathisia: implications for treatment," *Journal of Psychopharmacology* 1998;12:192-214.**

When this report was published in 1998, Lane was the Medical Director of Pfizer's Product Strategy Team for the SSRI Zoloft. Describing Prozac-induced akathisia and suicidality, Lane wrote: "It may be less of a question of patients experiencing Prozac-induced suicidal ideation, than patients feeling that 'death is a welcome result' when the acutely discomforting symptoms of akathisia are experienced on top of already distressing disorders. Hamilton and Opler (1992) stated that the term 'suicidal ideation' to describe the apparent suicidality associated with akathisia was misleading as the 'suicidal ideation' reported in patients receiving Prozac was a reaction to the side-effect of akathisia (i.e. unbearable discomfort and restlessness) and not true suicidal ideation as is typically described by depressed patients experiencing suicidal ideation."

**15. Marsalek M. "Do antidepressants increase the risk of suicide." *Ceska A Slovenska Psychiatric* 1998; 94(5):272-81.**

In 1998, Marsalek reviewed the literature on antidepressant-induced suicidality and stated: "There is clinical evidence of the link between akathisia and suicidal tendencies."

**16. Juurlink DN, Mamdani MM, Kopp A, Redelmeier. "The Risk of Suicide with Selective Serotonin Reuptake Inhibitors in the Elderly." *American Journal of Psychiatry*, 2006; 163: 803-812.**

This study examined data on over 1,000 cases of suicide. The authors found that "during the first month of therapy, SSRI antidepressants were associated with a nearly fivefold higher risk of completed suicide than other

antidepressants." The results were statistically significant: The odds ratio was 4.8 with a 95% confidence interval of 1.2-12.2. The authors concluded: "Initiation of SSRI therapy is associated with an increased risk of suicide during the first month of therapy compared with other antidepressants."

**17. National Institute of Mental Health (NIMH). "New NIMH Research Strives to Understand How Antidepressants May Be Associated with Suicidal Thoughts and Actions." November 13, 2006.**

Underscoring that the consensus now is that antidepressants can make some patients suicidal, this NIMH announcement provides information on new NIMH research initiatives. According to the announcement: "These new, multi-year projects will clarify the connection between SSRI use and suicidality," said NIMH Director Thomas Insel, M.D. "They will help determine why and how SSRIs may trigger suicidal thinking and behavior in some people but not others, and may lead to new tools that will help us screen for those who are most vulnerable," he added.

Conclusion

Analyses of GlaxoSmithKline's Paxil data demonstrate a causal link between the antidepressant and suicidal behavior. This has been true since 1989 although the "bad" Paxil numbers obscured the risk for a decade-and-a-half. But in the last year, both GlaxoSmithKline and the FDA have acknowledged the statistically significant increased risk of suicidal behavior for patients put on Paxil. GlaxoSmithKline's researchers' causality assessments also support a causal link between Paxil and suicidal behavior. Finally, the published medical literature indicates a causal link between antidepressants and suicidal behavior.
In the spring of 2006, GlaxoSmithKline added a warning to its official Paxil prescribing guidelines alerting doctors and patients that Paxil increases the risk of suicidal behavior in depressed adults more than six-fold. GlaxoSmithKline should have included such a warning back in 1992 when it introduced Paxil to the market based on the data from its initial studies of the drug to win FDA approval. It is my opinion to a reasonable degree of medical probability that had GlaxoSmithKline provided the warning all these years, Benjamin Bratt would still be alive today.

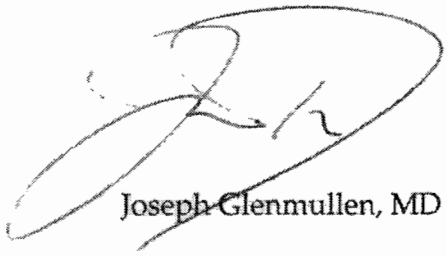
One of the most sobering aspects of the story of Paxil-induced suicidality is that GlaxoSmithKline was not forthcoming with its data demonstrating the risk and

regulatory agencies like the FDA did not take the initiative to get to the bottom of and expose the true risk. Rather, the impetus came from attorneys and medical experts surprised by what they found in GlaxoSmithKline's confidential documents, which only came to light through litigation. The GlaxoSmithKline documents that have so-far made it into the public record have in turn been critical to educating patients, the public, and the media about the true risk. The media—particularly the BBC in England—played a crucial role in turning the tide in the history of Paxil-induced suicidality.

Given the importance of GlaxoSmithKline's internal documents, it is unfortunate that so many of the documents cited in this report and the attached Appendix are still confidential. Given the stakes for public health and safety, GlaxoSmithKline should not be permitted to claim the documents are proprietary trade secrets. All the documents should be made part of the public record so the full story of Paxil-induced suicidality can be told and the additional necessary steps can be taken to fully protect patients and the public.

All of the opinions in this report are expressed to a reasonable degree of medical probability. Of course, my opinions are subject to change based on additional discovery.

Sincerely,



Joseph Glenmullen, MD

Attachments: Appendix A

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[1] Appendix A, Binder 6, Akathisia and Depersonalization, Tab 16, Doc 3.

[2] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm; http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm; http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf.

[3] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 1, Doc 1 and 2.

[4] Appendix A, Binder 5, Possibly & Probably Related, Tab 2, Doc 1, p 4 and Doc 2, p.2.

[5] Please note that in academic and professional journals, the chemical rather than the commercial names for drugs are typically used. For example, Paxil is referred to as paroxetine. When these journals are quoted in the text, for readability the well-recognized commercial names of the drugs have been substituted for their chemical names. In addition, abbreviations and shorthand commonly used in medical records have also been spelled out, again, for readability

[6] Appendix A, Binder 7, Paxil Deaths Data, Tab 10; see also the Transcript of the September 14, 2005 Deposition of Dr. Geoffrey Dunbar in Torrence v. GlaxoSmithKline, p. 111.

[7] M.B. Stone, M.L. Jones, "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," November 17, 2006. Department of Health and Human Services. Public Health Service, Food and Drug Administration, Rockville, Maryland. See p. 31; I. Kirsch, T. Moore, A. Scoboria, S. Nicholls, "The Emperor's New Drugs: An analysis of antidepressant medication data submitted to the U. S. Food and Drug Administration," *Prevention & Treatment*, 5(1), Jul 2002.

[8] T. Laughren, "Overview for December 13 Meeting of Psychophamcologic Drugs Advisory Committee (PDAC)," November 16, 2006. Department of Health and Human Services. Public Health Service, Food and Drug Administration, Rockville, Maryland. See Dr. Laughren's definition of a casual link on p. 2.

[9] M.H. Teicher, C. Glod, and J. O. Cole, "Emergence of Intense Suicidal Preoccupation During Fluoxetine [Prozac] Treatment," American Journal of Psychiatry 147 (1990): 207–10.

[10] J. Glenmullen, *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* (New York: Simon & Schuster, 2000), pp. 135-186.

[11] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 3, Doc 1.

[12] Appendix A, Binder 12, Additional Paxil Documents, Tab 21, Admission 52; Binder 1, Paxil Suicidality Numbers, Tab 4, Doc 3.

[13] Ibid.

[14] Ibid.

[15] Ibid.

[16] Appendix A, Binder 1, Paxil Suicidality Numbers, Tab 4, Doc 3.

[17] Appendix A, Binder 1, Paxil Suicidality Numbers, Tab 4, Doc 2.

[18] Appendix A, Binder 1, Paxil Suicidality Numbers, Tab 4, Doc 3.

[19] Appendix IV and Appendix VII to GlaxoSmithKline's Briefing Document. http://www.gsk.com/media/paroxetine/app4.pdf

[20] T.P Laughren, FDA Memo: "Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC)," January 5, 2004; U.S. House of Representatives, Committee on Energy and Commerce, Hearing Before the Subcommittee on Oversight and Investigation: "FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children," September 23, 2004, Serial No. 108-125, Tab (exhibit) 1, page 136.

[21] GlaxoSmithKline May 2006 "Dear Doctor" letter. http://www.fda.gov/Medwatch/safety/2006/paroxetineDHCPMay06.pdf

[22] Appendix A, Binder 5, Possibly & Probably Related, Tab 2, Doc 1.

[23] *Physician's Desk Reference (PDR)*, (Montvale, NJ: Thomson PDR, 1997), pp. 2681–6. Paxil "withdrawal syndrome" is listed under nervous system side effects on p. 2686.

[24] *Physician's Desk Reference (PDR)*, (Montvale, NJ: Thomson PDR, 2004), p. 1588.

[25] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77–87.

[26] Appendix A, Binder 5, Possibly & Probably Related, Tab 2, Doc 1.

[27] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm; http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm; http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf.

[28] Appendix A, Binder 4, Paxil Adult Suicide, Tab 4.

[29] J. Glenmullen, *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* (New York: Simon & Schuster, 2000), pp. 135-196.

[30] Ibid.

[31] Appendix A, Binder 3, Paxil Adult Suicide, Vol I, Tab 3, Doc 2.

[32] Transcript of the Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, September 20, 1991. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Rockville, Maryland. Obtained through the Freedom of Information Act. p. 257.

[33] Ibid. p. 269.

[34] Ibid. p. 269.

[35] Ibid. p. 298.

[36] Ibid. p. 303.

[37] Ibid. p. 305.

[38] Ibid. p. 310-311.

[39] Ibid. p. 311-312.

[40] Ibid. p. 324.

[41] Ibid. p. 329.

[42] Ibid. p. 329.

[43] Ibid. p. 330.

[44] Ibid. p.335

[45] G. Harris, "Debate Resumes on the Safety of Depression's Wonder Drugs," *New York Times*, August 7, 2003.

[46] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm; http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm; http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf.

[47] Appendix A, Binder 3, Paxil Adult Suicide, Vol I, Tab 3, Doc 3.

[48] J. Glenmullen, *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* (New York: Simon & Schuster, 2000), pp. 135-186.

[49] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 6, Doc 1.

[50] J.J. Mann, FK Goodwin, CP O'Brien, DS Robinson. "Suicidal Behavior and Psychotropic Medication," *Neuropsychopharmacology* 1993;8(2): 109-115.

[51] Ibid.

[52] Appendix A, Binder 14 Additional Paxil Documents, Volume III, Tab 63

[53] Transcript of the Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, October 5, 1992. Department of Health and Human Services, Public Health

Service, Food and Drug Administration, Rockville, Maryland. Obtained through the Freedom of Information Act. p. 92.

[54] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 5, Doc 2.

[55] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 7.

[56] Appendix A, Binder 12, Additional Paxil Documents, Tab 21, Admission 52; Binder 1, Paxil Suicidality Numbers, Tab 4, Doc 3.

[57] Appendix A, Binder 2, Paxil Suicidality Numbers, Vol II, Tab 6, Doc 2. See Table 8 on p 10 of the paper.

[58] S.A. Montgomery, DL Dunner, GC Dunbar, "Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo." *European Neuropsychopharmacology*, March 1995; 5(1): 5-13.

[59] P. Breggin, *Talking Back to Prozac* (New York: St. Martin's Press, 1994), pp. 173-4.

[60] Appendix A, Binder 14, Additional Paxil, Volume III, Tab 62.

[61] Appendix A, Binder 2, Paxil Suicidality Numbers, Vol II, Tab 6, Doc 4.

[62] Appendix A, Binder 7, Paxil Deaths Data, Tab 5.

[63] Appendix A, Binder 7, Paxil Deaths Data, Tab 8, Doc 1.

[64] Appendix A, Binder 13, Additional Paxil Documents, Volume II, Tab 31.

[65] Appendix A, Binder 7, Paxil Deaths Data, Tab 10

[66] Appendix A, Binder 2, Paxil Suicidality Numbers, Tab 11, Doc, 1

[67] Appendix A, Binder 7, Paxil Deaths Data, Tab 12, Doc 3.

[68] P.J. Hilts, "Jury Awards $6.4 Million in Killings Tied to Drug," *New York Times*, June 8, 2001; A16.

[69] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm; http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm; http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf.

[70] J. Glenmullen, *The Antidepressant Solution: A Step-by-Step Guide to Safely Overcoming Antidepressant Withdrawal, Dependence, and "Addiction"* (New York: Simon & Schuster, 2005).

[71] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77–87.

[72] J.S. Price, P.C. Waller, S.M. Wood, A.V. MacKay, "A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal," British Journal of Clinical Pharmacology 1996;42(6):757–63.

[73] J. Glenmullen, *The Antidepressant Solution: A Step-by-Step Guide to Safely Overcoming Antidepressant Withdrawal, Dependence, and "Addiction"* (New York: Simon & Schuster, 2005).

[74] P. Breggin, Declaration of Peter Breggin, MD in Lacuzong vs Jessica Davidson et al., Superior Court of the State of California, County of Santa Clara, Case No.: CV773623, July 21, 2001.

[75] Appendix A, Binder 12, Additional Paxil Documents, Volume 1, Tab 18.

[76] Appendix A, Binder 12, Additional Paxil Documents, Volume 1, Tab 17.

[77] M.B. Stone, M.L. Jones, "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," November 17, 2006. See Table 16, p. 26.

[78] Appendix A, Binder 2, Paxil Suicidality Numbers, Volume II, Tab 8, Doc 1.

[79] Appendix A, Binder 2, Paxil Suicidality Numbers, Volume II, Tab 8, Doc 3.

[80] Appendix A, Binder 2, Paxil Suicidality Numbers, Volume II, Tab 8, Doc 3.

[81] Panorama, "The Secrets of Seroxat [Paxil]," The British Broadcasting Company (BBC), October 13, 2002; Panorama, Note: the British name for Paxil is Seroxat.

[82] "Seroxat [Paxil]: Emails from the Edge," BBC, May 11, 2003. Note: the British name for Paxil is Seroxat.

[83]http://medicines.mhra.gove.uk/ourwork/monitorsafequalmed/safetymessages/_ssrioverview_101203.htm; S. Boseley, "Drugs for depressed children banned," The Guardian, December 10, 2003.

[84] GlaxoSmithKline, "Dear Doctor" Letter, June 10, 2003, sent to doctors in the United Kingdom.

[85] http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm; http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[86] Ibid.

[87] Ibid.

[88] *Physician's Desk Reference (PDR)*, (Montvale, NJ: Thomson PDR, 2002), pp. 1609-1615.

[89] C.T. Gualtieri, "Paradoxical effects of fluoxetine [Prozac]," *Journal of Clinical Psychopharmacology* 1991;11:393-4; M.H. Teicher, C.A. Glod, and J.O. Cole, "Antidepressant drugs and the emergence of suicidal tendencies," *Drug Safety* 1993;8:186-212.

[90] SmithKlineBeecham [now GlaxoSmithKline], Central Medical Affairs team (CMAt), "Confidential, For Internal-Use Only Report: Paxil Adolescent Depression: position piece on the phase III clinical studies," October 1998.

[91] M. Keller et al., "Efficacy of paroxetine [Paxil] in the treatment of adolescent major depression: a randomized clinical trial," Journal of the American Academy of Child and Adolescent Psychiatry 2001;40(7):762–72.

[92] C. Whittington, T. Kendall, P. Fonagy, D. Cottrell, A. Cotgrove, E. Boddington, "Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data," *Lancet* 2004;363:1341–5.

[93] Editorial, "Depressing research."

[94] J. Jureidini and A. Tonkin, "Paroxetine [Paxil] in major depression," *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(2): 514–5; M. Freudenheim, "Behavior drugs lead in sales for children," The New York Times May 17, 2004.

[95] G. Harris, "New York State official sues drug maker over test data: Glaxo challenged in the use of Paxil for children," *The New York Times*, June 3, 2004, p. A1; B. Martinez, "Spitzer charges Glaxo concealed Paxil data," Wall Street Journal, June 3, 2004, p. B1.

[96] B. Tansey, "Glaxo settles fraud suit: drug firm to post results of trials on its web site," *San Francisco Chronicle*, August 27, 2004.

[97] T. Laughren, "Overview for December 13 Meeting of Psychophamcologic Drugs Advisory Committee (PDAC)," November 16, 2006. Department of Health and Human Services. Public Health Service, Food and Drug Administration, Rockville, Maryland.

[98] http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[99] http://fda.gov/cder/drug/advisory/SSRI/200507.htm, "FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications."; http://fda.gov/bbs/topics/ANSWERS/2005/ANS01362.html, "FDA Talk Paper: FDA Reviews Data for Antidepressant Use in Adults" T05-25, dated July 1, 2005.

[100] Appendix A, Binder 13, Additional Paxil Documents, Tab 40.

[101] Appendix A, Binder 13, Additional Paxil Documents, Tab 43.

[102] Appendix A, Binder 13, Additional Paxil Documents, Tabs 41 and 43.

[103] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 8.

[104] Appendix A, Binder 5, Possible & Probably Related, Tab 2, Doc 1.

[105] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tabs 1 and 6.

[106] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 1.
[107] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 1.
[108] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 1.
[109] Appendix A, Binder 8, Article 31 Analysis, p.10.
[110] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 2.
[111] Appendix A, Binder 13, Additional Paxil Documents, Tabs 42 and 43.
[112] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tabs 4 and 8.
[113] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 6.
[114] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tabs 6 and 8.
[115] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 4.
[116] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 6.
[117] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 6.
[118] Appendix A, Binder 13, Additional Paxil Documents, Tab 40.
[119] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 8.
[120] Appendix A, Binder 13, Additional Paxil Documents, Tab 46.
[121] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 9.
[122] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 10.
[123] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 13.
[124] T. Laughren, "Overview for December 13 Meeting of Psychophamacologic Drugs Advisory Committee (PDAC)," November 16, 2006. Department of Health and Human Services. Public Health Service, Food and Drug Administration, Rockville, Maryland.
[125] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tabs 8 and 9.
[126] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 12.
[127] Deposition of Dr. Pam Barrett in Tucker v. GlaxoSmithKline, January 5, 2007.
[128] GlaxoSmithKline Briefing Document and Appendices I, IV, and VII.
http://www.gsk.com/media/paroxetine/briefing_doc.pdf;
http://www.gsk.com/media/paroxetine/app1.pdf;
http://www.gsk.com/media/paroxetine/app4.pdf;
http://www.gsk.com/media/paroxetine/app7.pdf.
[129] Ibid.
[130] For example, the 1989 data included all studies of patients with major depression disorder, whereas the 2006 analysis only included placebo-controlled studies of patients with major depression.
[131] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tabs 15 and 16.
[132] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 17.
[133] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 18.
[134] Appendix A, Binder 11, 2006 Paxil Adult Suicide Analysis, Part II, Tab 18.
[135] GlaxoSmithKline May 2006 "Dear Doctor" letter.
http://www.fda.gov/Medwatch/safety/2006/paroxetineDHCPMay06.pdf
[136] GlaxoSmithKline Briefing Document and Appendices I, IV, and VII.
http://www.gsk.com/media/paroxetine/briefing_doc.pdf;
http://www.gsk.com/media/paroxetine/app1.pdf;
http://www.gsk.com/media/paroxetine/app4.pdf;
http://www.gsk.com/media/paroxetine/app7.pdf.
[137] Ibid.

[138] T. Laughren, "Overview for December 13 Meeting of Psychophamcologic Drugs Advisory Committee (PDAC)," November 16, 2006. M.B. Stone, M.L. Jones, "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," November 17, 2006. M. Levenson, C. Holland, "Statistical Evaluation of Suicidality in Adults Treated with Antidepressants," November 17, 2006. Department of Health and Human Services. Public Health Service, Food and Drug Administration, Rockville, Maryland.

[139] Ibid. See Table 16, p. 26 of Stone and Jones' report.

[140] The FDA report includes the statement that "although the values for some individual drugs are statistically significant at the 0.05 level, the significance of those findings must be discounted for the large number of comparisons made." M.B. Stone, M.L. Jones, "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," November 17, 2006, p. 21. But, according to biostatistician Roger Grimson, another expert consultant, this statement "refers to the issue of multiple comparisons. But it is incorrectly applied here. If many comparisons are being made in a study, then statisticians may suggest that the investigators adjust the significance level (alpha level, i.e. the 0.05 level) downward to account for the likelihood that the more comparisons being made, the more likely it is that a result will be significant (<= 0.05) by chance. P-values do not change, only the cut point, say 0.05, is made lower so a p-value would need to be lower than the new reduced cut point to be statistically significant. Methods have been published for doing this. (Many reports do not involve such adjustments and this area is not without controversy.) Anyway, Table 16 (and others) of the Stone and Jones report are not reporting p-values of a unified study. Rather this is a summary of previous results from many documents. Multiple comparison adjustments are not called for. Each p-value stands on its own and can be judged on the basis of its original alpha level which is customarily 0.05. If what they say were valid, and I wanted to give the impression of no statistical significance anywhere, then all I would need to do is introduce more studies or parts of studies (with moderate p-values) until none of the individual studies which do have small p-values could possibly be significant (lower than the new reduced cut point which keeps getting lower as I introduce new p-values to the mix). In fact I could argue that no comparison ever made in history has a statistically significant finding!—using that logic. (Another issue arises for AE comparisons for which trials are typically under powered. Most AE analyses involve discrete distributions which introduce extra problems for multiple comparisons.)"

[141] Appendix A, Binder 5, Possibly & Probably Related, Tab 1.

[142] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 16, Doc 3.

[143] Appendix A, Binder 5, Possibly & Probably Related, Tab 2, Doc 1.

[144] J. Glenmullen, *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* (New York: Simon & Schuster, 2000), pp. 135-186.

[145] Appendix A, Binder 5, Possibly & Probably Related, Tab 3.

[146] Appendix A, Binder 5, Possibly & Probably Related, Tab 5.

[147] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 4.

[148] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 2.

[149] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 5.

[150] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 3.

[151] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 3.

[152] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 3.

[153] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 5.
[154] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 5.
[155] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 5.
[156] Appendix A, Binder 6, Akathisia & Depersonalization, Tab 6.

JOSEPH GLENMULLEN, M.D.

*Curriculum Vitae*

Academic Appointments

1988 to present: Clinical Instructor in Psychiatry, Harvard Medical School, in the Department of Psychiatry, Cambridge Hospital, Cambridge, MA
1988-89: Associate Director, Medical Student Education, Cambridge Hospital/Harvard Medical School, Cambridge, MA
1987-89: Instructor, Psychiatry 700 Course, Harvard Medical School

Clinical Practice

*Clinical Practice*
1988 to present: Psychiatrist, Harvard Law School Health Services, Cambridge, MA
1986 to present: Private practice in Harvard Square, Cambridge, MA

*Forensic Practice*
2001 to present: Expert witness and forensic consulting
2002-present: Member, Program in Psychiatry and the Law, Harvard Medical School

Teaching, and Awards

*Teaching*
1988-present: Supervision of social work interns, psychology fellows, and psychiatry residents at the Cambridge Hospital/Harvard Medical School.

*Awards:*
May, 2001: Annual Achievement Award in Medicine, American College for Advancement in Medicine (ACAM), and delivered the keynote address, the Linus Pauling Lecture, at ACAM's annual convention.

Education and Training

*Education*

1984: MD, Harvard Medical School, Boston, MA

1972: BA, magna cum laude, Brown University, Providence, RI

*Postdoctoral Training*

1987-88: Psychiatry Fellow, Harvard University Health Services, Cambridge, MA

1987-88: Chief Resident, Outpatient Department, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA

1986-88: Residency, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA

1984-85: Internship, Department of Medicine, Cambridge Hospital/Harvard Medical School, Cambridge, MA

*Board Certification*

1990: Board certified in psychiatry by the American Board of Psychiatry and Neurology

*Licensure*

1985 to present: Medical License, Massachusetts Board of Registration in Medicine

Bibliography

Wanzer, Sidney and Glenmullen, Joseph. *To Die Well: Your Right to Comfort, Calm, and Choice in the Last Days of Life*. New York: Perseus Books Group, 2007

Glenmullen, Joseph. *The Antidepressant Solution: A Step-by-Step Guide to Overcoming Antidepressant Withdrawal, Dependence, and "Addiction."* New York: Free Press (division of Simon & Schuster), 2005

Glenmullen, Joseph. *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil and Other Antidepressants with Safe, Effective Alternatives*. New York: Simon & Schuster, 2000

Glenmullen, Joseph. *Sexual Mysteries: Tales of Psychotherapy* with a Foreword by Robert Coles. New York: Harper Collins, 1993 (hardcover). Cambridge, MA: Orbit Publishing, 2000 (paperback).