EXHIBIT O (PART 1)

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August 10, 2007

Ms. Karen Barth Menzies
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12100 Wilshire Boulevard, Suite 920
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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 Tom Turek.

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. While in this report I will follow GlaxoSmithKline's methodology, other sources of information are useful in determining causality including assessments, evaluations, and conclusions from authoritative bodies, such as the FDA; case studies, including challenge—dechallenge—rechallenge case studies; trends and patterns in reports of adverse drug reactions; the existence of recognized antidepressant side effects that may be precursors to antidepressant-induced suicidality, such as akathisia, agitation, anxiety, insomnia, mania, depression, and psychosis; and, finally, clinical experience.

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 Healthcare Provider" 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, Tom Turek 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

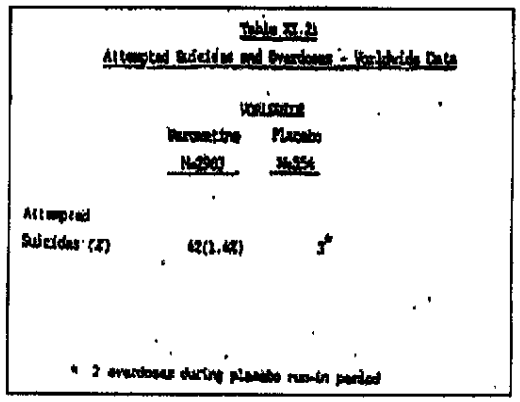


Table XI.21

Attempted Suicides and Overdoses - Worldwide Data

	Paroxetine N=2963	Placebo 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.

Table 2
GlaxoSmithKline 1989 NDA

Table XI.17
Deaths Reported in Worldwide Clinical Trial Program

	PAROXETINE N=2953	PLACEBO*
Number (%)	13 (0.4%)	2

* Two deaths occurred during the placebo run-in period.

In 1989 GlaxoSmithKline Improperly Counts Wash-Out Suicides and Suicide Attempts Against Placebo when Submitting Its Original Data to the FDA

Note that an asterisk appears in both of GlaxoSmithKline's tables: In Table 1 next to the number three, the count for suicide attempts in patients on placebo, and in Table 2 next to the word "placebo." Below the tables, the asterisks state that two of the three suicide attempts occurred "during the placebo run-in period" and that both of the completed suicides occurred during the placebo run-in period. The run-in period, also called the wash-out period, occurs *before* the official study begins. All patients are taken off their existing psychiatric drugs to let the old drugs wash out of their systems. For GlaxoSmithKline's Paxil studies, the pre-study wash-out phase typically lasted one to two weeks.[6] The rationale for washing out old drugs is to prevent them from confounding the results of the study, so that all patients start out the study in similar condition.

During the wash-out period, all patients are given daily placebo pills. Hence, another name for this pre-study period is the "placebo wash-out phase." Patients whose depressions quickly improve during this time are labeled "placebo responders" and *excluded* from the actual study. Administering a placebo during the wash-out phase is also a technique used by pharmaceutical companies to weed out patients who would respond quickly to a placebo in the official study.

This weakens the performance of the placebo by removing quick placebo responders, thereby making the performance of the antidepressant look better.

Pharmaceutical companies use this technique because the placebo effect accounts for such a high percentage of an antidepressant's effect. According to the FDA, the placebo effect accounts for about 80% of the effect of antidepressants.[7] That is, of 100 people who respond to antidepressants, 80 would have responded to placebo. If the pharmaceutical companies did not use the placebo wash-out procedure, the difference between placebo and antidepressants would be even smaller. Thus, the placebo wash-out phase accomplishes two tasks: washing out patients' old drugs and weeding out placebo responders.

The official study only begins after the wash-out phase is completed, at which point patients are randomly assigned to receive either the new antidepressant or a placebo, against which the antidepressant is being tested. The random assignments are double blind, meaning both the patients and researchers do not know which patients are getting the active drug versus placebo. The patients who receive placebo in the actual study are called the "placebo group." GlaxoSmithKline's asterisks and footnotes in its 1989 tables are tantamount to saying: Anyone who committed or attempted suicide in the week *before* the study, we'll assign all those suicidal events *as if* they happened to the patients on placebo *during* the actual study. Confusing the pre-study placebo *wash-out phase* with the placebo *group* in the actual study is improper, especially when the concern is a potentially lethal side effect.

GlaxoSmithKline's "Bad" Numbers

The tables below compare GlaxoSmithKline's 1989 "bad" numbers with the actual data, in which the wash-out suicides and suicide attempts are removed from the placebo count, leaving only one suicide attempt for the placebo group. Table 3 compares GlaxoSmithKline's 1989 "bad" numbers with the correct data on suicide attempts. Whereas GlaxoSmithKline's "bad" numbers do not show a statistically significant difference between Paxil and placebo, the correct data shows that suicide attempts in patients on Paxil occurred at a rate eight times higher than the rate in patients on placebo. This eight-fold increase in risk on Paxil is statistically significant: the p value is 0.01. Thus, GlaxoSmithKline's correct data demonstrates a causal link between Paxil and suicidal behavior.[8]

Table 3
GlaxoSmithKline 1989 Data
Suicide Attempts – Worldwide data

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
42 1.4%	3* 0.54%	2.6	No p = 0.10
42 1.4%	1 0.18%	8.0	Yes p = 0.01

GSK's "bad" 1989 numbers, submitted to FDA for Paxil approval. *Includes 2 wash-out suicide attempts counted as though they occurred in the placebo group.

1989 correct data in which the wash-out suicide attempts are removed.

Table 4 compares GlaxoSmithKline's 1989 "bad" numbers with the correct data on suicides. As seen in the table, both of the suicides GlaxoSmithKline reported occurring on placebo, in fact occurred during the wash-out phase. This time GlaxoSmithKline's "bad" numbers make Paxil look like it has a protective effect, lowering the suicide rate relative to placebo, when, in fact, it had the opposite effect.

Table 4
GlaxoSmithKline 1989 Data
Suicides – Worldwide data

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
5 0.17%	2* 0.36%	0.47	No p = 0.30
5 0.17%	0 0%		All suicides occurred on Paxil; none on placebo.

GSK's "bad" 1989 numbers, submitted to the FDA for Paxil approval. *Included 2 wash-out suicides counted as though they occurred in the placebo group.

1989 correct data in which the wash-out suicides are removed.

The next table, Table 5, combines suicidal behaviors—suicides and suicide attempts—in the Paxil database. This is the comprehensive way to evaluate Paxil-induced suicidal behavior: by using the complete data combining suicides and suicide attempts. The accurate data shows a greater than eight-fold increase in the risk of suicidal behavior in patients on Paxil. The increased risk on Paxil is statistically significant: the *p* value is 0.004. The correct data dating to before Paxil was approved by the FDA demonstrates a causal link between Paxil and suicidal behavior.

Table 5
GlaxoSmithKline 1989 Data
Combined Suicidal Behavior
(Suicides and Suicide Attempts)
Worldwide data

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
47 1.6%	5* 0.9%	1.8	No p = 0.33
47 1.6%	1 0.18%	8.9	Yes p = 0.004

GSK's "bad" 1989 numbers, submitted to FDA for Paxil approval. *Includes 4 wash-out suicides and suicide attempts counted as though they occurred in the placebo group.

1989 correct data in which the wash-out suicides and suicide attempts are removed.

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 Improperly Counts More Wash-Out Suicide Attempts Against Placebo, Making Its "Bad" Paxil Numbers Worse: The "Before" and "After"

As we have seen, GlaxoSmithKline's correct 1989 data demonstrates a causal link between Paxil and suicidality. For the public health and safety, in 1991 the FDA needed to establish whether or not this new class of drugs was associated with an increased risk of suicidality. Unfortunately, in 1991 GlaxoSmithKline did not provide the FDA with the correct data. Instead, this time the company improperly counted even more wash-out suicide attempts than in its earlier report to the FDA, counting them as though they occurred in the placebo group.[12] This made the placebo group look even worse and therefore made Paxil look even better. At the same time, GlaxoSmithKline reduced the number of suicide attempts in the Paxil count. The net result made the drug look significantly better than placebo when, in fact, the opposite was true.

The graph below shows the "before" and "after" numbers, the correct 1989 data versus the numbers submitted to the FDA in its April 29, 1991 report. Note that the darker bars on the left showing the rate of suicides and suicide attempts in patients on Paxil decreases slightly from GlaxoSmithKline's 1989 report to its 1991 report, the details of which are explained later in this section. But the far greater change is the dramatic increase in the placebo number as seen in the white bars on the right. GlaxoSmithKline has now acknowledged that this is the same 1989 data improperly reported in 1991.[13] The result is that in the 1991 report to the FDA, there is virtually no difference between Paxil and placebo.

Graph 1
GlaxoSmithKline 1989 vs 1991 Data
Suicides and Suicide Attempts
Worldwide Data

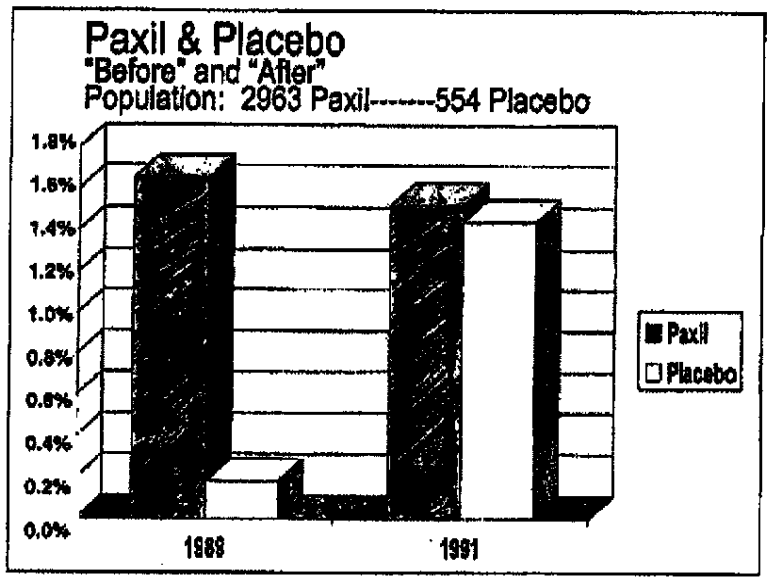


Table 6 and Table 7 below are photocopies of GlaxoSmithKline's tables presenting the data on suicides and suicide attempts in patients on Paxil versus placebo in the company's April 29, 1991 report to the FDA. *This time GlaxoSmithKline omitted the asterisks from the two tables acknowledging that suicides and suicide attempts attributed to placebo, in fact, occurred during the wash-out phase.* Instead, in the text of the report, GlaxoSmithKline included the statement: "of the two suicides committed by patients 'randomized' to placebo.... The acts of suicide were committed during participation in the placebo 'run-in' phase." This statement is misleading. Patients in the run-in, or wash-out, phase had not yet been randomized. *In fact, these patients never made it into the randomized, official study because they died before the study.* GlaxoSmithKline makes no mention of the fact that suicide *attempts* that occurred in the wash-out phase were added to the placebo count. Similarly in the appendices, GlaxoSmithKline included lists of the patients who committed or attempted suicide. The appendix on patients who committed suicide includes an asterisk noting that the placebo suicides occurred during the wash-out phase, but no such asterisk appears in the appendix on suicide attempts.

Table 6
GlaxoSmithKline 1991 Report to FDA

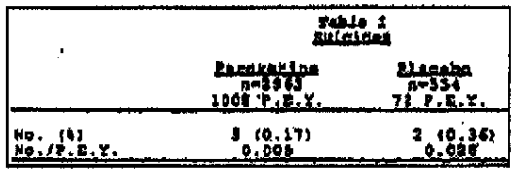
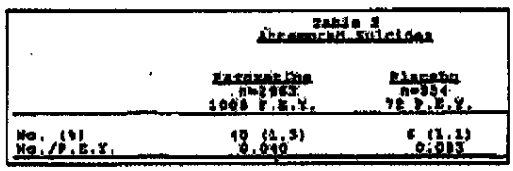


Table 7
GlaxoSmithKline 1991 Report to FDA



Compare Table 7 with GlaxoSmithKline's 1991 data on suicide attempts with Table 1, GlaxoSmithKline's 1989 table on suicide attempts on page three of this report. Note that the 42 Paxil suicide attempts reported in 1989 mysteriously decreases to 40 in 1991, while the three placebo suicide attempts reported in 1989 have doubled to six in 1991. In the 1991 report, GlaxoSmithKline did not include a table combining suicides and suicide attempts. In general, when analyzing data statistically, disaggregating the data, or breaking it down into smaller pieces, hides significant phenomena.

Tables 8, 9, and 10 below compare GlaxoSmithKline's 1991 data with the correct data now acknowledged by the company.[14] Table 8 shows the data on suicides and compares GlaxoSmithKline's "bad" 1991 numbers to the correct data. Both of the placebo suicides in GlaxoSmithKline's "bad" 1991 data, in fact, occurred during the wash-out period and not in the placebo group, as seen earlier.

Table 8
GlaxoSmithKline 1991 Data
Suicides – Worldwide data

GSK's "bad" 1991 numbers, submitted to the FDA. *Included 2 wash-out suicides counted as though they occurred in the placebo group.

The correct data in which the wash-out suicides are removed.

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
5 0.17%	2* 0.36%	0.47	No p = 0.30
5 0.17%	0 0%		All suicides occurred on Paxil; none on placebo.

Table 9 shows the data for suicide *attempts* and compares GlaxoSmithKline's "bad" 1991 numbers to the accurate data. Five out of six of the placebo suicide attempts in GlaxoSmithKline's "bad" 1991 data, in fact, occurred during the wash-out period and not in the placebo group.[15]

Table 9
GlaxoSmithKline 1991 Data
Suicide Attempts – Worldwide data

GSK's "bad" 1991 numbers, submitted to the FDA. *Includes 5 wash-out suicide attempts counted as though they occurred in the placebo group.

The correct data in which the wash-out suicide attempts are removed.

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
40 1.3%	6* 1.1%	1.2	No p = 0.84
40 1.3%	1 0.18%	7.6	Yes p = 0.02

Table 10 shows the data for combined suicides and suicide attempts and compares GlaxoSmithKline's "bad" 1991 numbers to the correct data. The net result is that patients on Paxil have a statistically significant greater than eight-fold increase in suicidal behavior.

Table 10
GlaxoSmithKline 1991 Data
Combined Suicidal Behavior
(Suicides and Suicide Attempts)
Worldwide data

Paxil 2963 patients	Placebo 554 patients	Odds Ratio Paxil/ Placebo	Statistically Significant?
45 1.5%	8* 1.4%	1.1	No p = 1.0
45 1.5%	1 0.18%	8.5	Yes p = 0.007

GSK's "bad" 1991 numbers, submitted to the FDA. *Includes 7 wash-out suicides and suicide attempts.

The correct data in which the wash-out suicides and suicide attempts are removed.

GlaxoSmithKline included a May 10, 1991 cover letter with its report to the FDA. In the cover letter, GlaxoSmithKline's director of FDA affairs, Dr .Thomas Donnelly, incorrectly asserts:[16]

> To summarize in brief, this analysis of data from prospective clinical trials [studies] in depressed patients clearly demonstrates that patients *randomized* to Paxil therapy *were at no greater risk* for suicidal ideation or behavior than patients who were *randomized* to placebo or other active medication [emphasis added].

GlaxoSmithKline's failure to provide the correct data to the FDA in 1991 when the FDA was trying to get to the bottom of this potentially lethal side effect delayed warnings for fifteen years and placed countless people at risk.

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:

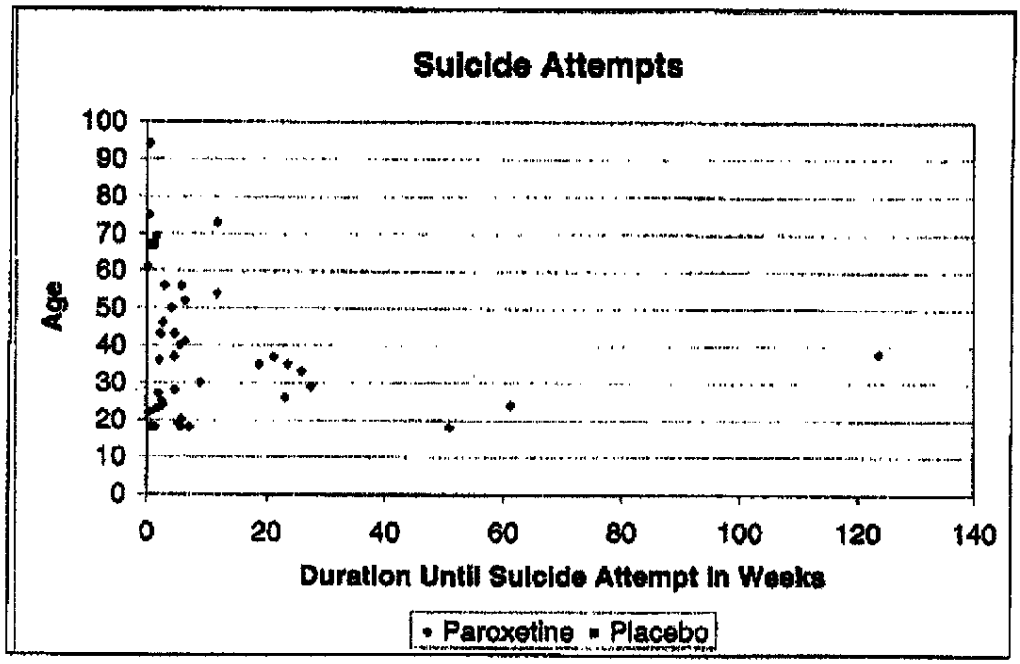
> most suicide attempts occurred early, especially during the first week of therapy.

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.

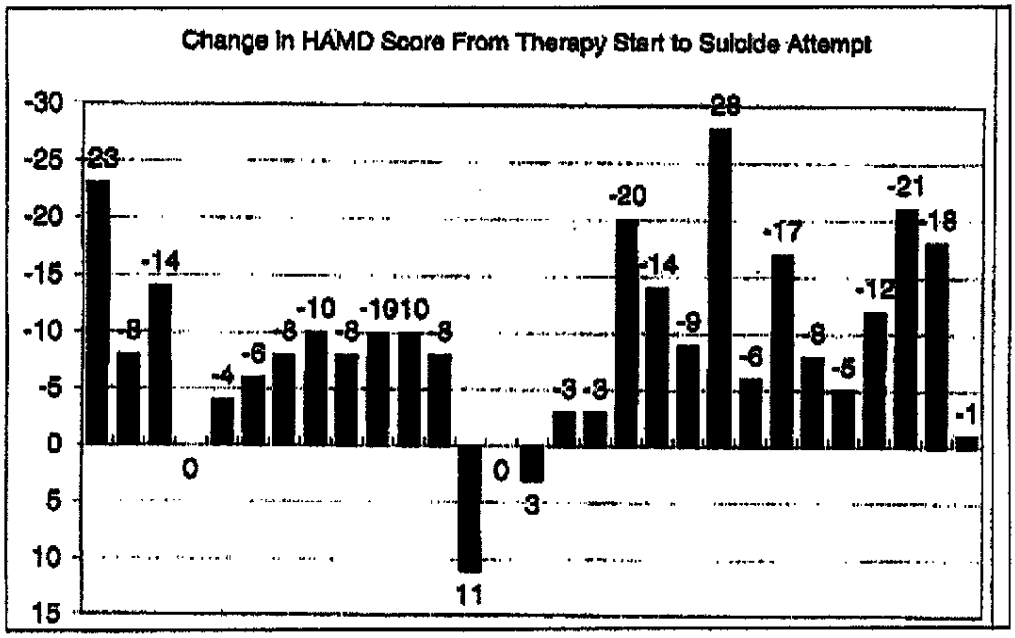
Graph 2



Researchers have long noted that depression rating scales, including the best known Hamilton Depression Rating Scale, or HAM-D, do not predict treatment emergent suicidality. Indeed, GlaxoSmithKline's data demonstrate that HAM-D scores *improve* in patients on Paxil prior to suicide attempt. In GlaxoSmithKline's studies to win FDA approval for Paxil, the change in the company's HAM-D score can be calculated for 71% of patients who made suicide attempts in the studies.

Graph 3 depicts the change in HAM-D score from the start of therapy to the time of a suicide attempt for each patient. As seen in Graph 3, almost all the patients showed an *improvement* in their HAM-D score, prior to making a suicide attempt.

Graph 3



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:[16]

> 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 nature of clinical trials mitigates against suicidality. Patients in clinical trials are monitored closely and typically seen weekly. The patients are given considerable attention. Patients have hope of being helped by the new drug. In other words, clinical trials provide the kind of emotional support, encouragement, and hope that helps to prevent suicidality. In addition, 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=534 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

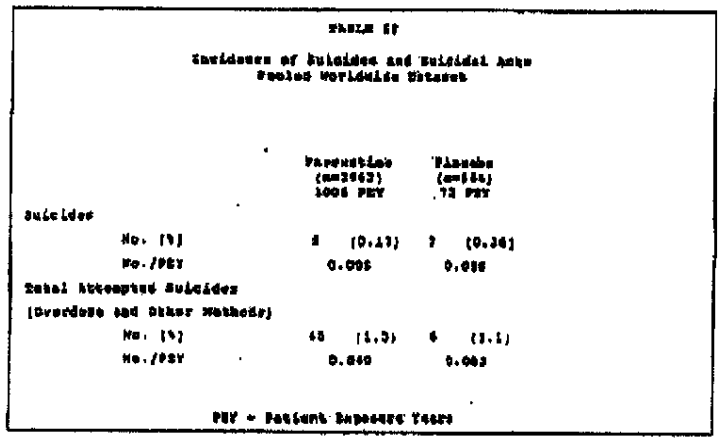


TABLE 17

Incidences of Suicides and Suicidal Acts
Pooled Worldwide Dataset

	Paroxetine (n=3963) 1005 PEY	Placebo (n=154) .72 PEY
Suicides		
No. [%]	8 (0.2)	2 (0.36)
No./PEY	0.008	0.036
Total Attempted Suicides (Overdose and Other Methods)		
No. [%]	48 (1.2)	6 (1.1)
No./PEY	0.048	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 1.2%	6* 0.96%	1.2	No p = 0.84
49 1.2%	1 0.16%	7.5	Yes 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 0.15%	2* 0.32%	0.45	No p = 0.28
6 0.15%	0 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 1.3%	8* 1.3%	1.0	No p = 1.0
55 1.3%	1 0.16%	8.4	Yes 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 1005 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 Healthcare Provider" 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.

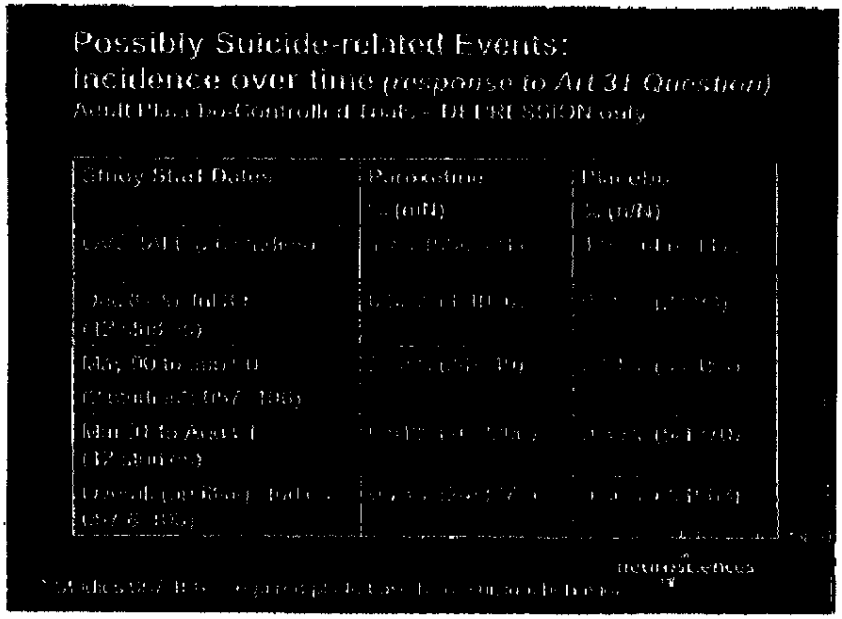
The FDA Requests GlaxoSmithKline's Adult Paxil Data

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.

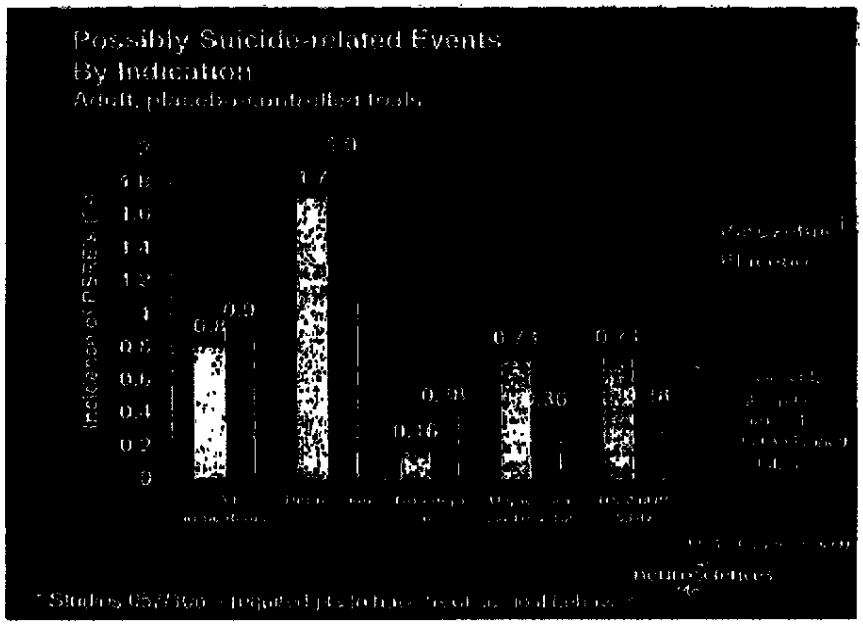
GlaxoSmithKline's global safety board met on January 24, 2005 to discuss the FDA's excluding the data from Studies 057 and 106.[105] Table 21 reproduces a slide prepared for the global safety board.[106] Note that all the other Paxil studies have relatively low rates of suicidal behavior ranging from 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



Graph 4 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 4
GlaxoSmithKline Global Safety Board Meeting
January 24, 2005



The last two pairs of bars in Graph 4 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.

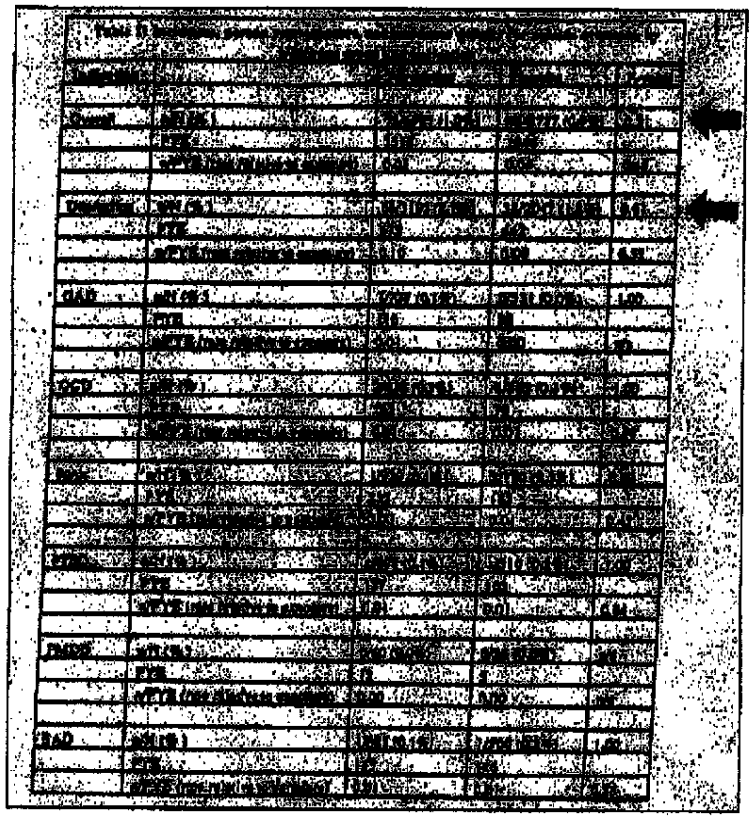
Another slide prepared for the global safety board meeting reported on a recent analysis of its adult data that GlaxoSmithKline conducted for the European Agency for the Evaluation of Medicinal Products, the European-wide equivalent for the FDA.[108] According to the slide, GlaxoSmithKline's analysis 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% CI 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 4. 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



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 1.0%	43 0.9%	1.15	No p = 0.51
Overall with the data from Studies 057 and 106 excluded	35 0.5%	10 0.2%	2.38	Yes 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 2.1%	38 1.9%	1.12	No P = 0.61
Depression with the data from Studies 057 and 106 excluded	29 0.9%	5 0.24%	3.61	Yes 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 Healthcare Provider" 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 HCl) and PAXIL CR (paroxetine HCl 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, clinical trials provide frequent appointments, close monitoring, emotional support, encouragement, and hope that help to prevent suicidality. 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

EXHIBIT O (PART 2)

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 Neuropsychopharmacology	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] Moreover, compensatory mechanisms in brain cells may cause reduced serotonin production and release; down-regulation of serotonin receptors; and compensatory efforts on the part of the reuptake system, all of which may lead to a decrease in serotonergic neurotransmission in response to the initial over-stimulation by the SSRI.]

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

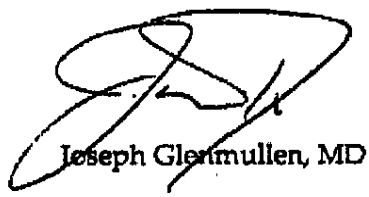
GlaxoSmithKline provided the warning all these years, Tom Turek would still be alive today.

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 Psychopharmcologic 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 Healthcare Provider" 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.

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

[28] 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.

[25] 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.

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

[84]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 Healthcare Provider" Letter, June 10, 2003, sent to doctors in the United Kingdom.

[85] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.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 Psychopharmcologic 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 Psychopharmacologic 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 Healthcare Provider" 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 Psychopharmcologic 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, MD
1563 Massachusetts Ave.
Cambridge, MA 02138

August 17, 2007

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

Dear Ms. Menzies:

This report details my expert opinion on the tragic suicide of fifty-four-year-old Robert "Bobby" Collins on February 14, 2002. This report on specific causation is a companion to two accompanying reports on general causation, one relating to adults and one relating to children and adolescents, which are incorporated by reference herein. It is my opinion based on a reasonable degree of medical certainty and based on my education, training, and clinical experience that Paxil was a substantial factor in causing Bobby's death. Bobby was on Paxil less than a month. Unfortunately, on Paxil, Bobby developed classic symptoms of antidepressant-induced suicidality, including akathisia (agitation), increased anxiety, worsening insomnia, paranoia, uncontrollable crying spells, and ultimately irresistible suicidal urges. A little more than two weeks after his Paxil dose was increased, Bobby shot himself in the head. Since Bobby's death in 2002, the FDA and GlaxoSmithKline have warned doctors and the public that antidepressants may make patients suicidal, especially in the period after starting the drugs or increasing the dose.[1]

Qualifications

A graduate of Harvard Medical School, I am a Clinical Instructor in Psychiatry at Harvard Medical School, on the staff of the Harvard Law School Health Services, and in private practice in Harvard Square. I am Board Certified in Psychiatry by the American Board of Psychiatry and Neurology. I am the author of two books on the side effects of antidepressants: *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* published in 2000 by Simon & Schuster and *The Antidepressant Solution: A Step-by-*

Step Guide to Overcoming Antidepressant Withdrawal, Dependence, and "Addiction" published by Simon & Schuster's Free Press division in January 2005.[2]

Prozac Backlash is annotated with over 600 footnotes from medical journals, books, and other sources. *The Antidepressant Solution* is annotated with over 350 footnotes. Both books include chapters on antidepressant-induced suicidality. In the title *Prozac Backlash*, I use the word "Prozac" generically to refer to the group of antidepressants known as SSRIs (selective serotonin reuptake inhibitors). Prozac was the first of these antidepressants introduced in this country and is the best known. Paxil, the antidepressant Bobby was taking at the time of his suicide, is also an SSRI. In this report, where I cite published research or reports involving antidepressants other than Paxil, they are included because they are relevant to the issue of antidepressants triggering suicide.

I am a moderate in the debate over the risks and benefits of antidepressants. I prescribe antidepressants for patients whose conditions are serious enough to warrant the drugs and have had numerous patients report their beneficial effects. But, I am a critic of the drugs being over-prescribed for mild, even trivial, conditions and of patients not being adequately warned of their side effects. I testified at the FDA's February 2004 hearing that resulted in the historic March 2004 warning that antidepressants may make patients suicidal.

Since the publication of *Prozac Backlash*, I have become a national spokesperson for the appropriate, measured use of the drugs. I have been interviewed on numerous national television and radio shows including NBC's The Today Show, ABC News' 20/20, ABC's Good Morning America, ABC's World News Tonight, ABC's Primetime Live, CNN, Fox News, PBS, Court TV, and National Public Radio for my expertise on antidepressants. My work has been the subject of many reviews and articles including in the *New York Times* and *The New Yorker* magazine.[3] Among the honors I have received for writing *Prozac Backlash* is the American College for Advancement in Medicine's (ACAM's) Annual Achievement Award in Medicine in May 2001. I received the award at ACAM's 2001 annual convention and delivered the convention's keynote address, the Linus Pauling Lecture. My *curriculum vitae* is enclosed with this report as Exhibit 1.

Materials Reviewed for this Report

In preparing this report I interviewed Mary Collins, Kristen Collins, Dwayne Collins, Rose Collins, Ann Pohanka, and Dr. Howard Benensohn by phone after warning them that the interviews were not treatment but rather forensic in nature and therefore not confidential, which they understood. I have discussed the case with counsel for the plaintiff. I have also read and relied upon the following:

Expert Binder I:

1. Suicide/Suicidality Fact Sheet
2. Robert S. Berger
3. Giant Pharmacy
4. Georgetown University Medical Center
5. Office of the Chief Medical Examiner
6. Snowden at Fredericksburg
7. Dr. Howard S. Benensohn
8. Dr. Richard S. Castiello
9. MedStar Health
10. Georgetown University Hospital
11. Robert J. Pinney
12. Georgetown University Hospital – Gastroenterology Department
13. Waldorf Volunteer Fire Department
14. CVS Pharmacy
15. Allan H. Macht, MD
16. Georgetown University Medical Center – Department of Internal Medicine
17. Workers' Compensation Commission
18. Charles County Sheriff
19. Charles County Mobil Intensive Care Unit
20. Military Personnel Records
21. Metropolitan Police Department
22. Smithsonian Institute
23. Prince George's Community College
24. Anthem Blue Cross
25. E.L. Webster Insurance Agency

Expert Binder II:

26. Deposition of Mary Collins – June 7, 2007
27. Perpetuation of Testimony Deposition of Mary Collins – June 8, 2007

28. Department of Veterans Affairs
29. Capital Orthopedic Specialists, PA
30. Georgetown University Hospital
31. Gary Malinkoff, MD
32. Smithsonian Institute
33. Highmark Medicare Services
34. Social Security Administration
35. Deposition of Kirsten Collins
36. Deposition of Ann Poharka
37. Deposition of Howard S. Benensohn, MD
38. Deposition of Dwayne Collins
39. Deposition of Dr. John Carroll
40. Deposition of Dr. Robert Pinney
41. Deposition of Dr. Carlos Collin
42. Deposition of Sgt. Donald Stahl
43. Deposition of Sgt. John Shoemaker
44. Deposition of Howard Blum

I have also researched the medical literature on antidepressant-induced suicide and violence and drawn on my extensive knowledge of this side effect. As detailed in my books, I have treated patients with this side effect in my psychiatric practice. In addition, attached hereto in Appendix A and Appendix B are lists of data and other information I have considered in forming my opinions and/or which relate to my opinions.

For my time doing telephone conferences, research, reviewing documents, and writing this report, I am compensated at the rate of $500 per hour. For travel and testimony, I am reimbursed at the rate of $500 per hour, with 10 hours fee for a full day and 5 hours fee for a half day. In the last four years, I have given testimony in the following cases: In Re Paxil Products, MDL Number 1574 (United States District Court for the Central District of California) on January 27-28, 2005; Needleman v. John Hancock on April 27, 2005; Baxter v. Eli Lilly on May 31, 2005, Cartwright v. Pfizer on June 28, 2006, Witczak v. Pfizer on July 14, 2005; Rydin v. Comancho et al on August 4, 2005; Gould v. Teva Pharmaceuticals on September 30, 2005; Radke v. Barr Laboratories v. October 18, 2005; Perez v. Stop & Shop on February 16, 2006; Jones v. Rogers et al on March 2, 2006 and September 18, 2006; Texas v. Lohstroh on September 7, 2006 and September 12-15, 2006; Tucker v. GlaxoSmithKline on September 22, 2006; Miller v. GlaxoSmithKline on September 26, 2006; Giles v. Wyeth on January 15, 2007; Porter v. Eli Lilly on April 5, 2007; Mason v. GlaxoSmithKline on June 7, 2007;

Dobbs v. Wyeth on May 15, 2007; and Williams v. GlaxoSmithKline on June 29, 2007.

This report is divided into two parts:

- Part 1 discusses general causation, i.e. the phenomenon of antidepressant-induced suicidality
- Part 2 discusses specific causation in the events leading to Bobby Collin's suicide.

Part 1. General Causation: Antidepressant-Induced Suicidality

This report is accompanied by two reports on general causation, one relating to adults and one relating to children and adolescents. Since Bobby's suicide, GlaxoSmithKline and the FDA have issued a series of warnings alerting doctors and patients that antidepressants may increase the risk of suicidal behavior over and above any underlying depression.[4] The FDA warnings cover all antidepressants currently on the market, including Paxil, the drug Bobby was prescribed. The FDA warnings include a statement that "patients who are started on [antidepressant] therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior."[5] The FDA warnings specify 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."[6] All of these side effects are acknowledged in the GlaxoSmithKline's official prescribing guidelines for Paxil.[7] Experts describe them as "paradoxical" side effects of antidepressants because they can cause a worsening of the patient's condition.[8]

The Side Effects Linked to Antidepressant-Induced Suicidality

For the purposes of discussing a case like Bobby 's, one looks for evidence of any of the side effects that the FDA warns may lead to antidepressant-induced suicidality—anxiety, agitation, panic attacks, insomnia, irritability, hostility, akathisia, manic-like reactions, and hypomanic-like reactions. Experts on antidepressant-induced suicidality often add two other side effects to this list: paranoia and psychotic reactions.[9] These side effects form a cluster of over-stimulating antidepressant side effects that can cause or exacerbate suicidality. These side effects have long been linked to drug-induced hostility and suicidality

in reports and studies published in medical journals going back decades.[10] Of these side effects, the one most tied to antidepressant-induced suicidality is akathisia, a toxic form of drug-induced agitation that has long been linked to suicide and violence.[11]

Akathisia has two sides, or faces: outer, objective restlessness and inner, subjective agitation.[12] The outer, visible restlessness particularly affects the legs and may be mild, moderate, or severe. The inner, subjective agitation of akathisia is, in fact, its more dangerous side. The subjective agitation of akathisia has been described as "abject terror" that can include anxiety, tension, irritability, hostility, paranoia, rage reactions, and violence.[13] The abject terror is unlike anything the patient has ever experienced before. Patients report: "I feel like I'm going to explode, like the molecules inside my body are all sped up, bursting against my skin." "I feel like my bones are tuning forks rattling in my body." "I feel like I'm living twenty-four-hours a day with the sensation of nails scratching up and down a blackboard." "I feel like I have caffeine running in my veins." "I feel like jumping out of my skin." Experts describe akathisia as "more difficult to endure than any of the symptoms for which they [patients] had been originally treated."[14] The abnormal bodily sensations and anxiety can make it difficult for patients to think clearly, leaving them with feelings of confusion and unreality, to the point where they can appear almost psychotic. Some patients may regress to a state of almost child-like helplessness in the face of relentless agitation and anxiety whose origin they do not understand. Some patients have dissociative experiences, episodes in which they feel disconnected from themselves and others.

The FDA warns that the most dangerous time period for these side effects to cause antidepressant-induced suicidality is "especially at the beginning of therapy or when the dose either increases or decreases," in other words whenever the dose *changes*.[15] Here, too, the FDA is consistent with the decades-old reports of this side effect in medical journals.

While the most dangerous window of vulnerability is the initial one to two months after changing the dose of an antidepressant, some patients become suicidal or violent on the drugs after a longer period of time. This is particularly true of patients who have psychotic breaks as a result of being on antidepressants. The psychosis may develop much more slowly over a longer period of time.

Many antidepressant-induced suicides are sudden, extremely violent, out-of-character, and caused by a drug-induced obsession with suicide. Patients who survive suicide attempts often describe the suicidal urges as alien and intrusive. According to Harvard psychiatrists Drs. Teicher and Cole who wrote one of the earliest reports of Prozac-induced suicidality, antidepressant-induced suicidal thoughts typically involve an "intense, violent suicidal preoccupation" that can be "accompanied by abject acceptance and detachment."[15]

When evaluating cases like Bobby's, one looks for evidence that the patient deteriorated rather than improved while on an antidepressant. One looks for the occurrence of any of the side effects the FDA has warned are linked to antidepressant-induced suicidality. And one looks for evidence that the patient's suicidal urges occurred shortly after starting the drug or increasing the dose. As we will see shortly after starting Paxil and increasing the dose, Bobby developed akathisia, increased anxiety, worsening insomnia, paranoia, uncontrollable crying spells, and ultimately irresistible suicidal urges.

Part 2. Specific Causation: Paxil Was a Substantial Factor in Causing Bobby Collins's Suicide

Bobby Collins was born on December 30, 1947 and spent his early years in Bluefield, West Virginia. Bobby was one of three children of James and Mary Ann Collins. James was a plumber. Mary Ann was a homemaker. Bobby had an older sister, Rose, and a twin brother, Billy. Bobby's sister Rose says the family struggled financially in West Virginia: "There wasn't much work in Bluefield." She describes Bobby as a "happy-go-lucky boy" who liked to play basketball and football. Bobby and his twin brother, Billy, were close growing up. "They did everything together," says Rose. The Collins were devout Catholics. The children went to Catholic school. Bobby and Billy were altar boys.

The Collins moved to Washington, DC when Bobby was about seven years old because his parents felt there would be more opportunities for themselves and their children. James found work as a plumber and Mary Ann became an office worker. Bobby was an average student and would have liked to go to college. However, his parents could not afford to send him. So, when Bobby and Billy graduated from high school, they were both drafted into the army. Bobby was sent to Vietnam while Billy was sent to Germany.

According to his family, Bobby said little about his tour of duty in Vietnam. His wife Mary recalls him saying: "The press painted a rosier picture of how things were over there but actually in reality they were much worse." Mary and Rose say Bobby always walked a straight and narrow path when it came to alcohol and drugs. He rarely drank and never used drugs.

Bobby was promoted to sergeant and had an honorable discharge from the army. He was in good mental and physical health when he returned from Vietnam, unlike many traumatized veterans of the war. He returned to his parents' home in Washington. The Collins lived in a two-family house. The family upstairs had a grown daughter, Carol, who worked with Bobby's future wife Mary. One day, after Bobby had been home just a few months, in the spring of 1969, Carol said to Mary: "How would you like to meet a nice Catholic boy?" Says Mary today: "Sounded good to me." So, Carol set Mary and Bobby up on a blind date. Says Mary: "I did all the talking that night, I don't know why. Bobby went home thinking: Gosh, she talks too much. I went home thinking: Gosh, he doesn't say a lot. But he asked me out on a second date and that's when we hit it off. The rest is history." Bobby and Mary were engaged within six months and married within a year on May 23, 1970.

Bobby and Mary settled in Forestville, Maryland not far from where his parents had recently moved. Bobby worked as a forklift operator at Western Electric in Arlington, Virginia. Mary worked as a secretary for the National Letter Carriers Association. Bobby and Mary were an unusually close couple. Says Mary: "We did everything together. We communicated really well. We shared the same sense of humor. We were best friends."

Not long after Bobby and Mary were married, Bobby's father died. Bobby and Mary were very attentive to his mother in the years after his father's death. Says Mary: "Bobby and his mother were unusually close. They were very alike, really. He was always supportive of her. When she had people in, he'd be in the kitchen helping her out, more like a daughter would be. His mother and I had a wonderful relationship. At first I wasn't sure she would accept me because she and Bobby were so close. But we became good friends."

Bobby Becomes a Washington, D.C. Police Officer in 1970

Bobby's ambition in life was to be a police officer. When I asked Mary what appealed to Bobby about the job, she said: "Bobby became a police officer because he wanted to help people and society. On the police force, it was

detective work Bobby really loved. He loved solving crimes." Bobby had to go through rigorous psychological and physical testing to get a job on the police force.

Bobby began working for the Washington, D.C. police force in September 1970. He went through an intensive training program that Mary thinks lasted about eight months. Bobby started out as a uniformed officer but quickly became a plainclothes, undercover officer who specialized in vice work.

Bobby and Mary Have a Son, Dwayne, Born in 1972

Bobby and Mary's son, Dwayne, was born on July 12, 1972. "Bobby was thrilled with Dwayne," says Mary. "Bobby was a very involved father. He didn't hesitate to change a diaper, unlike a lot of men we knew. He helped me around the house to lighten my load with an infant. He'd clean the kitchen and wash the dishes. Bobby was always very organized and meticulous. I never had to pick up after that man once the entire time we were married."

As Dwayne grew older, Bobby and Dwayne were very close. "They did everything together," says Mary. Says Dwayne: "He was a very caring, loving father." Dwayne liked to play sports, especially basketball and baseball. "He took me to all my games," says Dwayne. Dwayne did not like football: "I went to one practice and quit. My dad didn't push me. He was great about it." Says Mary: "I picked Dwayne up from the practice. The coach was this really tough guy. He was barking orders at the kids. At the end of the practice I heard him ask: 'So is there anyone who's not going to be here for practice tomorrow?' And there was Dwayne with his hand up. I came home and told Bobby. He said, 'That's okay. I don't think I'd want to be out there getting pushed around with that coach, either.'"

Bobby liked to play pool but did not like to hang out at pool halls. So, he bought a pool table for the Collins' house. Bobby taught Dwayne how to play pool. Says Mary: "He tried several times to teach me. But he gave up because I kept scratching the felt tabletop. Playing pool was a Bobby and Dwayne thing."

Bobby Takes Disability Retirement from the Police Force in 1974

Unfortunately, a series of traumatic experiences cut Bobby's police work short. In one incident, Bobby stopped a young boy who Bobby realized was truant. The boy ran into a nearby house. Bobby went to the house and knocked on the door.

Unfortunately, it turned out to be a house of the Black Panthers, who had considerable animosity towards police. When several men came out, Bobby had to call for backup. His sergeant had several of the men arrested for rowdiness.

Unbeknownst to Bobby and his sergeant, the Black Panthers decided to retaliate. Some months later Bobby and his sergeant responded to a distress call from the Safeway on Pennsylvania Avenue. The distress call was false, an effort to set Bobby and his sergeant up to be ambushed. As their cruiser pulled up, the Black Panthers opened fire, shooting out all the windows in the car and wounding Bobby's sergeant. Fortunately, Bobby himself was not injured. His sergeant was so traumatized that he left the police force and instead went to work on the harbor patrol. Bobby then had another incident that was even more traumatizing.

By this time, Bobby was an undercover officer. He and another officer were staking out a liquor store that had had a series of robberies. Bobby and the other officer were positioned behind a two-way mirror when a young man in about his late teens came into the store saying he was holding it up. When Bobby and his fellow officer stepped out to arrest the man, he pulled a gun on them. Both officers responded by shooting in self-defense. When the young man died, forensic examination later showed it was Bobby's bullet that had killed him. Moreover, it turned out the gun the suspect brandished was a toy gun. Both Bobby and the other officer were exonerated in the incident. Although Bobby could not have known that and was acting in self-defense, he felt terrible over the young man's death. A conscientious man who had become a police officer to help people and society, he felt terrible that he had killed someone when it was unnecessary. Bobby told Mary this was very different from his Vietnam experience. In Vietnam all the fighting he had done was at night. He had never seen anybody he might have killed. This was different: Bobby had been face to face with the young man just before he died.

Following these and at least two other incidents, Bobby developed severe gastrointestinal symptoms: nausea, vomiting, and bloody diarrhea that would eventually be diagnosed as ulcerative colitis and peptic ulcer disease. He also developed intrusive thoughts and nightmares of the shooting incident. The symptoms eventually made Bobby unable to function on his job, especially fearful of going into Washington in the vicinity of where the incident had occurred.

Bobby saw Dr. Irving Brick, who was the head of gastroenterology at Georgetown Medical Center. When Bobby's symptoms did not respond quickly to treatment, Dr. Brick referred Bobby to a psychiatrist. Bobby was ultimately referred to Dr. Howard Benensohn who he saw in weekly psychotherapy, which he found helpful in dealing with the traumatic events. Bobby had an extremely good rapport with Dr. Benensohn. Dr. Benensohn stated at his deposition that Bobby suffered from what would now probably be called post-traumatic stress disorder, or PTSD. As part of the PTSD, Bobby had symptoms of anxiety and depression. When I spoke with Dr. Benensohn, he said he never diagnosed Bobby with major depression, or any equivalent in the terminology used in the 1970s and '80s. In addition to psychotherapy, Dr. Benensohn treated Bobby with Valium.

As a result of his gastrointestinal and PTSD symptoms, Bobby was ultimately granted disability retirement on April 26, 1974. Taking disability retirement at age 26 was one of the most difficult decisions Bobby ever made. Says Mary: "He didn't really want to do it, but he felt he had no choice. He would have had a great future in the police force but it was cut short by those traumatic events. I went with him to the disability hearing. His was an open and shut case. Nobody thought he could go back on the police force." Bobby's disability retirement had to be re-evaluated every two years. In 1991, the every two year re-evaluations were waived indefinitely in Bobby's case.

Bobby Courageously Rebuilds His Life

Bobby remained in psychotherapy with Dr. Benensohn for about a year-and-a-half. He went on an as-needed basis from 1977 to 1981, about four to six times a year. Bobby did not see Dr. Benensohn from 1981 to 1987. Between September 1987 and January 1992, Bobby returned to Dr. Benensohn sporadically for a total of eight times. Bobby last saw Dr. Benensohn in 1992.

In addition to psychotherapy, Dr. Benensohn treated Bobby with Valium. According to records of the police retirement board's periodic evaluations, Bobby took Valium on an as-needed basis until about the mid-1980s. According to Dr. Benensohn:

> Bobby had no history of drug abuse in Vietnam. I don't ever recall him abusing the Valium. I don't recall whether or not he was a social drinker but if he'd had any history of getting sloshed, I wouldn't have encouraged his use of Valium.

Said Dr. Benensohn of his work with Bobby:

> I liked the guy. I thought he was someone who had served his country and had this terrible trauma happen to him. Intellectually, he knew a police officer can't take the time to see if a suspect's gun is a toy. But emotionally, he was devastated by the trauma of killing the young man. When Bobby first came to see me, he could barely function. I thought he'd be able to one day function again.

Indeed, as soon as he was able, Bobby went back to work. He washed cars for a car dealership owned by his sister-in-law Ann's husband's family in Marlow Heights. The job was not very demanding. Says Mary: "Bobby believed in doing whatever you could to put food on the table for your family. He didn't sit at home feeling sorry for himself. He went out to work. That was the best he could do and he did it. I was proud of him. Bobby was a fighter. And he was devoted to his family." To help financially, Mary went back to work as a secretary. Bobby worked days, nine to five. Mary worked the evening shift from five o'clock to one in the morning. They hired a teenage girl in the neighborhood to take care of young Dwayne for an hour-and-a-half in the early evening, from the time Mary left the house until Bobby got home from work.

Bobby and Mary Buy a Home in 1975

Bobby and Mary bought their first home in Waldorf, Maryland in 1975. The house was a fixer-upper which Bobby and Mary renovated over the years. Says Mary: "We loved improving and furnishing the house together. Bobby especially liked gardening and keeping a nice lawn. We were homebodies who enjoyed nesting together." The couple bought the house with a Veterans Administration mortgage that required no down payment or closing costs.

Bobby had a long commute to the car dealership in Marlow Heights. So, after a number of years he took a job at Pargas in Waldorf, close to the Collins' home. Pargas supplies propane fuel to homes. Bobby drove a truck delivering the gas. For a time Mary switched to working days as a school bus driver so she would have the same schedule as Dwayne.

During these years, the Collins had a rich family life. Bobby put up a basketball hoop in the backyard for himself and Dwayne. He would take Dwayne out to a field to practice batting and catching baseballs. Bobby and Dwayne would go

fishing at a nearby stocked pond. Bobby taught Dwayne how to swim at a local swimming pool. This was the house that Bobby installed a pool table in. The Collins lived in the house in the Saint Charles subdevelopment for fifteen years. Bobby was a quiet and easygoing man with a dry wit. A meticulous dresser, he liked to keep everything around him neat – including, for example, his house and car. To relax, he enjoyed playing cards with his male friends and doing yard work.

Bobby's mother was diagnosed with breast cancer and died in 1980. Mary took Bobby's mother for her radiation treatments, commuting across the city with her to the hospital. Says Mary of Bobby's reaction to his mother's death: "It was very difficult losing her. But even at a time like that, I never saw him cry. I'm sure he did but he did it in private."

Bobby Returns to Detective Work in 1984

Bobby continued to have periodic flare-ups of his ulcerative colitis. But, the episodes were manageable and did not disrupt Bobby's life. By 1984, Bobby had recovered enough from his gastrointestinal symptoms and PTSD that he was able to start a full-time job as a security guard at the Smithsonian. Before long, he was promoted from a uniformed guard to a plainclothes guard and ultimately an investigations officer. So, Bobby was back doing what he most loved: being a detective at the national museum.

Bobby solved all kinds of crimes that occurred at the Smithsonian, from pickpocketing to theft of museum pieces to at least one murder. Bobby reported the job to the police retirement board, who allowed Bobby to keep his disability because the work was different enough from being a police officer in the city.

Bobby was very successful at his job at the Smithsonian, which he held for eighteen years until the time of his death. He was apparently particularly adept at spotting, trailing, and catching pickpockets. His employment file contains unsolicited letters from museum patrons praising Bobby for his kindness and perseverance helping them. Bobby received outstanding annual evaluations and got along well with his bosses with the exception of his last boss, Howard Blum, with whom he had a cooler relationship. One year Blum gave Bobby a high evaluation but not quite outstanding. Bobby questioned the evaluation, asking for an explanation. In the end, the evaluation was changed to outstanding. Although Bobby and Blum did not have a particularly friendly relationship,

Blum testified that this did not get in the way of their working effectively together. At his deposition, Blum testified:

> I had to choose my words correctly and think about what I was going to say.... I had to be prepared for his questions that maybe somebody else might not ask.... [But] Mr. Collins was a professional and when he did his job, he did it well.... He was very competent and knowledgeable.... I did feel he was an honest guy.

Bobby and Mary Adopt a Daughter in 1985

The Collins were church-going Catholics at Our Lady Help of Christians Parish Church. Bobby was the head usher responsible for seating people, handing out church missals, collecting the weekly donations from parishioners, and cleaning the church up after Mass. In about 1983, one Sunday at Mass, the priest announced that there were some 600 babies in Korea needing adoption. When they got home, Mary asked Bobby: "Do you think we could adopt a baby girl or would it be a problem that she was foreign?" Bobby responded: "That doesn't matter. A baby's a baby. I'd love a foreign baby just like she was my own." So, the Collins embarked on adopting a girl. They had to go through a rigorous screening process, including psychological evaluations and evaluations of the mental health of their family. Fourteen-year-old Dwayne was thrilled at the idea of having a little sister. He hoped she would arrive on his birthday July 12, 1985. While she didn't exactly arrive that day, on Dwayne's birthday the Collins did get word that she would be arriving the next week on July 19th. The Collins were thrilled with Kristen Suh Collins when she arrived at the Baltimore Washington International airport. Bobby adored Kristen. She was "Daddy's little girl," who he loved to spoil just a bit. Says Kristen:

> He was a great dad. He was always there for me, to support me in whatever I wanted to do. We were close. We could talk about anything.

Bobby and Mary Buy Their Dream House in 1991

In 1991, Bobby and Mary bought their "dream house" in one of the nicest neighborhoods in Waldorf. Says Mary:

> It was a two story brick house on a corner lot, a builder's model home, the kind of house Bobby and I never thought we'd be able to afford. But we did well on the first house we'd fixed up and were able to swing it. We

couldn't furnish the whole house initially. But we saved and did that slowly, one room at a time. The house had a large yard and garden, which Bobby loved to tend.

The mid-1990s were a satisfying time for Bobby and Mary. "We were a close family," says Mary. "We played cards, watched TV, and rented movies that we all watched together."

Dwayne graduated from high school in 1990 and went to college for one year at the College of Southern Maryland. When Dwayne began working, he continued to live with his parents for a number of years. In August 1995, Dwayne and Tricia Graff had a son named Riley. Mary and Bobby were very involved in Riley's life until about 1999 when Tricia made it difficult for Dwayne, Bobby, and Mary to see Riley. Dwayne ended up in a custody battle with Tricia. Bobby and Mary became involved, petitioning for grandparents' visitation rights. Fortunately, the custody and visitation issues were resolved to everyone's satisfaction: Dwayne was allowed to have Riley every weekend, when Bobby and Mary could also see him. Dwayne later married Jennifer Lilly. They had two daughters, Haley and Kelsi. At his deposition, Dwayne said he and Jennifer were divorced in 2001.

Mary Is Diagnosed with Breast Cancer in September 2001

On September 20, 2001 Mary was diagnosed with breast cancer and had a radical mastectomy about a month later. On November 17th, she began receiving chemotherapy. Over the next several months, Mary would go for chemotherapy once every three weeks. Naturally, Bobby was upset by this turn of events. Kristen, then sixteen, stopped attending the local high school and began taking her classes at home on-line in order to help her mother.

Bobby Takes Vacation Time Over the Christmas Holidays 2001

Starting on December 15, 2001, Bobby took time off from work to use his allotted vacation time for the year. The government required employees to use up extra vacation time or they would lose it. Bobby often took vacation from about mid-December to mid-January. At Christmas, Bobby experienced some nausea and loss of appetite. At the time, the family thought he might be suffering from a virus rather than another, periodic flare-up of his ulcerative colitis.

Shortly after Christmas, Bobby's twin brother, Billy, died from liver disease. According to Rose, Billy had distanced himself from the family for some time. Since Bobby and Billy had not had much contact in years, the loss was not as upsetting as it might have been. Indeed, Bobby found a positive, gratifying role for himself at his brother's funeral: he helped bring together Billy's children and his second wife, who did not get along, so that they could all support one another through Billy's funeral.

Bobby Sees a New Gastroenterologist, Dr. John Carroll, in January 2002

In early January 2002, Bobby began noticing blood in his stool. Bobby's longtime gastroenterologist, Dr. Irving Brick, had retired. So, the Georgetown University Hospital referred Bobby to a new gastroenterologist, Dr. John Carroll. Bobby saw Dr. Carroll for the first time on January 9th. After examining Bobby, Dr. Carroll increased his dose of sulfasalazine, an anti-inflammatory agent used to treat ulcerative colitis, from two to three grams a day. He also recommended a colonoscopy "in approximately two weeks." Dr. Carroll also prescribed "a short course" of 10 milligrams a night of Ambien because Bobby was having difficulty sleeping.

Dr. Carroll Prescribes Paxil on January 16, 2002

Over the next week, Bobby continued to see blood in his stool. He also had trouble eating. On January 16th, Bobby went back to see Dr. Carroll. Thinking that Bobby's continued gastrointestinal distress might respond to a proton pump inhibitor, Dr. Carroll gave him samples of 30 milligram Prevacid pills.

In this appointment, Dr. Carroll, who was still getting to know Bobby, recognized a potential psychological component to Bobby's gastrointestinal symptoms. According to Dr. Carroll's note:

> Mr. Collins has a generalized feeling of upper digestive discomfort, nausea, which he feels is exacerbated by recent stressful situations. In speaking with Mr. Collins, he seems moderately upset to almost on the point of being tearful. He discussed his numerous recent stressors and feels that he is , quote, "at the end of his rope," end quote. Additionally, he has been taking the Ambien which I have prescribed at his last visit for sleep troubles and this has had some benefit but has not completely restored
> his sleep pattern.

> Regarding his overall emotional state and some apparent anxiety and depression, it looks as though he needs more urgent attention. I had planned on plugging him in with one of our internal medicine doctors here at Georgetown. But we will additionally try to reach one of our psychiatrists on the phone today and arrange a more immediate office visit, hopefully in the next day or so.

Bobby also saw an internal medicine resident, Dr. Greenberg, who was working with Dr. Carroll on January 16th. Dr. Greenberg diagnosed Bobby as a:

> 54-year-old man with symptoms of depression and gastrointestinal complaints of frequency and urgency.

Regarding his depression, Dr. Greenberg noted:

> We discussed at length the need for counseling and the possibility of medicinal therapy, i.e. SSRI. *He is not suicidal*, but would benefit from the aforementioned interventions. [emphasis added].

Dr. Carroll managed to page the psychiatrist on-call at the Georgetown University Medical Center before Bobby left his offices. Fatefully, the psychiatrist recommended that Dr. Carroll start Bobby on Paxil even before he had a full psychiatric evaluation. At his deposition, Dr. Carroll testified:

> I think I also asked him [the psychiatrist on-call] if I should started him on some medication. And so I think I prescribed Paxil this day. I can't remember this. And I don't think I would have come up with that. I think I probably asked him, and he maybe suggested that name and dose, and then I prescribed it [Paxil].

Dr. Carroll did not document the Paxil prescription in Bobby's medical record:

> And I'm surprised I didn't dictate that, because usually we put that in.

However, Bobby's pharmacy records confirm that he did indeed fill a prescription for Paxil 10 milligrams a day from Dr. Carroll. When asked whose idea the Paxil was, Dr. Carroll testified:

> I'm pretty certain either if I suggested and bounced it off him or he suggested. My feeling was, we should probably get him on some type of, you know, pharmaco therapy that's been shown to help people in acute major depression, and I would be happy to prescribe it.

Bobby's Condition Deteriorates Sharply on Paxil

According to Mary, Bobby took his first dose of Paxil by noon on January 16, 2002. After taking Paxil the next morning on January 17th, Bobby became agitated. Mary reports that on Paxil Bobby gradually became more agitated, fidgety, irritable, anxious, and sleepless. Says Mary:

> He started wringing his hands like I'd never seen him do before. He'd twist his ring around and around on his ring finger. He'd take the ring off and on, off and on. He started bobbing his knees up and down, up and down. I couldn't figure out what was happening. When he started bobbing his knees, I said to him: "Bobby, do you need to go to the bathroom?" He said: "No."

On the night of January 17th, Bobby called Dr. Carroll to say he was feeling worse. Dr. Carroll told Bobby to go in to the Georgetown University Medical Center's emergency room where he was described as "tearful" and "defers to wife frequently when questioned." Says Mary:

> It's like Bobby couldn't answer for himself. I'd never seen the man cry before in his life. He became more and more helpless and dependent on me. The change in him was so sudden and dramatic.

Bobby was evaluated by the gastroenterology fellow, Dr. Din. After seeing Bobby, Dr. Din consulted with Dr. Carroll in the middle of the night. Dr. Carroll arranged for Bobby to be admitted to the gastroenterology service. But, said Dr. Carroll at his deposition, the main purpose was to get Bobby psychiatric services because of his rapidly deteriorating psychiatric condition:

> [His symptoms] seemed to be an *exacerbation* of the same concerning symptoms he had in the afternoon on the 16th, which is why I admitted him. Not because I was concerned about his stomach *but as a way to kind of get him into see psychiatry*...[emphasis added].

Having to admit Bobby to the hospital to the gastroenterology service just to see a psychiatrist is an indication of how rapidly Bobby's condition was worsening on Paxil and how concerned the doctors were. Side effects like those Bobby was experiencing can occur immediately after starting the drug. Moreover, doctors tell patients that it can take weeks for the drug to work. Patients often assume that means side effects, too, do no occur for weeks, making it even more difficult for them to identify Paxil side effects when not warned. Dr. Carroll testified:

> And then for this drug in particular, typically I explain that it is not going to work immediately; that there will be a, usually, gradual—hopefully a gradual effect of the benefit on the order of several weeks.

The Georgetown Medical Center Psychiatrists
Are Mystified by Bobby's Deterioration

The next morning on January 18th, Bobby was seen by the consultation-liaison psychiatric service. He was evaluated by a psychiatric resident named Dr. Julianna Brown and an attending psychiatrist named Dr. Mark Clifford. Dr. Brown wrote a lengthy consultation note vividly documenting Bobby's deteriorating condition. Bobby is described as "tearful, crying throughout most of [the] interview" and exhibiting "possible mild paranoia." In his rambling discourse, Bobby complained of "harassement by email" at work "to the extent that his co-workers contacted his wife accusing him (the patient) of having an affair." Bobby apparently felt "somewhat responsible for his ulcerative colitis flare-up" because "if he could be mentally stronger, he would be well with less physical problems." And, Bobby somehow "blames himself ... for his wife's breast cancer...." Finally, for the first time in his life, after starting Paxil, Bobby expressed treatment-emergent "suicidal thoughts, without intent or plan."

Bobby posed a serious dilemma for Dr. Brown and Dr. Clifford: His paranoia and fantastical thinking were almost psychotic but otherwise he did not seem out of touch with reality. Mary told Dr. Brown she had never received emails from Bobby's co-workers. She explained that Bobby had been engaged to a woman named Judy Smith years before Mary and Bobby met. Over the years, Bobby and Judy had been in touch periodically to update one another on their lives. In about 1999, Bobby had more regular telephone contact with Judy. This was at the time when Bobby and Mary were having difficulties with Riley's mother over custody and grandparents' visitation rights. Says Mary:

> For a period, that's all we talked about and it was a pretty discouraging subject until it all got resolved. I think talking to Judy might have been a relief from all of that. She may have been supportive, too.

When Mary confronted Bobby about the increased telephone contact, it stopped. Says Mary:

> Bobby always insisted it was never more than telephone contact, never more than a friendship. Bobby and I were always together. We worked a block and a half from one another. We commuted to work together. We were homebodies who spent evenings and weekends together. Judy Smith lives seven hours away in West Virginia. She was raising her own family. There was never any time when Bobby could have slipped away to meet her. I don't believe it was ever anything more than increased telephone contact that ended in about 2000. I'm sure they continued to have some telephone and perhaps email contact like they had before. I told Dr. Brown I knew they'd been in touch over the years and about the increased contact in 1999. Dr. Brown used the word "affair" but I corrected her.

Dr. Brown could not figure out what was happening with Bobby. Unfortunately, because GlaxoSmithKline had failed to warn of Paxil-induced clinical worsening, the doctors at Georgetown Medical Center were not given the opportunity to consider whether or not Bobby's heightened anxiety, distorted thinking, agitation, confusion, crying spells, worsening insomnia, paranoia, helplessness, and inability to cope were classic manifestations of the affects of Paxil-induced clinical worsening, as described earlier in the general causation section of this report. Lacking this information from GlaxoSmithKline, the doctors were mystified by Bobby's clinical presentation, unable to consider Paxil-induced decompensation as the cause of his problem.

Dr. Robert Pinney was another Georgetown Medical Center psychiatrist who began seeing Bobby as an outpatient the next week. Dr. Pinney spoke with Dr. Brown and Dr. Clifford. Describing the dilemma Dr. Brown and Dr. Clifford faced, Dr. Pinney testified at his deposition:

> *The big dilemma they were having was trying to understand was he delusional or having bizarre thinking* about certain aspects of his life, because he was talking about co-workers who were following him and who had somehow obtained his own e-mails from, I guess, his work computer. And they

were incriminating with regard to his—it was discussed, I have no facts—affair of some sort with a former high school sweetheart.

I think as this all bubbled out in the conversation to Dr. Brown, it seemed a little fantastic, you know, a little out of the ordinary. And in comparison to his other high-functioning qualities, *it was hard to assess.* So that was kind of what she put on the plate for me. *She* [Dr. Brown] *was most fascinated to know did I think he had a thinking disorder* [i.e. psychosis] *or was his life full of drama* [emphasis added].

In my opinion, Bobby's condition was "hard to assess" only because the doctors could not recognize his Paxil-induced decompensation. This confusion and dilemma would remain the problem until the time of Bobby's death weeks later.

Dr. Brown diagnosed Bobby with "major depressive disorder, moderate" and also suggested he "continue Paxil at 20 milligrams a day." Dr. Brown noted that Bobby "has [an] outpatient appointment scheduled for Tuesday, January 22 with Dr. Pinney at Georgetown Medical."

In addition to Dr. Brown, Bobby was seen by the attending psychiatrist on the consult service who also documented that Bobby had new, treatment-emergent suicidality:

> Complains of decreased sleep, some crying spells, *suicidal thoughts without plan or intent,* decreased appetite and weight loss, decreased concentration, decreased interest in normal activities [emphasis added].

However, according to the attending psychiatrist's mental status exam, Bobby:

> adamantly denies suicidal ideation.

So, although the attending psychiatrist's note earlier stated that Bobby had "suicidal thoughts without plan or intent," Bobby was apparently not suicidal at the time of this interview. Still a third doctor in the hospital documented on the same day, January 18th, that Bobby had "suicidal ideation without plan."

Bobby was in the hospital just two days. During this time, his gastrointestinal doctors replaced his Prevacid with another proton-pump-inhibitor, Protonix because "[the Prevacid] pill is too big and he has difficulty swallowing it."

Bobby Continues to Deteriorate on Paxil

When Mary, who was still undergoing regular chemotherapy treatments for her breast cancer, picked Bobby up from the hospital on January 19th to take him home, he was still not himself. Mary testified:

> The ride home was very tough because he was – he was still nauseous. He was anxious. He was rubbing his fingers.

Bobby exhibited irritability, another side effect that has been linked to antidepressant-induced suicidality. Says Mary:

> He was irritated with me being on the cell phone, which he'd never been before. It was very out-of-the-ordinary. People were calling to see how he was. He'd say: "Will that thing ever stop ringing?" Bobby never talked like that normally. Some phone or other was always ringing and it never bothered him before.

At home Bobby's anxiety and paranoia continued to escalate. Mary testified that she and Bobby would be walking down the street when Bobby would "take a sudden right-hand turn." When Mary asked why they had changed course, Bobby would insist, "You didn't see that Jeep following us?" Bobby became paranoid that people parked in cars at a school bus stop across the street from their house were watching them. Says Mary:

> I didn't see anybody with binoculars. They were just waiting for the bus to come with their kids. Occasionally people would park there and go jog. The bus stop had always been there. Bobby had never been afraid that people were spying on us before. He started taking down the license plate numbers of cars parked there. This was strange, new behavior.

Bobby Is Seen By a New Psychiatrist, Dr. Robert Pinney, on January 22, 2002

On January 22nd, 2002, Bobby met Dr. Robert Pinney in the outpatient department of psychiatry at the Georgetown Medical Center. Dr. Pinney's records and deposition document the same confusion and dilemma over Bobby's worsening condition that Dr. Brown and Dr. Clifford struggled with the week before when he was in the hospital. Once again, Bobby was paranoid and evidenced distorted thinking. According to Dr. Pinney's initial evaluation note:

> [Bobby] alleges that some of his coworkers took it upon themselves to disclose some private e-mail to his wife with regard to an alleged marital infidelity. He sees this as retaliatory on the part of his coworkers. During the session on today's date, Mr. Collins says he is of the opinion that his wife knows about the alleged marital infidelity and believes it to be true. He states that no such relationship is ongoing, but does acknowledge that it did take place at one time in the past.
>
> He has felt at times that some of his coworkers actually have harassed him and his wife and even have followed them on occasion.

Dr. Pinney's mental status exam summarized the dilemma:

> He demonstrated *no evidence of a frank psychosis* [i.e. Bobby was not hallucinating or unequivocally delusional] and in the context in which he placed the information regarding the workplace, *he does not appear to be frankly delusional* [i.e. maybe what he was saying about his workplace was true] [emphasis added].

Said Dr. Pinney at his deposition:

> So I really don't think he was *flagrantly* delusional. [But the question was:] Is he delusional that he has this story about people chasing him at work, or what. I mean, *that was the big flashing issue at the time* ... [emphasis added].

Psychosis can take two forms: Delusions and hallucinations. None of the doctors thought that Bobby was having hallucinations, either visual or auditory hallucinations. Nor was Bobby delusional in any flagrant way: He did not think Saddam Hussein was harassing him. But his paranoia and distorted thinking about his workplace was striking. Was it psychotic, in the absence of more flagrantly psychotic features? Or, was it true that Bobby was being harassed? Unfortunately, because GlaxoSmithKline had not warned that Paxil can cause worsening of a patient's condition, the doctors were unable to consider that Bobby's heightened anxiety and distorted thinking could have been Paxil-induced worsening of his condition.

From Dr. Pinney's note, it is clear that he did not distinguish between Bobby's pre- and post-Paxil symptoms or consider the role of the drug may have played in Bobby's decompensation. Indeed, Dr. Pinney noted that Bobby's "energy level

was good when speaking with his Georgetown Psychiatry Consult Service, but that he had been having increased sadness and worrying." Paxil's over-stimulating side effects may make patients feel like they have more energy while at the same time making them more anxious and distressed. The increased energy can be misconstrued by both the doctor and the patient as a partial improvement in the patient's condition even as the patient is deteriorating, as described in the accompanying report on GlaxoSmithKline's adult documents. As described in that report, in GlaxoSmithKline's studies, the HAM-D scores of the majority of patients who made suicide attempts on Paxil *improved* prior to the attempts.

According to Dr. Pinney's notes:

> He disclaims any current suicidal ideation or intent or plan and does not acknowledge any prior episodes of self harm.

Dr. Pinney too diagnosed Bobby with "major depressive disorder moderate" and recommended that he "continue Dr. Carroll's prescription of Paxil 20 milligrams...."

With regard to the alleged "affair," Dr. Pinney took the extraordinary step—given the stress the couple was under with Mary's cancer and the flare-up of both Bobby's ulcerative colitis—of telling Mary that he thought Bobby had had an affair. Says Mary:

> Neither Bobby nor I had ever referred to his contact with Judy Smith as an "affair." Dr. Pinney really shocked me. I confronted Bobby who said that was not true, that he hadn't told Dr. Pinney that. Dr. Pinney saying that really knocked me back. I'd had breast cancer, I'd had a mastectomy, I was undergoing chemotherapy, I'd lost my hair. That's not something you tell a wife at a time like that especially when you don't even know whether or not it's true.

Dr. Pinney acknowledged at his deposition that with regard to the alleged affair and e-mails: "I have no facts."

Bobby saw Dr. Pinney again on January 25th and January 30, 2002. In his January 30th note, Dr. Pinney wrote:

> [Bobby] explained details of [a] pending lawsuit against his employer where in he is a witness and it has been going on for several years with the employer's (and his) attorney's role not consistantly supportive of candor in testimony which leads to tension and anxiety between him and supervisors and co-workers.

At his deposition, Dr. Pinney elaborated:

> When he was being asked questions somewhere along the line, he was—what did I learn the word is—suborned? In other words, that someone was asking him to give testimony different than the fact, and that someone was in his chain of command.
>
> And when he alleged he would not play ball with them, that's when the e-mails were snarfed up out of his computer and sent to the wife, or he was threatened with them being sent to the wife.

It is my opinion based on the evidence I have reviewed that Bobby's fears appear to have been more of his distorted thinking on Paxil.

Bobby's Paxil Dose Is Increased on January 30, 2002

It is my opinion that Bobby's anxiety was escalating due to the Paxil-induced akathisia. At the January 30th meeting, Dr. Pinney decided to increase his Paxil dose to 30 milligrams a day:

> Agreed that *due to continued ambient anxiety*, a trial of slight *increase in Paxil* to 30 milligrams per day (either 20 plus 10 at bedtime or he can try 10 in the morning and 20 at bedtime) agreed upon as an attempt to deal with symptoms *without the use of Xanax or Valium* which may be habit-forming.

Bobby had told Dr. Pinney that his former psychiatrist of many years, Dr. Benensohn, had prescribed Valium for him for an extended period. Dr. Pinney did not have Dr. Benensohn's records. Nor had he spoken to him. Yet, Dr. Pinney testified that he assumed Bobby might have abused Valium and withheld this class of medication from him. Said Dr. Pinney at his deposition:

> The suspicion that we've already alluded to earlier today, that his prior doctor of some years gave him Valiums for some time that correlated with a period of not working and so forth, the think—I think there's reason to

> explore, if you could in hindsight, how savvy was he about drugs of abuse. Certainly with training—well, from the Vietnam era, in the military, and having been a police officer in D.C., I should think he's pretty knowledgeable about street drugs and how to obtain them and so forth.

Dr. Pinney was asked:

> Is there anything in the record that we have that was explored that indicated that he—he may have been taking some sort of street drug or other anti-depressant?

Dr. Pinney acknowledged:

> Nothing that I know....

As described earlier, Dr. Benensohn has no recollection of Bobby ever abusing Valium. He said that Bobby did not use street drugs and had no history of drug abuse in Vietnam. And, he would not have encouraged Bobby's temporary use of Valium to control his symptoms of anxiety if Bobby had a history of alcohol abuse. According to the police retirement board records, Bobby only used Valium on an as-needed basis until about the mid-1980s. Bobby had not seen Dr. Benensohn in ten years. And, Bobby's medical records repeatedly state that he did not use drugs or alcohol. According to Mary, Bobby rarely even drank: "Maybe a couple times a summer he'd have a beer after mowing the lawn." Dr. Pinney's leap to alcohol or drug use as a possible explanation for Bobby's clinical worsening, despite evidence to the contrary is telling. As GlaxoSmithKline failed to warn and historically mislead doctors about Paxil's true side effects Dr. Pinney was inclined to attribute Bobby's worsening to anything other than Paxil.

Additionally, GlaxoSmithKline's marketing of Paxil encouraged doctors to think the way Dr. Pinney did regarding the Valium. GlaxoSmithKline's Paxil brochures distributed to doctors' offices explicitly stated:[17]

> Some people [with anxiety disorders] may be treated with a class of drugs called benzodiazepines (ben-zo-di-az-uh-pines). Some well-known benzodiazepines include Xanax, Valium, and Ativan. Unlike SSRIs [such as Paxil], benzodiazepines are *potentially addictive and should be used with caution.*

> Paxil has been studied both in short-term and long-term use and is not associated with dependence or addiction. Paxil belongs to the class of drugs called SSRIs. Another class of drugs called benzodiazepines [e.g. Valium] may also be used to treat certain anxiety disorder but *unlike Paxil, benzodiazepines* have been associated with dependence in some patients [emphasis added].

Not only is this inaccurate, since GlaxoSmithKline did not study Paxil in both short- and long-term use, the company's brochures failed to acknowledge that Paxil itself can cause severe withdrawal reactions.[18]

Bobby Deteriorates Even More Dramatically Once His Paxil Is Increased

Antidepressant-induced akathisia is a dose-dependant side effect; the higher the dose, the worse the akathisia. Unfortunately, doctors can mistake akathisia for worsening of the patient's underlying psychiatric condition and increase the dose, making matters worse. When Bobby was prescribed Paxil in 2002, GlaxoSmithKline's official prescribing guidelines warned that depression can make patients deteriorate but did not warn that Paxil may cause patients to decompensate, thereby encouraging doctors to raise rather than lower the Paxil dose. This is what happened in Bobby's case.

Says Mary of Bobby's condition after the Paxil was increased:

> After they increased his dose, I did not recognize the man. He became completely unable to cope. The fidgeting was worse. He started pacing in my kitchen. He was more anxious. He became more paranoid. He could not sleep well. Before when he couldn't sleep at least he could lie in bed quietly. But after he went on Paxil and especially when the dose was increased, he'd rustle back and forth, toss and turn. I'd wake up in the middle of the night and find him sobbing. I'd say: "Bobby what's wrong?" He'd say: "I don't know what's wrong." I'd say: "Bobby, we'll just take it one day at a time." He'd repeat back like a child: "That's good, Mary. We'll just take it one day at a time."

Bobby saw Dr. Pinney again on February 6, 2002. According to Dr. Pinney's note:

> Patient complained of continued trouble with sleep onset and midcycle awakening despite Ambien 10 milligram dose from the GI doctor, Dr.

> Carroll, dated 1/9/02, that he just refilled for first time on February 5, 2002....

So, Dr. Pinney was forced to try a higher dose of Ambien to compensate for Bobby's worsening insomnia on the higher dose of Paxil.

Dr. Pinney did not set up a specific follow-up appointment with Bobby, documenting in the section of his note entitled "next follow-up interval":

> One or two weeks, patient will call to set up time to plan to return to work. 2/11/02 and uncertain of logistics.

In fact, this was Dr. Pinney's last appointment with Bobby, who died eight days later.

Bobby Returns to Work

On Monday, February 11th, Bobby returned to work at the Smithsonian for the first time since December 15th. Mary did not think he was ready to go back to work, but Bobby was afraid of losing his job if he stayed out much longer. When Bobby came home from work on Monday evening, his behavior was quite out-of-character. Says Mary:

> Bobby always changed his clothes when he got home from work. Bobby was a modest man, so he would change in the walk-in closet in our bedroom. So Monday night he comes home and he starts undressing in the kitchen. He took his tie off. He started to unbutton his shirt. I said, "Bobby, what are you doing?" He looked like he was lost and said dumbfounded, "I don't know what I'm doing." He was lost.

The next day, Tuesday February 12th, Bobby went to work again. On Tuesday night, he was still not himself. On Monday or Tuesday night, Mary moved a handgun Bobby kept in the house. Mary gave the gun to Bobby as a present many years earlier on their first anniversary. At the time, Bobby was a police officer and supposed to wear a gun even when off duty. Mary bought Bobby the same gun he had at work only a smaller, snub nose model so it would be easier to carry. Bobby kept the gun in the walk-in closet in the master bedroom. Mary moved the gun to a different place in the closet.

On Wednesday morning, February 13, 2002, Bobby again wanted to go to work. Bobby was scheduled to interview people as part of an investigation and Mary did not think he was up to it. Bobby was so agitated and anxious that he kept asking Mary for permission to do everything: "Can I shave now, Mary?" "Can I eat now?" After Bobby's death, one of his co-workers, Beverly Medlock came to the house and told Mary that she had done the interviews with Bobby. Mary testified:

> Beverly said she knew something was wrong because he was to interrogate these witnesses, that something had happened, and *he was very nervous, very upset, very agitated. So unlike him* is how she put it [emphasis added].

After the interviews, Bobby got lost walking in the vicinity of the Smithsonian complex. Says Mary:

> I don't know if he was walking back from the interviews or it was a little while later, but he called me sobbing and said, "I'm lost. I don't know where I am or where I'm going. I can't function." I said, "Bobby look at the street signs." He was crying. He didn't know what to do. He'd apparently tried to get back into one of the Smithsonian buildings and his ID badge, which functioned as electronic key swipe, wouldn't work. He was probably so out of it that he didn't swipe the key right but he insisted, "They won't let me back in. They've cut off my ID badge. They're trying to get rid of me."

Mary talked to Bobby for awhile, attempting to calm him down. Says Mary:

> Bobby said, "I'll call you back." He must have found someone who pointed him in the right direction. I think he bumped into someone he knew, because he called me back a little while later to say he'd made it the short distance, a block and a half, to the building where I worked, which was where the car was parked. He sounded a little better. He wasn't crying anymore. But I didn't want him driving home in that condition. So I said, "I'll come get you. Stay right there. Don't leave." He repeated back to me, again like a child, "I won't leave. I'll stay right here." I rushed upstairs to get Kristen. I said, "Your father's in trouble. We've got to go get him."

> Bobby had taken the truck [a 4 Runner] out of the parking garage. He was parked on the street, sitting in the driver's seat. When I opened the driver's door, instead of getting out and going around to the passenger side, Bobby climbed over the console, which I thought was very odd. He'd never done that before. As I got in, Bobby started waving his ID badge at me. He became agitated and upset again, saying, "They turned off my ID. They're trying to get rid of me." On the way home I tried to reassure Bobby by saying: "You won't have to go back there [to the Smithsonian]." He kept repeating: "You promise, Mary?" I'd say: "I promise" and he'd repeat: "You promise, Mary?"

When they got home, Mary called Dr. Pinney's office. Dr. Pinney was busy and could not come to the phone. Mary left a message, asking Dr. Pinney to call her back. Dr. Pinney documented that he spoke with Mary and told her to bring Bobby to the emergency room. Mary says that is not accurate; when she could not reach Dr. Pinney she called Bobby's old psychiatrist, Dr. Benensohn. Says Mary:

> When Dr. Benensohn heard the condition Bobby was in, he said, "Bring him to the nearest emergency room." The Georgetown Medical Center is not the nearest emergency room, but that's where I took him because that's where all his doctors were.

At his deposition, Dr. Benensohn said he recalled the telephone call from Mary:

> Q: Mrs. Collins indicated that she had called you on February 13, 2002 about her husband's condition. Do you recall that conversation or a conversation with Mrs. Collins around about that time?
>
> A: I recall a conversation where she called, I said I would be glad to see him if she brought him in, and I didn't hear back.
>
> Q: She had indicated in her deposition that she had talked to you about her husband's condition and his distress and you had advised her to take him to the nearest hospital. Does that sound familiar to you? Does that refresh your recollection?
>
> A: I don't recall it but it's possible. If she said she was concerned that he was suicidal—I don't recall where she was living but I said—it would be consistent with what I would say to someone that if you think they are suicidal, you call 911 or take them to the nearest hospital emergency room. So I don't recall it but it's quite possible I would have said that.

Mary had, in fact, been worried about Bobby's safety, which is why she had moved the gun.

The Georgetown Doctors Are Again Confused by Bobby's Sharply Deteriorating Condition

At the Georgetown University Medical Center, Bobby was seen by a resident on-call named Dr. Carlos Collin. Bobby and Mary spent the rest of the day and early evening in the emergency room. Dr. Collin evaluated Bobby multiple times trying to decide whether or not to hospitalize him. According to Mary, Bobby was also evaluated by at least four other doctors and doctors-in-training: attendings, residents, interns, and/or medical students. The emergency room records and doctor's testimony once again vividly capture the doctors' confusion as they tried to assess Bobby's rapid decline, his worsening anxiety, sleeplessness, agitation, paranoia, and helplessness.

An initial assessment note written by a medical student described Bobby as:

> [A] fifty-four year old recently diagnosed with depression and anxiety returned to work as criminal investigator 2 days ago after several weeks off. Reported *increased tension for 1-2 days, increased sense of paranoia when wife is absent, decreased sleep with no sleep yesterday, 2 hours the day before.* Denies suicidal or homicidal ideation [thoughts]. Denies auditory or visual hallucinations. *Reports not thinking rationally for 2 days. Wife verifies* [emphasis added].

Mary reports that in the examining room, Bobby thought an ophthalmology screen used to test patients' vision was a camera spying on him. According to Dr. Collin's note:

> [Bobby has] *worsening depression and anxiety....* Patient reports feeling *"incoherent and not well".... At times he becomes incoherent but.... Patient can be very coherent and logical when discussing his past history and situation at work* [emphasis added].

Once again because of Bobby's unusual, perplexing presentation the question was: Was Bobby psychotic, i.e. incoherent, or not? At his deposition, Dr. Collin elaborated:

> He would come across as paranoid, very disorganized, incoherent; but that was only when the patient was under pressure.
>
> He—when he was calm and more relaxed or maybe not aware of the importance of his surroundings, he would be able to make very clear statements and carry a conversation about his past medical history, his past life.
>
> When he was confronted about the current situation, he would immediately change his attitude, I would say, and *become very agitated and incoherent, almost to a point that would sound psychotic or suffering from a cognitive disorder* [emphasis added].

Dr. Collins performed a mini mental status exam on Bobby. As part of the exam, Bobby was asked to write a sentence. Poignantly, in retrospect, given what happened, Bobby wrote:

> I need help.

Elsewhere, in his mental status examination, under the category "Sample of speech," Dr. Collin wrote that Bobby said:

> I don't know what I need. I trust my wife. I need help.

At his deposition, Dr. Collin recounted:

> A: He was very preservative on that statement.... He rambles and reiterates. Like, you know, "I want help. I trust my wife. I need help."
> Q: You mean he repeats himself?
> A: Repeats himself.

The emergency room records and Dr. Collin's statements corroborate Mary's descriptions of Bobby as so disorganized and overwhelmed, that he appeared almost childlike. Again, sadly this is classic behavior for patients suffering from undiagnosed Paxil-induced akathisia and clinical worsening. Dr. Collin documented in his note:

> Wife reports [she has] *never seen her husband like this before* [emphasis added].

Apparently there was some back and forth about whether or not Bobby should be hospitalized. Ultimately, Dr. Collin let Bobby go home. Bobby wanted to be hospitalized on a medical unit rather than a psychiatric unit, as he had been in January. Bobby told Mary:

> I need help. I'm not crazy.

Dr. Collin testified that Bobby could not be admitted to a medical unit now that he was in treatment with the psychiatrists. Dr. Collin did not feel Bobby was committable, that is, he could not be hospitalized on a psychiatric unit against his will, because Bobby was not suicidal. Multiple doctors documented in the emergency room record that Bobby was not suicidal at the time. And Dr. Collin did not think Bobby was psychotic despite his being "incoherent" at times when acutely anxious.

According to Dr. Collin's note:

> Patient *reports not feeling well with his current treatment on Paxil 20 milligrams POQD* [a day]. He has been compliant with treatment [i.e. taking his antidepressant] and follow ups but he is unhappy with his current treater... [emphasis added].

Bobby had certainly been cooperating with treatment including calling and coming back repeatedly when he wasn't doing well, just as the doctors had instructed. When patients are warned appropriately about Paxil-induced clinical worsening and suicidality, the information provides them with tremendous control over their fate. By contrast, when patients like Bobby are not warned, they feel out of control and helpless at the mercy of side effects they do not understand.

Mary testified that she and Bobby repeatedly asked for some Valium-type medication to help quickly calm Bobby down. Surprisingly given Bobby's severe anxiety, he was never given any Valium-type medication. As described earlier, Dr. Pinney testified that he wanted to avoid this class of medication with Bobby. Dr. Collin testified at his deposition that he was in contact with Dr. Pinney during the afternoon and coordinating his treatment with him.

When Dr. Collin discharged Bobby home, for Bobby's severe insomnia, Dr. Collin prescribed an old, sedating, tricyclic antidepressant called Doxepin.

Again, this is consistent with withholding Valium-type sleeping pills from him. Dr. Collin's discharge diagnosis was "depression." But, Dr. Collin added "rule out psychosis" because Bobby had deteriorated so rapidly on Paxil. Dr. Collin instructed Bobby to "follow-up with Dr. Pinney in the next 48 hours."

Bobby Shoots Himself in the Head

After breakfast on the morning of Thursday, February 14th, 2002, Bobby went into the family room. Mary brought him his pills – 30 mg of Paxil and some Prevacid. Bobby, as Mary recalled, was "anxious and fretful." They sat there waiting for Mary's sister, Ann, who was coming with her daughter, Janice, from Fredericksburg to take Kristen to her 9 am court hearing related to a speeding ticket. In addition, for some time, Bobby and Mary had been planning to relocate to Fredericksburg, Virginia. They were concerned that the town they lived in, Waldorf, Maryland, was going downhill and not a good environment for Kristen. Says Mary: "Our neighborhood was still fine. But some parts of town including the town center were going downhill." Mary's sister, Ann, lived in Fredericksburg. Mary's doctors were there. Kristen had been accepted to a private Christian school in Fredericksburg. Bobby planned to commute by train to Washington, DC. Bobby and Mary had looked at houses in Fredericksburg. The plan was for Kristen to move down to her aunt's in order to start the new school. Mary and Bobby would move once they found a new house. So, Kristen was moving her aunt that morning. Before getting in the car with Kristen, Ann talked with Bobby. At her deposition, Ann testified:

> [Bobby] was just sitting there looking dazed saying none of this is important.... I remember him saying none of this is important. I just said you're going to feel better. I didn't know what to say.... He didn't look like Bobby.... He just wasn't—he just wasn't the same Bobby. That's all I can tell you. He wasn't.

At her deposition, Kristen elaborated on Bobby not being himself that morning:

> He was sitting on the couch and he was just completely out of it, kind of like he was zoned out, couldn't really say anything to me. He was crying, which I never saw him cry. He was just a completely different person.

After the brief court appearance, Ann and Janice returned to the house to pick up Kristen's belongings. As described earlier, Kristen was moving to Fredericksburg to live temporarily with her aunt in order to start her new school.

Recognizing that Bobby was not doing well and still needed help, that morning Mary called a psychiatric facility in Fredericksburg called Snowden. Snowden provides both inpatient and outpatient services. Says Mary:

> I thought of Snowden as another option. Maybe he'd be admitted there. If they wanted to treat him as an outpatient, we could stay with my sister. Kristen was going to be there. I just thought of it as another hospital I could take him to since Georgetown hadn't worked out.

After Ann, Janice, and Kristen left, Mary and Bobby were packing his suitcase in the master bedroom. Says Mary:

> Another thing happened that was so odd for Bobby. He was bringing me clothes from the closet to pack in his suitcase. As he handed me pairs of pants, I noticed they were dirty. Normally, Bobby was meticulous about his clothes. Some of the pairs of jeans were covered with dog hair from our Labrador, who sheds. Bobby had one of those sticky rollers you use to get lint and dog hairs off your clothes. Bobby was always using the roller to keep his clothes clean. But here he was handing me dirty pants to pack.

At one point, Bobby came out of the closet and went to a nightstand to get his glasses. Mary thought nothing of it. In retrospect, Bobby needed his glasses to open the combination lock on the gun case, which he had found in the closet. When Bobby went back into the closet Mary heard a "pop." Bobby had shot himself in the head with his Smith and Wesson .38 caliber revolver. Mary rushed into the closet and found Bobby lying in a pool of blood. Distraught, Mary called 911. When the police and ambulance arrived, Bobby was still "breathing but unresponsive," according to the Charles County Sheriff's office. The police and paramedics tried unsuccessfully to revive Bobby, who was pronounced dead at his home.

Mary called her sister Ann and told her what had happened. Ann turned around and brought Kristen back home. The police went to Dwayne's workplace and brought him to the house. Mary told each of the children that their father had died when they arrived at the house.

According to the police report:

> Mrs. Collins told me that the decedent, Bobby Ray Collins, had been very depressed. She explained that he was a Viet Nam veteran, and had retired from the Metropolitan Police, Washington, D.C., on disability in 1974. The reason for the retirement was depression, attributed to his service in Vietnam. She said he was never fully recovered. On December 15, 2001, the decedent took leave from his job as an investigator with the Smithsonian Institute due to his suffering from ulcerative colitis. He remained on leave for a month, and was hospitalized for two days during that time, for the colitis. Mrs. Collins said that as his leave ended he never was able to get back into his job. She said he returned for only a few days, before it became too much for him to handle. She said that he began to act as if he "wasn't himself". [*sic*] She said he complained of not knowing if he was coming or going. She said that one day he stood in the middle of the kitchen floor and took his shirt off. She explained that since they had been married they had always dressed and undressed in the closet with the door closed. She said he would never have taken his shirt off like that if he were behaving normally.

The police report contains a number of inaccuracies. According to the Police and Fireman's Relief and Retirement Board records, Bobby's disability retirement was not attributed to his service in Vietnam. Rather, it was specifically attributed to the traumatic events that occurred while he was on the Washington, D.C. police force. Bobby did not take leave from his job on December 15, 2001. He took vacation to avail himself of his unused vacation days for the year, which he would otherwise lose. At some point in the last weeks of his life, he may have gone on medical leave. In my experience, police and coroner's reports often contain inaccuracies because everything is so chaotic and everyone is so distressed at the scene of a suicide.

The police report goes on to say:

> The deceased's son and daughter arrive at the home. I spoke with both of them in reference to the incident.
>
> The daughter, Kristen Suh Collins, was able to offer some information in regards to her father's recent behavior. The son, Dwayne Richard Collins, would not offer any information in regards to his father.

> Ms. Collins is the deceased's daughter.... I asked Ms. Collins how she became aware of the incident and she told me her mother had called her and told her her father had shot himself. She was traveling to Fredericksburg, Virginia at the time of the incident and returned home when her mother called her cellular phone.

In fact, Mary called Ann on her cell phone, not Kristen. The report continues:

> I asked Ms. Collins if she had any idea why her father would want to harm himself and she provided the following information.
>
> Ms. Collins advised there had been several major incidents in recent months concerning her father. According to Collins her mother had recently been diagnosed with cancer and the deceased was not handling that well. She also told me the deceased's brother had passed away sometime in January of this year. In addition, Collins said her mother had recently confronted the deceased about an extra marital affair. Ms. Collins also commented her father often complained about work related problems, but she did not know specifically what those problems were. She did say he was a detective with the Smithsonian Police in Washington D.C.
>
> Ms. Collins told me she had never heard her father threaten suicide in the past, but did say his behavior seemed a little out of the ordinary when she saw him earlier in the day. She could not elaborate on what she meant, saying he just was not himself.

Bobby's brother died in December, not January. Kristen testified that she overheard Mary confront Bobby after Dr. Pinney told her about the alleged affair. At her deposition, Kristen testified:

> My father never said anything, and I wouldn't use the word "affair" because it was more so he—you know, my mom would tell me how he had been talking to an old friend that had knew back when he was younger, a woman friend. So I wouldn't say the word "affair," but she told me that he had been e-mailing or speaking to this woman. And of course that upset her, but—

The police report continues:

> I attempted to speak with Mr. Collins after speaking with his sister. Mr. Collins [Dwayne] offered no opinion as to why his father may have shot himself. The only thing Collins could say is "that was the last thing I thought he would do." He also said his father had owned a handgun for a long time and he knew exactly which one he had used. He made no comments about his father's mental state or recent behavior. He seemed extremely agitated with my questioning and I eventually told him we did not have to speak any longer, but Detective Stahl may contact him in the future.

In fact, Bobby only owned one handgun. At his deposition, Dwayne described how his father looked the last time he saw him, within two weeks of his death:

> He just looked like he was staring off into space like he was kind of out of it. I just took it as tired, but.... It looked more like drugged to me, but he never drank or did anything like that. That's why I said he seemed to be tired....

At their depositions, Dr. Carroll, Dr. Pinney, and Dr. Collin were all asked a question like:

> If you had been advised that prior to approval in 1992 of Paxil, that the clinical trial data showed a statistically increased risk in suicidal behavior, again suicides and attempt, in fact an eight-fold increased risk, would that—would you take that into consideration in whether or not to prescribe Paxil to your patients?

Dr. Carroll answered:

> If—yes, if—like, if there was data to suggest a certain risk, then you incorporate that into your decision, yeah.

Dr. Pinney answered:

> You said if I knew that at the time, would it be relevant to consider? I'd say, generally, yes.

Dr. Collin answered:

> Sure. You need to know that information.

At his deposition, Dr. Pinney said of the abrupt change in Bobby when his condition plummeted in mid-February:

> The *quick* change, it was *surprising* [emphasis added].

The change was so abrupt that it suggested a reaction to an illicit drug to Dr. Pinney:

> Nobody knows....whether he took...any other anxiolytics or alcohol or any of the street drugs or other anti-depressants that people can get on the street these days.

Dr. Pinney was correct that Bobby's abrupt decline is *not* characteristic of the natural course of depression, which is typically more gradual and, instead, suggests a drug reaction. Dr. Pinney was not given the opportunity to consider that Bobby's rapid decline could have been due to Paxil because of GlaxoSmithKline's failure to warn in 2002. Numerous doctors at the Georgetown Medical Center, a highly regarded medical school and teaching hospital, also were not given the opportunity to consider Paxil's possible role in Bobby's bizarre behavior because of GlaxoSmithKline's failure to warn.

Bobby's tragic suicide has had a devastating impact on his family, friends, and coworkers. The doctors at the Georgetown Medical Center who treated Bobby were also traumatized. All of them vividly recalled Bobby and the diagnostic puzzle he presented. Dr. Collin, the psychiatrist who evaluated Bobby in the emergency room the night before his death, telephoned the Collins' home shortly after Bobby committed suicide. Dr. Collin testified:

> [Bobby's case] was very striking, *I will never forget that.* Although, you know, I have seen many patients die on my watch, on the medical floor or any other circumstances, *but this was very traumatic.* I had a long day and night. I didn't sleep and all that, but still had the interest in find—in seeing whether, you know, he might have changed his mind or I could have sent him to another hospital or whatever. And when I called, she—I asked her, hello, Mrs. Collins. How is your husband. Terrible. He just shot himself. And I realize now that this happened—my phone call was

> minutes after he had shot himself.... And of course I told her that this was terrible, that I was very sad for what's happened, and that we would be available to her and her family to help in any way or condition that we could. And I was going to relay this information right away to Dr. Pinney and everybody else. I did that, and....
>
> You always have second thoughts about what you do, whether you do well or you do wrong. And I think, if I would have to do what I did at the time again, I would have done exactly the same thing. Because this is the nature of medicine. My peers were very supportive, because they were all, you know, concerned about this. And what we usually do when this kind of thing happens—death in the general medical care is different than when someone kills himself in your care, under your care, even if you are collaterally involved. So it was difficult for me to—to, how would I say, go back to work the following day, but, you know, you do it. You have to do it.

Naturally, Bobby's death has been particularly hard on his wife, Mary, whose breast cancer has now been diagnosed as incurable. Now virtually housebound and in considerable pain, Mary has been told by her doctors she has less than six months to live. As she testified:

> [Bobby] was everything to me. We had few friends except maybe friends that what you call circle of friends at work that even though you consider them friends you didn't socialize with them. We were very much homebodies and that's what we relied on was each other.
>
> And I sit there at nights and I have nobody to talk to.

Kristen testified:

> I lost my father, didn't get to see me graduate high school or college, awards, talk about careers, and just have more adult conversations that [*sic*] I could have had when I was 14, 15.

Dwayne, who has three children, testified:

> You know, he was a good dad to me and the kids—the grandkids....You had to know him. It wasn't something—he had goals and things he

> wanted to do and grandkids to take care of and, you know, play with and things....Like I said, it wasn't nothing that I expected.

When I interviewed Mary, I was struck by her remarkable fortitude, courage, and sense of humor despite all she has been through. Said Mary:

> I know that in his right mind there's no way Bobby would have done what he did. He never would have left me alone to go through dying of breast cancer. We were devoted to one another.

Differential Diagnosis

When diagnosing conditions in medicine and psychiatry, one considers all the possible diagnoses that might account for the patient's symptoms. In a process called the "differential diagnosis," one rules each of the diagnoses in or out to arrive at a final diagnosis. In Bobby's case, after considering the factual information contained in the documents I reviewed, the information I obtained from the depositions in this case, and my interviews, below are the other diagnoses I considered and ruled out:

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to his depression. Bobby had a history of *symptoms* of depression dating back to the 1970s as part of what would now be called post-traumatic stress disorder. But his former psychiatrist of many years, Dr. Benensohn, states that he did not diagnose Bobby with major depression. Depressive symptoms that are part of post-traumatic stress disorder do not constitute major depression. Moreover, Dr. Benensohn has no recollection of Bobby ever becoming suicidal. Through the years, Bobby had periodic flare-ups of his gastrointestinal symptoms. Unfortunately, when Bobby had a flare-up in January 2002, a new gastroenterologist who thought Bobby was depressed, prescribed Paxil on the recommendation of a psychiatrist who had never seen him. What seemed like just a periodic flare-up of his gastrointestinal symptoms turned into a nightmare of Paxil-induced akathisia, heightened anxiety, worsening insomnia, distorted thinking, paranoia, uncontrollable crying spells, helplessness, and an inability to cope, a cluster of antidepressant side effects that have been linked to antidepressant-induced suicidality. Prior to going on Paxil, Bobby had no history of ever being suicidal. GlaxoSmithKline's own data shows that Paxil increases the risk of suicidal behavior in depressed adults more than six-fold.[19] Bobby took his life less than a month after starting Paxil and a little over two weeks after

increasing the dose. Bobby's own doctor thought his abrupt decline suggested some sort of drug reaction rather than the natural history of depression, which is typically more gradual. Unfortunately, his doctors did not think of Paxil because GlaxoSmithKline had not yet warned of the phenomenon. It is my opinion based on a reasonable degree of medical certainty that Paxil was a substantial factor in causing Bobby 's suicide. If Bobby had not been prescribed Paxil, it is my opinion based on a reasonable degree of medical certainty that he would still be alive today.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to an underlying anxiety disorder. Bobby also had a history of symptoms of anxiety as part of what would now be called post-traumatic stress disorder. But again, Bobby had no prior history of becoming suicidal. In 2002, prior to starting Paxil, Bobby was diagnosed with depression. He was not diagnosed with an anxiety disorder. Even after he started Paxil, when Bobby was hospitalized in January on the gastroenterology service, the consultation liaison psychiatrists diagnosed him with depression, not an anxiety disorder. Bobby only developed prominent symptoms of anxiety as a side effect of Paxil. It is my opinion based on a reasonable degree of medical certainty that Bobby's escalating symptoms of anxiety were due to Paxil, not to an underlying anxiety disorder.

In my opinion, based on a reasonable degree of medical certainty, Bobby's suicide was not due to post-traumatic stress disorder. Bobby had a history of post-traumatic stress disorder, PTSD. However, he had not been in treatment for the PTSD in over a decade. In 2002, Bobby was not diagnosed with a recurrence of the PTSD. Based on my review of his medical records, the deposition testimony, and my interviews, I did not see any evidence that Bobby had a return of his PTSD at the time of his death in 2002. It is my opinion based on a reasonable degree of medical certainty that Bobby's past history of PTSD was not responsible for his death.

In my opinion, based on a reasonable degree of medical certainty, Bobby's suicide was not due to Mary's cancer. As any caring husband would be, Bobby was upset when Mary was diagnosed with breast cancer in the fall of 2001. But, Bobby was coping well with Mary's situation and actively involved in supporting and helping her. Based on my review of his medical records, the deposition testimony, and my interviews, I did not find any evidence that Mary's breast cancer made Bobby suicidal. In fact, the last thing one expects a supportive husband such as Bobby to do would be to leave his wife to deal with the cancer on her own. It is my

opinion based on a reasonable degree of medical certainty that Bobby's suicide was not due to Mary's breast cancer.

In my opinion, based on a reasonable degree of medical certainty, Bobby's suicide was not due to job stress. Prior to going on Paxil, Bobby was stably employed at the Smithsonian for eighteen years. Bobby liked his job and was very successful at it. He received outstanding evaluations and had good relationships with his bosses. Although he had a cooler relationship with his last boss, his boss testified that it did not interfere with their working together effectively. Only after Bobby went on Paxil did he become paranoid that he was being harassed at work as part of his distorted thinking on the drug. Based on my review of his medical records, the deposition testimony, and my interviews, I did not see any evidence that work stress had ever made Bobby suicidal.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to an alleged extra-marital affair. Mary confirmed that Bobby had been engaged to Judy Smith before she and Bobby met. She knew that Bobby was in periodic contact with Judy years before Bobby's death and that he had increased telephone contact with her some time around 1999. But Mary does not believe that Bobby ever had an affair. When Bobby died, Mary called Judy to tell her. Judy was shocked and said, "Billy must be upset." Billy was Bobby's twin brother who had died two months earlier. Since Judy had not known of Billy's death, she and Bobby had not been in recent contact. Based on my review of his medical records, the deposition testimony, and my interviews, I did not see any evidence that Bobby's lifelong friendship and intermittent contact with Judy made him suicidal. It is my opinion based on a reasonable degree of medical certainty that the friendship or allegations of an affair were not responsible for Bobby's suicide.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to an underlying psychotic disorder. Bobby did not have a history of a psychotic disorder such as schizophrenia or bipolar disorder. Only after starting Paxil did Bobby begin to exhibit symptoms of paranoia and distorted thinking that the doctors thought might be psychotic. Based on my review of his medical records, the deposition testimony, and my interview with Mary, I did not see any indication that Bobby had an underlying psychotic disorder that could account for his death.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to alcoholism or substance abuse. Bobby rarely drank alcohol and had no

known history of using illicit drugs. Based on my review of his medical records, the other discovery documents, and my interviews, I did not see any indication that Bobby ever had trouble with alcoholism or substance abuse. Based on a reasonable degree of medical certainty, it is my opinion that drugs other than Paxil did not play a role in Bobby 's suicide.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to a character disorder. Bobby did not have a character disorder, such as narcissistic personality disorder or borderline personality disorder. He had never been diagnosed with a character disorder. Based on my review of his medical records, the other discovery documents, and interviews, I did not see any indication that Bobby had a character disorder.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to another concurrent psychiatric condition. Bobby had no other psychiatric diagnoses. He had never been diagnosed with any psychiatric disorder other than those discussed above. Dr. Benensohn did discuss some old diagnostic terms used for Bobby in the 1970s and the contemporary equivalents, as described above. Based on my review of his medical records, the other discovery documents, and interviews, I did not see any indication that Bobby had another psychiatric condition.

In my opinion, based on a reasonable degree of medical certainty, Bobby 's suicide was not due to a concurrent medical condition. While in Vietnam, he contracted malaria, but the symptoms of this illness were gone by the time he returned to America. In the 1970s, Bobby developed gastrointestinal symptoms that were ultimately diagnosed as ulcerative colitis. He also had a history of pepticular disease. Although Bobby developed gastrointestinal symptoms in 2002, an endoscopy and colonoscopy showed no evidence of active gastrointestinal disease. During his long history of off-and-on gastrointestinal symptoms, they never made Bobby suicidal. Moreover, Bobby had no history of a medical condition (such as a brain tumor), which could account for the sudden changes in his behavior on Paxil. It is my opinion to a reasonable degree of medical certainty that Bobby's suicide was not due to his medical condition.

In my opinion, based on a reasonable degree of medical certainty, Bobby's suicide was not due to another prescription medication. Although Bobby had been on Ambien, he did not take it the night before his death. Bobby was prescribed Doxepin instead for sleep the last night of his life. Doxepine is an older, sedating, tricyclic antidepressant. The new FDA warnings that antidepressants may make some

patients suicidal are a class warning covering all antidepressants currently on the market, including Doxepin. But Bobby had become suicidal shortly after starting Paxil, weeks before starting the Doxepin. Over the course of weeks, Bobby had developed progressively worsening akathisia, anxiety, insomnia, uncontrollable crying spells, distorted thinking, paranoia, helplessness, and inability to cope on Paxil. Bobby only took one dose of Doxepin, the night before he died. It is my opinion to a reasonable degree of medical certainty that Paxil was a substantial factory in Bobby's death, regardless of whatever additional effect the Doxepin might have had. Finally, Bobby was also on two medications for his gastrointestinal symptoms: sulfasalazine and Protonix. Neither of these drugs has warnings that it may make patients suicidal. Based on a reasonable degree of medical probability, it is my opinion that Bobby's suicide was not caused by another prescription drug.

Protective Factors Versus Risk Factors for Suicide

Protective factors that reduce the likelihood of suicide have been identified.[20] And risk factors that increase the likelihood of suicide have been identified.[21] As seen in Table 1, Bobby had six out of seven factors protecting him from suicide. And, as seen in Table 2, he had only three of seventeen risk factors for suicide.

Table 1: Bobby 's Protective Factors for Suicide

1.	Effective clinical care for mental, physical and substance use disorders	√
2.	Easy access to a variety of clinical interventions and support for helpseeking	√
3.	Restricted access to highly lethal means of suicide	
4.	Strong connections to family and community support	√
5.	Support through ongoing medical and mental health care relationships	√
6.	Skills in problem solving, conflict resolution and nonviolent handling of disputes	√
7.	Cultural and religious beliefs that discouraged suicide and support self preservation	√

Table 2: Bobby 's Risk Factors for Suicide

1.	Mental disorders, particularly mood disorders, schizophrenia, anxiety disorders and certain personality disorders	√
2.	Alcohol and other substance use disorders	

3.	Hopelessness	
4.	Impulsive and/or aggressive tendencies	
5.	History of trauma or abuse	√
6.	Some major physical illnesses	
7.	Previous suicide attempt	
8.	Family history of suicide	
9.	Job or financial loss	
10.	Relational or social loss	
11.	Easy access to lethal means	√
12.	Local clusters of suicide that have a contagious influence	
13.	Lack of social support and sense of isolation	
14.	Stigma associated with help-seeking behavior	
15.	Barriers to accessing health care, especially mental health and substance abuse treatment	
16.	Certain cultural and religious beliefs (for instance, the belief that suicide is a noble resolution of a personal dilemma)	
17.	Exposure to, including through the media, and influence of others who have died by suicide.	

Conclusions

Prior to being prescribed Paxil in 2002, Bobby Collins had a classic American life. Born into a poor but happy family, in rural West Virginia, his parents moved to Washington, D.C. for greater opportunity for themselves and their children. When Bobby could not afford to go to college, he served his country in Vietnam. After Vietnam, he fulfilled his lifelong dream to become a Washington, D.C. police officer. Unfortunately, Bobby's police work was cut short by a series of traumatic events that led to debilitating ulcerative colitis and post-traumatic stress disorder. With the help and support of his wife, Mary, Bobby overcame the adversity and re-built his life. He worked hard in weekly psychotherapy and did so well that he was eventually able to return to detective work despite periodic flares of his ulcerative colitis. Bobby and Mary had two children and a loving family. They did volunteer work in their church. Through hard work they were eventually able to live a middle class lifestyle that included their "dream house." When Mary was diagnosed with breast cancer, Bobby steadfastly supported her through surgery and chemotherapy. Bobby was a remarkably well-rounded man, a Vietnam veteran and former police officer who was close to his mother, changed diapers and helped out in the kitchen, happily accepted his son not

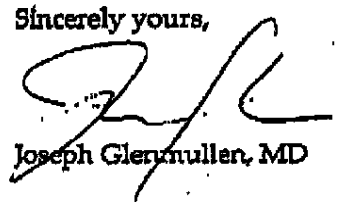
playing football, rarely drank, never used drugs, and thrived in years of weekly psychotherapy.

Unfortunately, when Bobby a had flare-up of his ulcerative colitis in early 2002, his new gastroenterologist prescribed Paxil on the recommendation of a psychiatrist who had never seen Bobby. On Paxil, Bobby lived less than a month, spiraling downward in a classic case of Paxil-induced clinical worsening including akathisia, heightened anxiety, worsening insomnia, irritability, paranoia, distorted thinking, helplessness, inability to cope, and ultimately irresistible suicidal urges. Numerous doctors at the Georgetown University Medical Center could not solve the diagnostic puzzle presented by Bobby's sudden clinical worsening and decompensation. His treating psychiatrist suspected a drug reaction because the natural history of depression is typically more gradual. But, the doctors did not consider Paxil as a possible cause because of GlaxoSmithKline's failure to warn.

It is my opinion based on a reasonable degree of medical certainty that Paxil played a substantial role in Bobby's suicide. It is my opinion based on a reasonable degree of medical certainty that but for Paxil, Bobby would still be alive today.

This completes my opinion at this time. Of course, my opinion is subject to revision based on additional discovery. Please keep me informed of the progress in this case.

Sincerely yours,



Joseph Glenmullen, MD

Encls: CV of Joseph Glenmullen, M.D.
Appendix A
Appendix B

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[1] 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. 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

[2] J. Glenmullen, *Prozac Backlash* (New York: Simon & Schuster, 2000); J. Glenmullen, *The Antidepressant Solution* (New York: Free Press Division of Simon & Schuster, 2005).

[3] J. Maslin, "Exploring a Dark Side of Depression Remedies," *The New York Times*, June 29, 2000. Acocella, J. "The Empty Couch: What is lost when psychiatry turns to drugs?" *The New Yorker*, May 8, 2000, pg. 112.

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

[5] Ibid.

[6] Ibid.

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

[8] 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..

[9] P. Breggin, "Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): a review and analysis," *International Journal of Risk and Safety in Medicine* 2003/2004;16:31-49.

[10] M.Y. Agargun, H. Kara, M. Solmaz, "Sleep disturbances and suicidal behavior in patients with major depression," *Journal of Clinical Psychiatry* 1997;58(6):249-51; P. Landry, "Withdrawal hypomania associated with paroxetine [Paxil]," *Journal of Clinical Psychopharmacology* 1997;17(1):60-1; J. Johnson, M.M Weissman, G.L Klerman, "Panic disorder, comorbidity, and suicide attempts," *Archives of General Psychiatry* 1990;47:805-8; M.M. Weissman, G.L Klerman, J.S. Markowitz, R. Ouellette, "Suicidal ideation and suicide attempts in panic disorder and attacks," *New England Journal of Medicine* 1989;321:1209-14; M. H. Teicher, C. Glod, and J. O. Cole, "Emergence of intense suicidal preoccupation during fluoxetine [Prozac] treatment," *American Journal of Psychiatry* 1990;147:207-10; T. Van Putten, "The many faces of akathisia," *Comprehensive Psychiatry* 1975;16:43-7; W.A. Keckich, "Neuroleptics: Violence as a manifestation of akathisia," *JAMA* 1978;240:2185; E.D. Shaw, J.J. Mann, P.J. Weiden, L.M. Sinsheimer, R.D. Brunn, "A case of suicidal and homicidal ideation and akathisia in a double-blind neuroleptic crossover study," *Journal of Clinical Psychopharmacology* 1986;6:196-1971; J.L. Schulte, "Homicide and suicide associated with akathisia and haloperidol," *American Journal of Forensic Psychiatry*, 1985;6:3-7.

[11] T. Van Putten, "The many faces of akathisia," *Comprehensive Psychiatry* 1975; 16:43-7; T. Van Putten, S.R. Marder, "Behavioral toxicity of antipsychotic drugs," *Journal of Clinical Psychiatry* 1987; 48(suppl 9): 13-19; T. Van Putten, "Why do schizophrenic patients refuse to take their drugs?" *Archives of General Psychiatry* 1974; 31:67-72; T. Van Putten, L.R. Mintalipassi, M.D. Malkin, "Phenothiazine-induced decompensation," *Archives of General Psychiatry* 1974; 30:102-5; T.R.E. Barnes, "A rating scale for drug-induced akathisia," *British Journal of Psychiatry* 1989; 154: 672-676. Akathisia's association with suicide and violence is well-known from an earlier class of drugs called antipsychotics.

[12] Ibid.

[13] T. Van Putten, "The many faces of akathisia," *Comprehensive Psychiatry* 1975;16:43-47.

[14] L.B. Kalinowsky, "Appraisal of the 'tranquilizers' [now called "major tranquilizers"] and their influence on other somatic treatments in psychiatry," *American Journal of Psychiatry* 1958;115:294-300.

[15] http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm.

[16] M. H. Teicher, C. Glod, and J. O. Cole, "Emergence of intense suicidal preoccupation during fluoxetine [Prozac] treatment," *American Journal of Psychiatry* 1990; 147:207-10.

[17] Ibid.

[18] J. Glenmullen, *The Antidepressant Solution* (New York: Free Press Division of Simon & Schuster, 2005).

[19] GlaxoSmithKline May 2006 "Dear Healthcare Provider" letter and the associated Briefing Document and Appendices.

[20] http://www.sprc.org/library/srisk.pdf

[21] Ibid.