

SPECIAL REPORT, PART III

Drug Company Suppressed Data on Paroxetine-Induced Stimulation: Implications for Violence and Suicide

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This is the third special report in a series that has published observations and excerpts from my 1999 product liability report in the California case of *Lacuzong v. GlaxoSmithKline*, alleging that Paxil (paroxetine) caused a double murder and suicide.

Shortly after the publication of my first special report in *EHPP* (Breggin, 2006a), the Food and Drug Administration (FDA) and the drug company GlaxoSmithKline (GSK) confirmed my basic conclusion that Paxil causes increased suicidality in adults (Kraus, May 2006). The GSK meta-analysis of all placebo-controlled clinical trials for Paxil demonstrated that adults of all ages with major depressive disorder suffered a 6.4 times increase in the rate of suicidal ideation and behavior compared to the controls receiving the sugar pill (0.32% vs. 0.05%). In addition to increasing suicidality in depressed adults of all ages, Paxil also increased suicidality in young adults (ages 18–24) suffering from anxiety disorders. My product liability report demonstrated that the drug company had been hiding and manipulating the relevant data for many years prior to the recent publication of data showing that Paxil causes suicidality in adults.

The product liability suit was brought by the wife of a man who drowned himself and their two children two days after beginning to take a daily 10-mg dose of the selective serotonin reuptake inhibitor (SSRI) antidepressant Paxil. Although GSK denied all allegations, the suit was resolved to the satisfaction of the plaintiffs. My original product liability report was sealed as a part of the settlement, but subsequent events in another lawsuit against GSK in which I was also the plaintiff's expert enabled me to make it public (discussed in Breggin, 2006a). That case has recently been settled as well.

My product liability report was based upon a 3-day trip to the offices of GSK in order to examine the company's complete library of documents relating to the development and marketing of Paxil. My initial report in *EHPP* focused on GSK's manipulation of data concerning Paxil-induced suicidality in adults (Breggin, 2006a). The second report in *EHPP* focused on how GSK hid data on drug-induced akathisia (Breggin, 2006b). Akathisia (psychomotor agitation) is very emotionally distressing and is known to cause suicide, violence, and an overall decline in the individual's mental condition (*DSM-IV-TR*, pp. 800–802). The current report focuses on the role of Paxil-induced central nervous system stimulation in causing violence and suicide and the manner in which GSK ob-

scured or disguised the antidepressant's stimulating effects. Akathisia can be viewed as a form of central nervous system stimulation, and therefore this current report dovetails with the second report.

In January 2005, the FDA compelled the manufacturers of antidepressants to include a great deal of new information about psychiatric adverse drug effects in their official labels. Closely paralleling observations I had been developing over more than a decade concerning the stimulating effects of these drugs (Breggin, 1991, 1997, 2001, 2003), the agency required the following observations to be placed on all antidepressant labels, including Paxil (Food and Drug Administration, January 26, 2005, p. 2):

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.

Note that the label change applies to both adults and children and to people given the medication for psychiatric or nonpsychiatric purposes. However, the drug company continued to maintain that there was no proof of Paxil causing suicide in adults until the recent publication of the results from the placebo-controlled clinical trials (Kraus, 2006). Also, the paragraph specifically mentions reports of hostility and aggressiveness, as well as akathisia, the drug-induced neurological disorder that can cause violent, suicidal, and psychotic behavior. Additional stimulant-related warnings were also added to the labels.

Despite the recent FDA-mandated label changes, there remains insufficient recognition at the agency and in the psychiatric profession concerning the extreme hazards posed by these stimulating drug effects. This failure is due in part to the successful campaigns waged by GSK and other drug companies to hide the stimulant effects of their products (Breggin, 1997). I have recently discussed the implications of the extensive label changes for the clinical practice of medicine and psychiatry, including the necessity of recognizing the stimulant syndrome in its earliest manifestations in order to prevent antidepressant-induced violence against self and others (Breggin, 2006c).

One of the following excerpts (section VII) was also published in the second report in *EHHS* on akathisia. It is included in this report as well because it describes the role of stimulation in causing violence and suicide. My complete product liability report in the case of *Lacuzong v. GlaxoSmithKline* can be found on www.breggin.com.

EXCERPTS FROM REPORT AND AFFIDAVIT OF PETER R. BREGGIN, MD, IN THE CASE OF *LACUZONG V. GLAXOSMITHKLINE*, PART A: ANALYSIS OF DATA FROM DISCOVERY

I. FDA Criticism Relating to SmithKline Beecham (SKB)¹ in Regard to Paxil Promotional Claims

The material in this section illustrates the tendency by SKB to make Paxil look safer than it is, and safer than other antidepressant medications. Material like this increased the likelihood that Mr. Lacuzong would be prescribed Paxil. Furthermore, SKB minimized the stimulating effects of Paxil, including agitation, anxiety, irritability, and insomnia, as well as akathisia. Indeed, SKB tried to promote Paxil as especially effective for anxiety associated with depression.

(1) **1.6.93 Letter from FDA's Janet L. Rose to SKB.** In a 1.6.93 letter from Janet L. Rose, Division of Marketing, to Thomas Donnelly, (00000265),² the FDA criticized many parts of their "Launching Sales Aid" (475-P2-158-01), including the following. The FDA challenged the basis for SKB's claim "The most extensively studied antidepressant to be introduced" (p. 3 of SKB document). The FDA required the phrase "unsurpassed control" (p. 5) to be "deleted" because it is "not known how Paxil will ultimately compare with other SSRIs." The FDA challenged the term "fewer concerns" in emphasizing the safety of Paxil (p.5). The FDA observed that this general statement needed to emphasize that there were fewer concerns in regard to tricyclic antidepressants but not in regard to other SSRIs.

In addition, the FDA noted that the claim "improves sleep quality" (p. 9) is incorrect because Paxil causes insomnia in 13% of patients.

The FDA was also concerned about a potentially dangerous and unfounded claim that "In the elderly, Paxil significantly improves symptoms of depression" (p. 10). The FDA declared that "general conclusions about the efficacy of Paxil in the elderly" must be "disallowed" because they were based on studies with no placebo control. The FDA concluded (p. 2 of their letter), "While a purely factual description of relevant studies and results of those studies may be acceptable, generalizations from study data must avoid pseudoscientific claims which would imply particular efficacy in arbitrarily identified patient subgroups and must be based on scientifically adequate evidence. This claim should be deleted."

The FDA required the deletion of many other misleading statements about the use of Paxil for the treatment of the elderly.

SKB left out Adverse Drug Reactions with a rate of less than 15% (p. 14), for example omitting ejaculatory disturbances that occurred at a rate of 12.9%. SKB also tried to make claims for Paxil in regard to efficacy in severe depression (p. 15). The FDA required that "All references to Paxil efficacy in severe depression should be deleted" (p. 4 of FDA letter).

(2) **8.31.94 Letter from FDA's Sherry Danese to SKB.** In an 8.31.94 11-page letter another lengthy critique of SKB drafts of promotional efforts was sent from Sherry Danese, Regulatory Review Officer, Division of Drug Marketing to Michael J. Brennen, PhD of SKB (00002339). The letter lists 7 materials, such as "A Unique Profile of Benefits Brochure" (Px 1004; also Px 1014, BRS-Px:L4, Px 1634, Px 1614, Px 1554, and Px 1604). Apparently, these materials were already in use. The FDA declared, "These materials misrepresent the safety and efficacy of Paxil; contain claims and representations of superiority of Paxil over Prozac (fluoxetine); and fail to provide fair balance. Therefore, these materials are in violation of the Federal Food, Drug and Cosmetics Act. We will address each violation individually." The letter concluded, "SKB should immediately discontinue use of these and all other similar violative [sic] materials on receipt of this letter."

Some of the FDA's criticisms echoed much earlier criticisms that the drug company had seemingly failed to comply with, including the use of false claims such as Paxil is "Proven effective and safe in elderly patients."

Another outrageous claim stated, "Significant improvement seen in over 86% of patients treated with Paxil" (Px 1004, p. 2; Px 1634, p. 5). The FDA pointed out that the data came from "open label" studies and was used improperly.

(3) **1.23.97 Letter from FDA's Paul Leber to SKB.** In earlier letters, SKB had been criticized by the FDA for making unfounded "pseudoscientific" claims about the safety

and efficacy of Paxil in the elderly. Now the FDA criticized the company for doing the same thing in regard to children. SKB was unconscionably attempting to push Paxil at both ends of the spectrum of age vulnerability. Both children and the elderly are especially susceptible to adverse drug reactions. These fraudulent efforts not only illustrate a pattern of deception, they directly encourage the false notion that Paxil is especially safe for everyone, including an adult male like Mr. Lacuzong, because they are supposedly safe for children and the elderly.

Paul Leber [of the FDA] acknowledged a 12.17.96 letter from SKB requesting that the FDA approve "a pediatric depression indication" for the drug. Leber responded with uncharacteristic directness, "In fact, the preponderance of negative studies of antidepressants in adolescents and childhood depression raises a significant concern about such extrapolations."

Nevertheless, more than two years later, SKB was still trying to convince the FDA to endorse the use of Paxil for children, as indicated by a 4.28.99 letter from the FDA's Ralph Temple to Thomas Kline.

II. FDA Criticism of SKB Relevant to the Stimulating and Agitating Effects of Paxil

(1) *9.6.94 Letter from FDA's Sherry Danese to SKB.* In a 9.6.94 letter from Sherry Danese to Michael Brennen at SKB, the company's promotional materials are again heavily criticized. This letter is particularly important because it demonstrates a specific attempt on the part of SKB to mislead doctors concerning the stimulant effects of Paxil. This is directly relevant to the issue of murder and suicide, both of which can be related to the stimulating, agitating effects of antidepressants. From this material alone it can be concluded that SKB attempted to hide the dangers of Paxil in regard to stimulation and its adverse consequences of murder and suicide. In the letter, according to the FDA's criticism, SKB made the following statement:

Effective in treating anxiety and agitation associated with depression without inducing symptoms of arousal.

The FDA observed that the above handwritten letter and a two page typed "Paxil Overview" sheet "appear to have been distributed by a SmithKline Beecham (SKB) sales representative" (p. 1). The FDA was strongly critical:

This statement suggests that Paxil is not associated with side effects that might aggravate anxiety or agitation. To the contrary, Paxil is associated with an 8.3% incidence of tremor, a 5.2% incidence of nervousness, a 13.3% incidence of insomnia, a 5.0% incidence of anxiety, and a 2.1% incidence of agitation. Therefore this statement is false and/or misleading. (p. 3)

Importantly, the FDA analysis also establishes the rudiments of a stimulant profile for Paxil, including the following symptoms:

Tremor
Nervousness
Insomnia

Anxiety
Agitation

It also establishes that Paxil can cause or worsen “anxiety and agitation associated with depression.”

The FDA also criticizes the claim that Paxil is “less likely to cause agitation than currently available SSRIs.” The FDA states, “This claim is not supported by substantial evidence, and is false and/or misleading.”

The FDA also criticizes the unsupported claim that “Paxil costs 15% less.” According to the FDA (p. 2 of letter), “In the absence of supporting data, this claim is false and/or misleading.” Once again, these efforts to over-promote Paxil in general influenced its increasingly widespread use, leading to the increased likelihood of its prescription to Mr. Lacuzong.

(2) **9.19.94 Letter from FDA’s Paul Leber to SKB.** In a letter with two dates stamped on it (9/19/94; 9/13/94), Paul Leber writes to Michael J. Brennen to suggest post-marketing changes in the label for Paxil. The “request” is unusually strong, in fact requiring that the changes be added in the “next printing (but not later than 3 months from the date of this letter).” The changes pertain to four adverse drug events, two of which relate directly to stimulation and agitation effects. One relevant new addition is based on four reports of extrapyramidal reactions (EPS), including two for akathisia. The issue of akathisia will be addressed in more detail because akathisia is associated with violence and suicide [see below as well as my initial special report in *EHPP* (Breggin, 2006a)]. The other relevant addition is based on two reports of serotonin syndrome, an extreme [potentially fatal] reaction involving over-stimulation of the serotonin neurotransmitter system that can include agitation and excitement.

(3) **1.11.99 Letter from FDA’s Janet Rose to SKB.** Janet Rose wrote a critical letter to Donnelly concerning continued drug company efforts to sneak “depression associated with anxiety” into advertising materials as an indication for Paxil.

VII. The Role of “Central Nervous System Stimulation,” “Irritability” and “Excitement” in Suicide and Violence

1. Stimulation and Irritability in U.S. Trials. “Irritability” is used in psychiatry to describe the emotional hyper-reactivity of individuals that can lead to inappropriate or immoderate hostility and violence. It is closely related to excitability. (See, for example, *Stedman’s Medical Dictionary*, 2000, or the *PDR Medical Dictionary*, 1995.)

Irritability is a much stronger term in psychiatry than in common use. In the *Diagnostic and Statistical Manual of Mental Disorders, IV* (1994), a diagnosis of Substance-Induced Mood Disorder can be made on the basis of any of “irritable mood” by itself (p. 374, “Diagnostic criteria for Substance-induced Mood Disorder”).

Appendix V.8, “Adverse Experiences Which Occurred During Active Treatment: U.S. Phase II-III Trials” (SB 0000669, p. 198, stamped 199), lists CNS Stimulation as a preferred term. In the category of CNS Stimulation, investigator terms were usually related to abnormal behavioral reactions, such as “irritable,” “irritability,” and “increased irritability.”

There were 19 reports relating to irritability. There were 7 reports related to “excitement” and “intense rushes of excitement.” Other reports were related to feeling “wired” and “wound up.”

Of these approximately 41 patients with 50 reports of Central Nervous System stimulation, many occurred early in treatment. Eight occurred within 1–2 days of the start of treatment. Five adverse events occurred at the 10 mg dose, none of which were in the 1–2 day period.

2. *Anxiety and Suicide from Non-U.S. Phase II & III Studies.* A hand count of “agitation” as the preferred term (NDA 420 November 1989, p. 128 ff)³ disclosed 43 reports, including one completed suicide (2406 149) on the 32nd day of Paxil exposure.

A hand count of “anxiety” as the preferred term disclosed 63 reports with three attempted suicides on the same day, three days after the report, and 19 days after the report.

Once again there is evidence that suicide is related to stimulation (akathisia, agitation, anxiety) from Paxil.

VIII. Placebo Comparison and Dose Dependency

A drug’s capacity to cause ADRs [Adverse Drug Reactions] can be studied through a comparison between ADRs reported on placebo and ADRs reported on varying doses of the drug. Data concerning this can be found as “Attachment to FDA Approvable Letter NDA 20–031/S-023.” It is entitled “Dose Dependency of Adverse Events” (V. I. PAX-M-99 in the March section [no page number]).

The data in Table 1 are taken from the section on “Nervous System.”

Notice that placebo produced no increase in anxiety or nervousness, while the 10 mg Paxil showed a rate of 2% that increased to 5.8% and then 5.9% with increasing doses. *In regard to the Lacuzong case, placebo produced no increased nervousness, while 10 mg Paxil produced the maximum amount.*

(It is unclear why nervousness declined with the two largest doses.)⁴

IX. The Serotonin/Anxiety Spectrum of Adverse Effects

In the extreme, SSRI-treated patients can develop a Serotonin Syndrome. The syndrome is thought to be caused by over-stimulation of the serotonin neurotransmitter system.

The drug company performed an analysis of “Serotonin Group” symptoms from the worldwide data: Appendix XI.9, “Comparisons for Adverse Experiences Considered to be Related to the Serotonin group—Intent to Treat Population” (NDA 20031—V 449, October 26, 1989, pp. 223–227; SB 0000769). The serotonin group included 15 items (SB 000071): fasciculations, tremor, myoclonus, ataxia, agitation, nausea/vomiting, nausea, diarrhea, nystagmus, reflexes increased, Babinski sign positive, heel/toe gait abnormality, CNS stimulation, and sweating.

TABLE 1. Dose Dependence of Adverse Events

	Placebo NA	10 mg Paxil N = 102	20 mg Paxil N = 104	30 mg Paxil N = 102	40 mg Paxil N = 102
Anxiety	0%	2	5.8	5.9	5.9
Nervousness	0%	5.9	5.8	4.0	2.9
Somnolence	7.8 %	12.7	18.23	20.8	21.6

Of 2,963 patients, they found that 1343 (45%) developed some of these symptoms. Of 554 placebo patients, 131 (24%) developed them. The data confirms the dangerously stimulating impact of Paxil.

The company also did an analysis of “Comparisons of Adverse Experiences Considered to be Related to Anxiety Group—Intent-to-Treat Population” (Appendix XI.7). Worldwide, anxiety symptoms were found in 334 of 2,963 Paxil patients (11%) compared to 35 of 554 placebo patients (6%). However, the anxiety group was limited to patients with agitation, nervousness, and anxiety. When other anxiety symptoms are included, such as tremor (11%), insomnia (14%), CNS stimulation (4%) and mania (1%), the group becomes considerably larger. By contrast figures from the same source for the anxiety group were anxiety (5%), agitation (4%) and nervousness (4%) (NDA 20031 Vol. 1, November 1989, p. 153).

X. Adding Hostility to the Label

In a 4.29.96 17-page letter from FDA’s Paul David to SKB, Michael Brennen refers to “Final Labeling” based on a 4.5.96 submission. It adds “hostility” and “extrapyramidal syndrome” (EPS) to the label. The first addition of “hostility” to a draft of the label by the FDA was 3.15.96.

The FDA forced the company to add these closely related ADRs of EPS and hostility. Akathisia is an EPS.

XV. Adverse Reactions from the Original NDA Application (Volume 1, pp. 151–154).

The data in this discussion is derived from the placebo-controlled clinical trials. The table for Nervous System indicates a 1% rate for both mania and depression on Paxil, but 0% for both on placebo. Remember that 1% is considered frequent by the FDA. Yet the final label for Paxil calls manic reactions “infrequent.”

The capacity of a drug to cause manic reactions in 1% of placebo-controlled clinical trials against 0% for placebo is an extremely important piece of epidemiological scientific data.

The list of “frequent” ADRs under Nervous System (NDA 1, p. 157) is much more extensive than in final label, including, among other things, “depression” and “manic reaction.” This is consistent with the other data in this NDA. The following is the list of frequent CNS ADRs:

Abnormal dreams, agitation, anxiety, CNS stimulation, concentration impaired, confusion, depression, dizziness, drugged feeling, emotional lability, insomnia, libido decreased, myoclonus, nervousness, paresthesia, somnolence, tremor, vertigo, amnesia, depersonalization, lack of emotion, manic reaction.

There are only six in the final version of the label: amnesia, CNS stimulation, concentration impaired, depression, emotional lability, and vertigo.

Some appear scattered in several charts: Anxiety, tremor, insomnia, somnolence, paresthesia, drugged feeling, dizziness, confusion, concentration impaired, depersonalization, myoclonus, abnormal dreams, agitation. The scattering of these items is very misleading.

The scattered ADRs cannot be comprehended as patterns, for example, of CNS dysfunction by the reader and cannot be viewed all at once for their totality. Furthermore, the relatively short list of six frequent ADRs in the more accessible paragraph is very misleading.

More misleading, for the final label some ADRs were dropped into the infrequent category: manic reaction, abnormal dreams, depersonalization, and lack of emotion.

XVI. Summaries of Worldwide Adverse Experiences: Paroxetine v. Placebo

This material (see Table 2) is taken from Appendix V.2, "Comparisons for Adverse Experiences Listed by Preferred Term within the Body System, Intent-to-Treat Population" (SB 0000654 and following; p. 14, stamped p. 237). US data is in brackets and is taken from V.9.. Comparisons for Adverse Experiences Listed by Preferred Term with Body Systems: Intent-to-Treat Population (SB 0000760, p. 12, stamped p. 13). US data is entered only if it differs from worldwide. For the US, Paroxetine $N = 1562$ and Placebo $N = 497$.

Notice the overall stimulation profile that is obscured in the published label. Asterisks (*) are used to designate commonly accepted stimulant effects. However, all of the adverse effects in Table 2 can be caused by stimulants, including somnolence and depression. Somnolence, of course, is a less frequent and paradoxical reaction to stimulants.

In regard to mania, note that the worldwide data indicated it was frequent, while the US data did not. This may be SKB's justification for saying that mania was not frequent. When it was to their advantage in regard to suicide attempt rates, the company used worldwide data. When it is to their advantage to use worldwide data, as in regard to mania statistics, they do so.

(The zero percentage for mania does not mean that there were no manic reactions in US Paxil patients, but that they did not rise to a rate of 1%.)

TABLE 2. Selected "Nervous System" Adverse Experiences Worldwide From Appendix V.2

Preferred Term	% Paroxetine $N = 2963$	% Placebo $N = 554$
Abnormal dreams	2	1 [US 0]
Agitation*	4 [US 5]	2
Anxiety*	5 [US 6]	3 [US 2]
CNS stimulation*	4 [US 3]	3
Concentration impaired	3	0
Depersonalization	1	0
Depression	1	0
Emotional lability*	1	0
Insomnia*	14 [US 16]	7
Lack of emotion*	1 [US 0]	0
Manic reaction*	1 [US 0]	0
Nervousness*	4 [US 6]	2
Psychosis*	3	0
Somnolence	20 [US 27]	9
Tremor*	11 [US 9]	2

NOTES

1. Now GlaxoSmithKline (GSK).
2. The various parenthetical references are to citations in the New Drug Application (NDA) or the FDA correspondence that was included in the NDA, the basic document created by a drug company when applying for the right to market its experimental drug. The references are to sections and pages in the NDA. The NDA includes all the company's premarketing research.
3. NDA stands for New Drug Application. See endnote 1.
4. In retrospect, I believe it may be due to the increasing degree of somnolence (sedation) produced with higher doses.

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