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SUPERIOR COURT OF THE STATE OF CALIFORNIA
COUNTY OF SANTA CLARA

SHIRLEY LACUZONG, individually, and as successor-in-interest of Reynaldo Lacuzong, Rechelle Lacuzong and Reniel Lacuzong,

Plaintiffs

vs

JESSICA DAVIDSON, MILPITAS ACUTECARE & GENERAL MEDICINE, SMITHKLINE BEECHAM PHARMACEUTICALS, LONGS DRUG STORES CALIFORNIA, INC.,
and DOES 1 through 20,

Defendants

Case No.: CV 773623

DECLARATION OF PETER R. BREGGIN, MD.

Judicial Arbitration Hearing:
Date: August 14, 2001
Time: 10.00 a.m.
Arbitrator: Timothy J. Schmal

Trial Date: None

Complaint filed: April 28, 1998

IT IS HEREBY DECLARED UNER PENALTY OF PERJURY

1. My name is Peter R. Breggin, M.D. On October 3, 1999, I was retained as a consultant and expert witness by the plaintiff's attorney in this action. In this declaration I opine on the professional conduct and the standard of care given by defendant SmithKline Beecham Corporation, and on the inadequacy of safety warnings given to the physician on the drug Paxil by that defendant. I further opine on issue of causation, specifically that Paxil induced Reynaldo Lacuzong to commit the destructive acts in question.

2. I am licensed to practice medicine in Maryland, Virginia, Washington DC, and New York. I have been in the private practice of psychiatry since 1968 and I am identified in the State of Maryland as a specialist in psychiatry. I am the founder and International Director of the International Center for the Study of Psychiatry and Psychology (ICSPP), in Bethesda, Maryland, a professional organization with more than 1,500 members. I am the Founder and Co-Editor of the peer review journal, Ethical Human Sciences and Services and hold the position of editor on several other peer review journals. I have written more than two dozen peer review scientific articles and more than 15 professional books. My additional qualifications to testify as an expert are attached. I incorporate to this declaration, and declare to be truthful the attached appendices: (a) Summary and Annotated Resume of Peter R. Breggin, M.D., (b) Bibliography of Peter R. Breggin, M.D., and (c) Peter Breggin, M.D., Trial Testimony Accepted in Court.

3. In this declaration and in the expression of my opinions, I rely upon the totality of my professional career, including all of my writings listed in the appendices and the materials cited therein. In addition, I have reviewed and relied upon the written materials provided by plaintiff's attorney. They are substantial, and include 46 pages of medical charts of Reynaldo Lacuzong taken from 1995 to his death, the San Jose police report, and depositions of Shirley Lacuzong, Bert Ducusin, Jessica Davidson (two depositions), SmithKline's Ian Hudson, and David Wheadon. My opinions have also been formed as the result of extensive review of SmithKline Beecham and Food & Drug Administration ("FDA") documents on Paxil. They include Paxil's prescribing information as found in the label for Paxil as reproduced in the Physicians' Desk Reference and as produced by SmithKline, including those proposed to the FDA by SmithKline in 1992 and those in effect in 1996 and 1997. I joined plaintiff's counsel for 3 days of a Paxil document review at SmithKline facilities in Collegeville, Pennsylvania, in February 2000. We reviewed Paxil documents and files continuously for those 3 days, and received custody of approximately 1050 pages of documents. My notes for that period are extensive. The documentation reviewed included adverse events reported on Paxil patients during the clinical trials for depression, and correspondence between SmithKline and the FDA. In addition I requested from the FDA and received from them in the neighborhood of 1,000 pages of Paxil documents and microfiche via Freedom of Information procedures. I reviewed the 150 page transcript recorded during the FDA committee hearing held on 10.5.92 that cleared Paxil for the U.S. market.

Preliminary Report in Regard to Product Liability

At the beginning of this report it is important to affirm that SKB remains responsible for its behavior even though it must get FDA approval for its final label and its right to market the drug. FDA regulations always allow a company to upgrade its adverse reactions (to strengthen its warnings) without prior approval. In addition, the FDA can only respond to data that has been generated by the company, and SKB, as this report will document, repeatedly found ways to hide or simply not to generate data about adverse effects.

This is a preliminary report. I expect to elaborate and develop a number of issues in more depth, including areas pertaining to advertising and promotion, as well as documentation of the scientific evidence that Paxil and SSRIs in general can cause suicide and violence.

Part A will examine data generated from discovery. Part B will examine the label for Paxil. Part C will relate Part A and B to the Lacuzong case. Part D will present my conclusions.

Part A. An Analysis of Data from Discovery

I. FDA Criticism Relating to SmithKline Beecham (SKB) 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) , 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 anti-depressant 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 which 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 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. Those 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.

Leber 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 (defined below). The issue of akathisia will be addressed in more detail because akathisia is associated with violence and suicide (see below). The other relevant addition is base on two reports of serotonin syndrome, an extreme 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.

III. Eliminating Akathisia as Preferred Term and as an Investigator's Term

(1) Definition of Akathisia

Akathisia is a neurological disorder caused by medications. Stedman's Medical Dictionary, 27th edition (2000) defines akathisia as "A syndrome characterized by an inability to remain in a sitting posture, with motor restlessness and a feeling of muscular

quivering." The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, IV (DSM-IV) (1994) describes akathisia in the context of neuroleptic drugs, but the clinical manifestations are the same as akathisia induced by antidepressants. The DSM-IV observes that akathisia includes the following:

> …. Subjective complaints of restlessness and at least one of the following observed movements: fidgety movements or swinging of the legs while seated, rocking from foot to foot or "walking on the spot" while standing, pacing to relieve the restlessness, or an inability to stand still for at least several minutes. P. 744

In general, if the subjective experience of agitation, anxiety, irritability or similar feelings is accompanied by voluntary motor movements, such as pacing or foot swinging, the syndrome is identified as akathisia.

(2) Akathisia, Violence, and Suicide

The DSM-IV states without qualification, "Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts" (p. 745).

There is a considerable body of literature to confirm the association between akathisia and violence and suicide. I have reviewed some of the literature in Breggin and Breggin (1994) and Breggin (1997) in regard to psychiatric drugs in general and specifically the SSRIs of which Paxil is a member. Teicher, Glod, and Cole (1993) reviewed SSRI-induced violence and suicide. More recently, Glenmullen (2000) devoted a significant portion of a book to reviewing the literature and discussing SSRI-induced violence and suicide.

(3) The Expurgation of Akathisia

It is extremely important for physicians to know that a drug can cause akathisia. Akathisia, as a term, signals the dangers of emotional anguish and the potential for inducing suicide and violence. It is not only fraudulent, but hazardous to patients, to hide that a drug can cause akathisia. It is especially dangerous when the drug is being used to treat depression, because akathisia in depressed patients is especially likely to drive them to suicidal or violent acts.

Akathisia was systematically eliminated by SKB as a preferred term from the U.S. and non-U.S. studies (see ahead). This meant that symptoms typical of akathisia would not be coded as akathisia, but as something else, such as agitation or central nervous system stimulation.

Remarkably, akathisia does not even appear as an investigator's term on any U.S. reports that I located. It only appears as an investigator's term in about one dozen non-U.S. reports (see below) while symptoms attributable to akathisia abound in the summaries of adverse drug reactions. From this it must be concluded that SKB not only removed it from any lists of preferred terms, it also must have communicated to the principal investigators that the term should not be used in any of the adverse drug reports or clinical summaries.

Clearly SKB preferred not to let the FDA or the medical profession know that Paxil causes akathisia. Indeed, they left it out of the section entitled "Adverse

Experiences in Clinical Trials: Worldwide Data" (Section V—NDA. PAR Safety Summary 20-Nov-1989, pp. 83-88; also see Table V.7, p. 114).

Similarly, akathisia was left out of the section entitled "Adverse Experience which occurred during active treatment—U.S. Phase II & III Studies," "Nervous System" (Appendix V.8, in NDA 20031-Vol 422 November 1989, pp. 189/190-275/276). There is no listing at all for akathisia but many reports of related restlessness and nervousness.

(4) Akathisia Slips Through in Non-U.S. Reports

Nonetheless, some akathisia reports slipped through in non-U.S. reports. In the section entitled "Adverse Experiences which occurred during active treatment-Non-US Phase II-III Studies," V.1, pp. 129-199, we located 13 explicit reports of akathisia and motor akathisia (a synonym). In addition, there were many descriptions of akathisia listed under other preferred terms.

(5) The FDA Adds Akathisia to the Paxil Label

Eventually the FDA insisted that SKB add akathisia as a postmarketing finding without insisting on causation. The demand came in a letter in September 1993 from the FDA's Paul Leber to SKB (SB 0000247). Had the FDA been informed during premarketing of the large number of cases of akathisia in association with Paxil, it would have been a position to more firmly determine causation.

In response, a label version created by SKB and dated 2.05.94 does add akathisia and EPS as postmarketing findings. They should have been put in the label as a premarketing finding involving multiple cases (000022).

One of the two reports cited by the FDA was received from Ireland. However, the company already had many reports of akathisia in its possession from Europe, but must have failed to inform the FDA.

To repeat, the FDA required a mention of akathisia in the label based on merely two postmarketing reports, while SKB already had about one dozen explicitly identified akathisia reports in its possession from the non-U.S. premarketing studies and, as we shall document, dozens of other akathisia cases coded under different preferred terms, such as agitation and central nervous system stimulation, in the U.S. premarketing studies.

(6) How the FDA Codes Akathisia

The FDA has developed a coding system for adverse reaction terms. The dictionary is entitled "COSTART: Coding Symbols for Thesaurus of Adverse Reaction Terms." I have the Fifth Edition (1995) in my library, but it has not changed in regard to akathisia. Like any pharmaceutical company, SKB was supposed to base its collection and analysis of adverse reaction data on the COSTART system. This is discussed, for example, in an SKB Memorandum, "FDA Conversation Record" (9.5.91), that memorializes a conversation with the FDA's Thomas Laughren concerning, among other things, the use of COSTART terms (SB 0000158). In fact, the memo comments that Laughren (the "Division," meaning the FDA's Division of Neuropharmacological Drug Products) would make decisions about what terms to cut from the label.

From the beginning, COSTART has coded akathisia as akathisia. That is, the preferred term for akathisia is akathisia. This was true during the development of the first SSRI, Prozac.

Therefore, SKB deviated from the FDA's coding system in order to classify cases of akathisia as something else, such as agitation. In reclassifying akathisia, as well as stopping the use of the term in general, SKB made it impossible for the FDA or anyone else to accurately determine the total number of patients who suffered from akathisia as a result of taking Paxil. This was extremely fraudulent.

(7) Purposefulness of the Fraud Concerning Akathisia

The fraud had to be carried out with full knowledge, because it was well-known that the original SSRI, Prozac, caused akathisia. The original Prozac label listed akathisia but estimated its occurrence as "infrequent." However, it quickly became apparent that Prozac-induced akathisia was very common and very dangerous. In 1989 Joseph Lipinksi and his colleagues from McLean Hospital and Harvard Medical School published five cases of Prozac-induced akathisia involving considerable emotional disturbance. Based on a literature review, the researchers estimated the rate of Prozac-induced akathisia at between 9.7% and 25%. In the June 1990 the Public Citizen Health Research Group (related to Ralph Nader's organization) in their Health Letter similarly estimated the rate of Prozac-induced akathisia as 15%-25%. Furthermore, as reports by Teicher et al. (1990) and Rothchild and Locke (1991) illustrate, SSRI-induced akathisia as a potential cause of suicide and violence was a subject of discussion in the literature even before the approval of Paxil.

In the next section, we shall find a direct link between suicide and stimulation, including akathisia, in SKB's own NDA files.

IV. Re-Analysis of Preferred Terms in U.S. Trials

In addition to akathisia, Paxil commonly causes a variety of related symptoms of central nervous system stimulation, including CNS stimulation itself, anxiety, agitation, nervousness, irritability, and insomnia. These symptoms of stimulation are extremely important because they, too, are associated with suicide and violence (Breggin and Breggin, 1994, Breggin 1997). It is common knowledge in the medical profession that stimulation can induce depressed patients to make acts of suicide. Therefore, it is extremely important for physicians to know that an antidepressant drug causes stimulation, and it is fraudulent and dangerous to hide that information from them.

Unfortunately, SKB not only tried to hide the facts about Paxil-induced stimulation and akathisia, the company made false claims concerning Paxil in this regard. I have already documented that the FDA protested at times against these false claims. As another example, SKB developed a lengthy document entitled “Paxil (paroxetine hydrochloride): Hospital Formulary Product Information” (SB 0000261, dated December 11, 1992). In it, SKB claimed that Paxil was effective in “depressed patients with associated symptoms of anxiety” (SB 0000271) and that the drug possessed an adverse reaction profile with “a low incidence of nervousness, agitation, and anxiety.” These statements are false. In fact, as the FDA stated (above) and as we shall continue to document, Paxil causes nervousness, agitation, irritability, anxiety and related symptoms of stimulation in a large percentage of depressed patients, often in the first three days.

We shall also find that cases of akathisia were hidden in company-defined preferred terms—i.e., terms preferred by the drug company—such as agitation, anxiety, stimulation, nervousness, and tremor.

The following is a re-analysis of several categories CNS-related adverse effects that the company organized according to its selected preferred terms:

(1) Preferred Term Agitation

Agitation had 75 entries (pp. 191-193). Forty-nine of 75 agitation patients were in fact suffering from akathisia. Of these, 47 were described by the term “restless” and 10 mentioned leg or foot [one case] movement. As the definition of akathisia indicated (above), these cases are most likely akathisia. Consistent with the Lacuzong case, twenty-one occurred in the first 1-3 days. Another 11 occurred in 4-5 days. Again consistent with the Lacuzong case, seven cases developed on low doses of 10 mg.

(2) Preferred Term Anxiety

Of the 86 reports in the category for "anxiety," 24 were described as “tense” and 1 as “restlessness.” Although it is not as definitive as in the case of the preferred term "agitation," many of these cases were probably akathisia. Of great importance, 26 occurred in the first 1-3 days. Another 9 occurred in 4-5 days. Eight occurred at the 10 mg dose.

(3) Preferred Term Nervousness

Under the category "nervousness" (pp. 235-238), 44 of 91 were probably related to akathisia. They were identified by the following terms: pacing, jumpy, jittery, and fidgety. Jittery was the most common. Twenty-three of 91 reports occurred in the first 1-3 days. Another 15 occurred in 4-5 days.

(4) Preferred Term Tremor

Under the “Preferred Term Tremor,” there were a very large number of reports (pp. 268-273) that I have not fully evaluated. Many were related to akathisia.

V. Analysis of Akathisia in the Non-U.S. Phase II and III Clinical Trials

(1) Reports of Akathisia by Investigator Term

Unlike the U.S., a few cases of akathisia were reported using the investigator's term akathisia in the non-U.S. Phase II – III studies (NDA Aropax [Paroxetine], November 1989, Appendix V.1). They were coded under the preferred term CNS stimulation rather than under akathisia:

	Patient #	Onset – days
1.	2218 072 (p. 137)	NA
2.	NA (p. 138)	1
3.	664 015 (pl 138)	1
4.	NA (p. 138)	9
5.	664 012 (p. 139)	2
6.	NA (p. 139)	-6

7.	6 162 005 (p. 139)	4 Suicide attempt
8.	NA (p. 139)	5

NA indicates Not Available.

(2) Akathisia Linked to Suicide Attempt

Of the 8 patients diagnosed with akathisia, only 4 were identified by patient number. Of the 4 identified patients diagnosed with akathisia, one (25%) attempted suicide. Furthermore, the patient attempted suicide on the *same day* as the akathisia report (see NDA Suicide Report, Appendix 2, page 17).

It is very important to have the company identify the other four patients.

(3) Rapidity of Akathisia Onset

Of special importance to the Lacuzong case, akathisia often begins within the first few days of treatment. Of the 4 identified patients, one did not have onset data. Of all 7 patients with onset data, all were diagnosed in 9 or fewer days of treatment. Six were diagnosed within 1 week of treatment. Three were diagnosed within 1-2 days of treatment.

(4) Reports of "Motor Akathisia" by Investigator Term

Motor akathisia is identical to akathisia. The term simply emphasizes the external manifestation of the symptoms. There were five cases:

Patient #	date of onset
1. 7119 028 (p. 157)	16
2. 7119 058 (p. 157)	120
3. 7121 003 (p. 158)	21
4. 7124 012 (p. 158)	6 -- Suicide (completed)
5. 7126 008 (p. 158)	28

(5) Motor-Akathisia Linked to Suicide

Of the 5 patients diagnosed with "motor akathisia," 1 (20%) committed suicide.

Thus, of the 13 identified patients diagnosed with "akathisia" or "motor akathisia," 2 (15%) attempted or completed suicide.

(6) Completed Suicides Linked to CNS Adverse Effects, Including Akathisia

We have been able to trace five completed suicide cases to their original case summaries. Of the 5 patients who successfully committed suicide on Paxil, all were diagnosed with CNS-related AERs before suicide. Of those 5 cases, at least 2 pre-suicide diagnoses (40%), agitation and motor akathisia, were related to stimulation and/or akathisia. All of them had central nervous system adverse drug reactions.

The following are the 5 completed suicide cases followed by the investigator terms for their adverse drug reactions.

1. 1.13.126 "severe insomnia"
2. 2206.005 lightheadness, drowsiness, malaise

3. 2406.149 "restlessness (agitation)"
4. 6.47. 003 vertigo
5. 7124-012 motor akathisia. "mild hyperkinsia"

VI. Rapid Onset of ADRs Documented from the Spontaneous Reporting System

Postmarketing data from the Spontaneous Reporting System dated July 1993 confirms that severe ADRs can develop in the first day or two of treatment, including reactions that adverse affect behavior (NDA20031; SB 0000912). Here is a small sample excerpted or extracted from the Adverse Experience Reports.

Day 1: Afraid, agitated, insomnia, tension. (p 000152)
Day 1: EPS reaction. (p 000156)
Day 1: Tremors, restlessness, tearful. (p 000187)
Day 1 or 2: Disorientation, insomnia. (p 000081)
Day 1: Severe akathisia. (p 000340)
Day 1: Extremely restless, felt like screaming, dysphoric. (p 000543)
Day 1: Hallucinations. (page 000579)
Day 1: Hallucinations of insects and objects moving, dizzy. (p 000507)
Day 1: Drugged, out of body, shaky. (p 000487)
Day 1: Amnesia. (p 000467)
Day 1: Distressed, hot flashes, sort of breath. (p 000416)
Day 1: Distressed, hot flashes. (p 000417)
Day 2: Dystonia. (p 000138)
Day 2: Hallucination. (p 000471)
Day 2: Bugs crawling, feeling high. (p 000472)
Day 2: Drastic blood-sugar drop. (p 000482)
Day 2: Numbness all over. (p 000513)
Day 3: Severe muscle spasms. (p 140)
Day 3: Dystonia, anxiety. (p 172)
Day 3: Suicide attempt. (p 000106)
Day 4: Insomnia, could not walk or talk on 10 mg. (p 000372)
Day 5: Extreme agitation, jumped out window, disappeared 2 days. (p 000554)
Day 5: Extremely jittery, very dizzy. (p 115)

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) 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 can be studied through a comparison between ADRs reported on placebo and ADRs reported on 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" (Vol. PAX-M-99 in the March section [no page number]).

The following data are taken from the section on "Nervous System:"

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

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.)

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.

Of 2,963 patients, the found that 1343 (45%) developed 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 forces the company to add these closely related ADRs of EPS and hostility. Akathisia is an EPS.

XI. Evaluating Errors in the Compilation of Suicide Data

(1) Suicide Attempts: US Clinical Trials

A total of 14 suicide attempts were reported in the US clinical trials. None were completed suicides. An overview is presented in the following Table XI.19 (PAR Safety Summary 20-Nov-1989 p. 203, stamped p. 297).

Overview of Attempted Suicide-US Data

	Paroxetine N = 1562	Placebo N = 497	Other A.D. N = 464
Drug Overdose (imipramine)	9	0	1
Defenestration	2	0	0

Self-inflicted injury	1	0	0
Suffocation	0	1	0
Totals	12 (0.77%)	1 (0.20%)	1 (0.21%)

Note that the rate for suicide attempts on Paroxetine approaches 1% which the FDA considers "frequent."

Also note that the rate for suicide attempts on Paroxetine 3.8 times higher than for placebo and 3.6 times higher than for the comparison antidepressants (tricyclics).

Furthermore, the suicide attempt on imipramine is listed as a “possible suicide (p. 211, stamped 306).

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

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

2. Leaving Out Two Non-U.S. Suicide Attempts

There is evidence that some suicide attempts were omitted from the calculations sent to the FDA. In the report “Adverse experienced which occurred during active treatment. Non-US Phase II-III studies” (Appendix V.1) , I located two patients that appear to have been left out of the summaries of non-US suicide attempts. Case 647 002 (Volume 420, p. 157) made three suicide attempts on days 1, 8, and finally on day 15 when the drug was stopped. The first two were considered “related” and the third “possibly related.” Also, case 1 113 120 (Volume 420, p. 157) was considered “definitely drugged related.”

These two attempted suicides do not appear in the complete list of 40 in the April 29, 1991 suicide report (pp. 17-18).

These two suicide attempts, including one patient with three attempts, are not listed in the April 19, 1991 suicide report or in any other source that we have located.

This brings the total of non-US suicide attempts to 32.

3. Leaving Out Two Non-US Completed Paxil Suicides

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

Case Number	Duration (days)	Cause of Death and Comments
DFG124/12*	?	Suicide: Method—Overdose with doxepin

HDUK13/26*	144	Suicide: Method—Hanging
29060/149*	18	Suicide: Method—Overdose … 6 days after discontinuing paroxetine
HP-82-47/3*	47	Suicide: Method—Drowning
058/022**	?	Suicide: Method—Unknown
083.003.1090**	8	Suicide: Method—Hanging
2206.005/605*	150	Suicide: Hanging

Since only 5 non-U.S. suicides are listed in any of the tables or reports, it is apparent that there are two missing. Two more should be added to the suicide completed counts (see below).

I cross checked these numbers and have found that five are included (*see single asterisk) in the official lists of suicides.

We need to obtain the two missing cases (**see double asterisk).

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

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

4. Adding Two Placebo Run-in Completed Suicides to the non-U.S. Studies

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

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

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

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

5. Including Two Placebo Run-in Suicide Attempts in non-US Studies

The worldwide data for suicide attempts also includes placebo run-in data. This is confirmed in Table XI.21, Attempted Suicides and Overdoses—Worldwide Data (Par Safety Summary – 10-Nov-1989, p. 206, stamped page 300, SB 0000548). Exactly as in

the case of including completed suicides from the placebo wash-out phase, the inclusion of two placebo run-in patients in the non-US suicide attempt category is misleading and fraudulent. The two placebo run-in patients must be excluded from the non-US and worldwide data.

XII Re-Analysis of the Suicide Data

1. Re-Analyzing Non-U.S. Completed Suicides

Various SKB documents, including the April 29, 1991 suicide report, only list 5 completed suicides. As described above, we have found an additional 2 for a total of seven. Therefore the completed suicide rate for Paxil is seven in a population of 1401 patients for a rate of 0.499%.

As also described above, we found that two placebo wash-out completed suicides were wrongly counted in the suicide rate for placebo. The true occurrence for completed suicides in the placebo group is 1 in 544 for a rate of 0.180%. The suicide rate on Paxil is therefore 2.7 times that on placebo.

2. Creating a New Category of Suicidal Behavior or Suicides, Attempted and Completed

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

Based on this analysis, the rate of suicidal behavior is 47 out of 2963 for a rate of 1.58%.

If we add the additional two completed suicides that seem to have been left out of the data, we now have 49 (47 + 2 = 49) suicidal behaviors out of 2963 for a rate of 1.65%.

Whether we use the 1.58% figure or the 1.65% figure, this combined category of suicidal behavior is far more meaningful than the split categories of suicide attempts and suicides completed. It was grossly misleading not to create a combined category.

The above calculations were based on the assumption that there were 42 suicides as indicated in the original NDA. If we added the two suicide attempts that appear to have been left out of the data , there are at least 44 total suicide attempts. The corrected total for combined suicidal behavior on Paxil then becomes 51 (44 suicide attempts = 7 suicides = 51). Fifty-one out of 2963 produces a rate of 1.72% for suicidal behavior on Paxil.

3. Re-Analysis of the Worldwide Comparisons for Suicide Attempts

We have already found that two attempted suicides on Paxil were apparently not included in the worldwide calculations. As described above, this raises the original NDA figure from 42 to 44 for attempted suicides out of 2963 cases, for a rate of 1.48%.

In addition to undercounting suicide attempts on Paxil, SKB over-counted placebo-related suicide attempts.

For placebo, 3 suicide attempts are listed. But as we have documented, the correct number for placebo suicides is only one for the worldwide group. The other two suicide attempts were placebo wash-out cases. That makes the placebo suicide attempt rate a mere 1 out of 554 for a rate of 0.18%.

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

4. Hiding the Frequency of Suicide Worldwide in the April 29, 1991 Suicide Report

In the "Discussion and Conclusions" of the April 29, 1991 report (SB 0000819, report pp. 12-13) states the following conclusion:

> 2) The incidence of attempted suicides did not differ substantively among the three treatment groups (paroxetine, placebo, active controls).

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

Furthermore, there is no overall category of Suicidal Behavior or Suicides, Attempted and Completed. Therefore, when counting suicide attempts, suicides completed are excluded, badly misrepresenting the data. In addition, there appear to be two unreported suicide attempts and six unreported completed suicides worldwide.

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

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

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

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

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

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

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

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

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

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

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

(7) 05-02B-019 (Volume 410, p. 124). This patient was taking Paxil 50 mg for 57 days when the overdose occurred. “Adverse experiences reported during the study were mild rash, diarrhea, ‘shakiness’ (possibly drug related), and an overdose.” She took 20-50 unknown pills and was hospitalized.

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

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

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

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

(12) 09-01J-573 (Volume 410, p. 279). This patient was taking Paxil 10 mg according to the summary (p. 298) but taking 20 mg according to this case report. The

drug exposure was listed as 26 days but appears to have been 30 days. The patient "jumped from second story window" and "received multiple fractures."

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

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

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

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

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

XIV. Increasing Evidence of Suicidality on Paxil

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

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

XV. Adverse Reactions from the Original NDA Application (Volume 1, pp. 151-4).

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 1,0 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 o f emotion.

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

This material 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.

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

Notice the overall stimulation profile that is obscured by the published label. Asterisks (*) are used to designate commonly accepted stimulant effects. However, all of the adverse effects in the chart 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 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 about U.S. Paxil patients, but that they did not rise to a rate of 1%.)

XVII. Critique of the Rating Scales

The rating scales used by SKB, and unfortunately by many other pharmaceutical companies, are simplistic and allow for a great deal of investigator bias. Because a drug like Paxil causes very different adverse effects from the older comparison drugs, the tricyclics, and because it causes even more dramatically different adverse effects from placebo, it can be relatively easy for an investigator to determine whether or not the patient is taking Paxil.

The Clinical Global Impression Scale (GCI) of many of the efficacy conclusions (0000790 is an example). However, it is a very simplistic, subjective rating scale in which the rater is asked to rate any perceived improvement. The rater is asked, "Compared with his condition on admission to the project, how much has he changed?" The answers are then rated on a scale of 0-7 for Not assessed (0), Very much improved (1), Much improved (2), Minimally improved (3) , No change (4) , Minimally worse (5) , Much worse (6), and Very much Worse (7).

This scale is simplistic to the point that it is worthless. Improvement is not defined. The basis for the improvement is arbitrarily left up to the "global" impression of the clinician who could make the judgment based on anything from the patient "feel good" to specific symptom improvement. In fact, depression is not a one-dimensional disorder that improves on a single linear scale. It is a complex human phenomena in which, for example, individuals often seem improved when they are actively planning suicide, and in which individuals, conversely, may look worse while they subjectively feel better. An individual may seem to have more energy when in fact the individual is becoming manic and suffering from worsened insomnia. Overall, depression involves an infinite array of feelings and symptoms that vary in every individual.

The scale also allows for the subjectivity of the investigator to run wild. Since investigators can often tell which patient is taking the SSRI rather than the placebo or the tricyclic antidepressant, it becomes relatively easy and tempting to conclude that patients on the study drug are improving.

Similar criticisms can be made of the Hamilton Depression Rating scale (SB 0000783 is an example). It plays a key role not only in rating efficacy but also in re-evaluating adverse effects, in particular suicidality. In fact, it was never intended by Hamilton to be used for quantifying depression in a scientific manner. It is relatively

useless for evaluating suicidality since it has only one relevant item out of 21 items, and the rating is subject to extreme investigator bias and variation.

Part B: Analysis of the Paxil Label

I have already described in Part A, Section XV how the data generated in the NDA was distorted when placed in the official label. There are other problems with the label as well.

Page numbers cited are taken from the 1997 Physicians' Desk Reference.

A. Problems with 1997 Label

The 1997 label for Paxil reads:

> The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. P. 2683

(1) This label is misleading in that it implies that Paxil can cause a "significant remission." The term remission, according to standard medical dictionaries, indicating either a partial or complete abatement of symptoms. For example, the 1989 Psychiatric Dictionary, Sixth Edition, published by the Oxford University Press, defines remission as follows:

> **remission** Abatement of the symptoms and signs of a disorder or disease. The abatement may be partial or complete.

Clinicians deal with this ambiguity by speaking of "partial" and "complete" remission. By using the more general term, remission, and by calling it "significant," implying it may even be complete, the label misleads physicians into believing that Paxil has been shown to cause a complete abatement or remission of symptoms. There is no evidence that Paxil brings about a significant number of complete remissions. Instead, Paxil marginally improves depression in comparison with placebo.

The label does not provide information on the number of depressed patients "Very much improved" on Paxil; but the breakdown data provided for only one OCD study (p. 2682, second column) indicates that at the 20 mg dose, placebo and Paxil both resulted in a 7% "Very Much Improved" rating on the Global Improvement Item. However, 20% achieved that rating on the 40mg and 60 mg dose. There are no data for "complete remission."

(2) The label is further misleading in that it implies there is reason to believe that the risk of suicide will be diminished after "initial drug therapy" with Paxil. There is no evidence for this. Instead, as indicated below, Paxil increases the risk of suicide.

B. Contraindications To Be Added to the Label

Note that the Contraindication category is stronger than the Warning category, as it indicates that the drug should never be used under the specified conditions. The label for Paxil should, but does not, contain information consistent with the following observations:

(1) Paxil can cause or exacerbate suicidal tendencies, and is contraindicated in patients for whom there is a risk of suicide. In U.S. clinical trials, Paxil caused suicide at a rate well-above 1% of patients and at a considerably higher rate than other antidepressants or placebo. When adjusted correctly, the worldwide rates followed the same pattern. The rate for Paxil-associated suicide attempts was many times greater than the rate for patients taking other antidepressants or placebo.

The patient and family should be warned about the danger of Paxil-induced suicidality and instructed to immediately inform the physician of any suicidal thoughts or intentions while taking Paxil.

(2) Based on data from clinical trials and clinical reports, Paxil does not reduce suicidality or the rate of suicide attempts, and therefore Paxil should not be used as a treatment for ameliorating or preventing suicidality. The patient and family should be warned that Paxil cannot be relied upon to prevent suicidal tendencies, that instead it raises the rate of suicidal behavior, and the family should be instructed to immediately inform the physician of signs of suicidal thoughts or intentions.

(3) In a substantial portion of patients Paxil causes and/or aggravates anxiety, agitation, nervousness, irritability, insomnia, tremor, and other symptoms of central nervous system (CNS) stimulation, including emotional lability and mania. CNS stimulation is known to be associated with suicide and violence. Paxil is contraindicated in patients who are experiencing or who are at risk for symptoms of stimulation. The patient and family should be warned about the danger of Paxil-induced stimulation and instructed to immediately inform the physician about any signs of stimulation.

C. Warnings To Be Added to label

(1) Paxil commonly produces severe adverse reactions during the first one to five days of exposure to the drug in the starting dose range (10-20 mg per day). As a result, the patient is at risk for a worsening of his or her condition before there is any beneficial drug effect. The patient and family should be alerted to the possibility of adverse reaction occurring soon after starting the drug, including stimulation (insomnia, anxiety, agitation), suicidality, or violence. The patient and family should be instructed to inform the physician at the earliest sign of stimulation, suicidality, or violence.

(2) Paxil commonly produces akathisia, a drug-induced central nervous system disorder characterized by feelings of irritability and anxiety in association with restlessness and the inability to sit still. Akathisia is associated with an increased rate of suicidality and violence. The patient and family should be informed about the danger of akathisia and instructed to immediately contact the physician at the first sign of akathisia.

(3) Paxil is not indicated for the treatment of suicide and is associated with an increase rate of suicidality and suicidal behavior (See other Warnings).

(4) Paxil is not indicated for the treatment of aggression or violence and can increase aggression and violence (see other Warnings).

(5) Severe adverse reactions to Paxil may develop in the first several days of treatment even a low doses, but any therapeutic effect is likely to be delayed for a longer period of time. Therefore, the first several days of exposure to Paxil are particularly hazardous (see other Warnings). The physician should take appropriate precautions to monitor the patient and to respond to any signs of a worsening condition.

(6) Paxil belongs to the pharmacological class of serotonin reuptake inhibitors and is likely to produce any adverse drug reaction associated with other medications, such as fluoxetine, sertraline, fluvoxamine, and citalopram in that class of antidepressants.

D. Other Label Issues

(1) If an adverse reaction or event is listed in tables (e.g., Tables 1, 2, & 3), it is not repeated in text under "Other Events Observed During Premarketing Evaluation" (p. 2685, first column). As a result anxiety gets left out of the systematic listing of adverse reactions under **Nervous System** in this section.

Although this method is approved by the FDA, SmithKline was obligated to make the label properly informative. It should have made a large warning that both sources need to be examined or it should have combined the adverse reactions in a summary elsewhere in the label.

(2) The table minimizes the numbers of reports relating to anxiety by providing separate data for anxiety and nervousness (Tables 1 & 2) and for anxiety, nervousness, and agitation (Table 3).

E. Burying the Stimulant Profile

SSRIs as a group have a stimulant profile. I have discussed this in regard to Prozac in some detail (Breggin, 1997; Breggin and Breggin, 1994).

The data in the label, if properly understood through careful and time-consuming scrutiny, confirms that Paxil can be stimulating. Indeed, "CNS stimulation" is mentioned as "frequent" under **Nervous System** (p. 2685, column three). However, the data on stimulation is not organized in any one place in the label, and instead is obscured by being scattered among three tables and various places in the text. Furthermore, the term "frequent" indicates "at least 1/100 patients" or 1%, and therefore does not communicate the how extremely common stimulation is.

The following two tables compile the data confirming the high risk of patients developing stimulant reactions. The label itself should have organized this data in a fashion that would have similarly warned about the dangers of the stimulant syndrome.

F. Comparison of Stimulant Adverse Effects in Depression, OCD, and Panic Disorder

Patients with an "incidence of 5% or greater and incidence for *Paxil* at least twice that of placebo" were reported separately for Depression, OCD and Panic Disorder (Table 2, summarized in text p. 2684, first column). In **Table I**, I have organized this data in parallel to more readily compare and examine the pattern.

The information in this newly created table indicates that high rates of several stimulant profile reactions were found in all three groups for sweating, tremor, and decreased appetite. In patients treated for depression, stimulation profile reactions are especially prominent and include sweating, nausea, decreased appetite, tremor, insomnia, and nervousness. Dry mouth (OCD only), nausea (depression and panic disorder) and various sexual dysfunctions (all three groups) are also consistent with stimulant effects but not as specifically characteristic.

The criteria for this particular table were unusually high. If we examine the entire range of reported adverse effects at the level of 1% or greater rather than 5% or greater (and twice placebo) we develop a more obvious stimulant profile.

Table I: Very Frequent (5%) CNS/Psychiatric Adverse Reactions from Paxil Label

Depression	Panic Disorder	OCD
Asthenia	Asthenia	
Sweating	Sweating	Sweating
Nausea		Nausea
Decreased appetite	Decreased appetite	Decreased appetite
Dizziness		Dizziness
Somnolence		Somnolence
Tremor	Tremor	Tremor
Insomnia		
Nervousness		
Ejaculatory Disturbances	Abnormal Ejaculation	Abnormal ejaculation
Other male genital disorders		
	Impotence	Impotence
	Libido decreased	
	Female genital disorder	
		Dry mouth
		Constipation

Table II: Summary of Stimulant and Stimulated-Related ADRs from Paxil Label

Frequent Stimulant ADRs	**Stimulant-Related CNS ADRs**	**Stimulant-Related CNS ADRs**
[at least 1%]	[at least 1%]	[less than 1%]
<u>CNS</u>	Depression**	Hostility**
	Amnesia* **	Paranoid reaction**
CNS stimulation**	Asthenia*	Antisocial reaction**
Seizures+	Concentration impaired* **	Manic reaction**
Mania/hypomania+	Somnolence*	Manic depressive reaction**
Emotional lability**		Euphoria**
Anxiety*		Psychosis**
Nervousness*	<u>Serotonin Syndrome</u>++	Psychotic depression**
Agitation*		Depersonalization* ** ++
Insomnia*	Agitation [also *]	Hallucinations**
Tremor*	Confusion	Delusions**
	Diaphoresis [sweating*]	Delirium**
<u>Systemic</u>	Hallucinations [also **]	Abnormal thinking**
	Hyperreflexia [reflexes increased *]	Abnormal dreams*
Sweating*	Myoclonus [also *]	Lack of emotion**
Decreased appetite*	Shivering [chills*]	Neurosis**
Weight Loss**	Tachycardia [also **]	Convulsion**
Dry mouth*	Tremor [also *]	**Grand mal convulsion****
Tachycardia**		
Hypertension**		
Palpitation*		

ADR=Adverse Drug Reaction. The ADRs selected for this table are among those potentially related to stimulant effects. * From the Tables; ** From "Other Events Observed…"; + From Precautions; From footnote to Table 2;++ From Postmarketing Reports section.

In regard to the serotonin syndrome as listed in Table II, note that many of these symptoms are also reported as individual ADRs. To some extent, many of the individual ADRs may at times reflect a partial expression of a serotonin syndrome, although over-stimulation other neurotransmitters may be involved. Other stimulant aspects of the serotonin system, not listed in the Paxil label, include hypertension and convulsions.

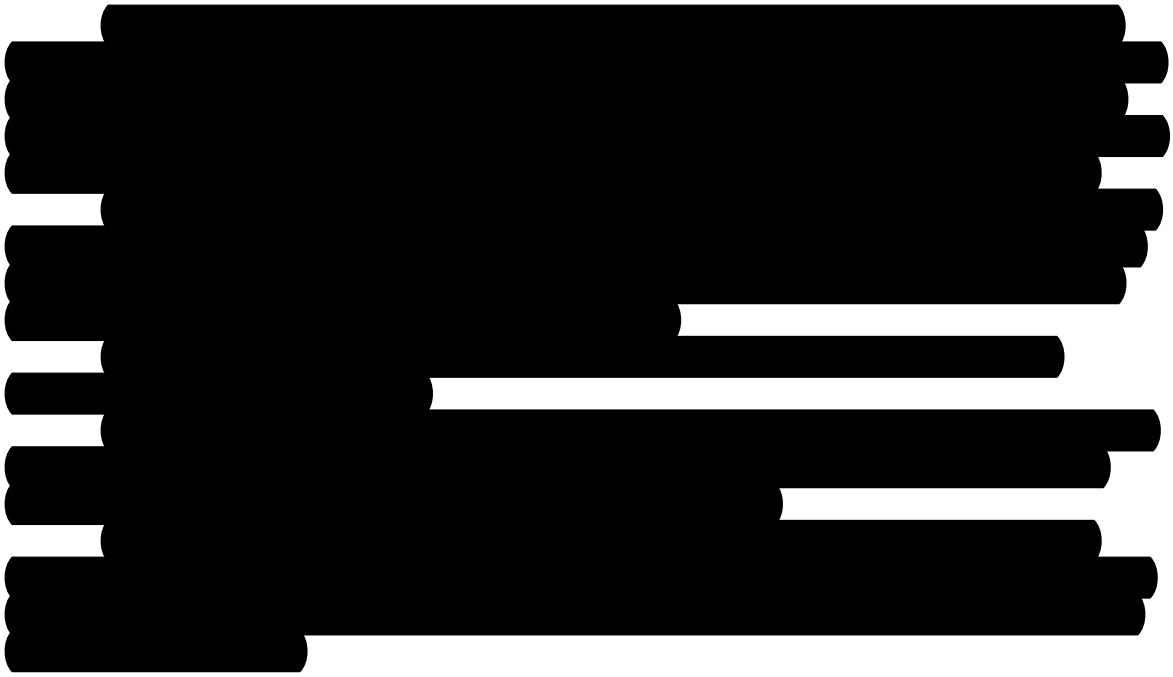
Part C: Application to the Lacuzong Case

[redacted]

Part D. Conclusions

The following opinions are offered to a reasonable degree of medical certainty.

A. Basic Facts of Mr. Lacuzong's Case



B. Negligence by SmithKline Beecham

The following acts of negligence and lack of due care by SKB contributed to or caused Mr. Lacuzong's suicidal and violent behavior:

(1) SKB was deceptive, fraudulent and negligent in hiding data concerning the stimulating effects of Paxil, including agitation, anxiety, nervousness, insomnia, and irritability. The label for Paxil was constructed to hide the stimulating pattern or profile of effects. Indeed, SKB attempted to promote Paxil as relatively free of these symptoms and even as an effective treatment for patients suffering from these symptoms and was criticized by the FDA for doing so.

Stimulation is an especially dangerous adverse effect in depressed patients, producing an agitated depression that can lead to suicide and violence. Physicians and patient need to know that a drug is potentially stimulating.

(2) SKB systematically eliminated the term akathisia as an investigational term and as a preferred term. In doing so, it acted in defiance of the FDA's own coding system. In this regard, SKB purposely misled the medical profession. When eventually forced by the FDA to include akathisia in the label, SKB allowed the term to be placed in the postmarketing section, lumped together with other adverse effects, rather than acknowledging to the FDA and in the label that it was detected at a high frequency in the premarketing clinical trials.

Akathisia is an extremely disturbing syndrome and is known to be associated with violence and suicide. Physicians and patients need to know the implications of akathisia and that a drug can cause akathisia.

(3) SKB hid and distorted data concerning the danger of suicide attempts and completed suicide. It manipulated the data to minimize the danger of suicidal behavior when in fact suicidal behavior was frequent on Paxil. The harm in doing this is great.

(4) SKB made no effort to develop additional controlled clinical trials to further investigate the alarming data concerning the high rate of Paxil-induced stimulation, akathisia, and especially suicidal behavior (confirmed by SKB's David Wheadon, deposition 10.18.00, p. 42 & p. 184).

(5) SKB attempted to make Paxil seem safer and more effective than other SSRIs, increasingly the likelihood that it would be prescribed to Mr. Lacuzong and that his physician and the clinic would lack sufficient concern about its dangerousness. In general SKB conducted a campaign of exaggerating the safety of Paxil, even trying to promote it for children and the elderly. Their efforts created an atmosphere in which Paxil was considered by the medical profession to be more safe than it is.

(6) SKB hid the fact that a large portion of patients develop severe adverse effects, including stimulation and akathisia, in the first one-to-three days of exposure to the drug. This data is of extreme importance, because the drug will not have its presumed beneficial effect during this time of potentially severe adverse reactions, including stimulation and akathisia. Thus the patient remains depressed while undergoing, in addition, painful stimulation and akathisia. Knowledge that adverse effects occur early in the treatment is also important because patients and many physicians falsely believe that, since it takes weeks for therapeutic effects to develop, it must take weeks for adverse effects to develop as well. In other words, physicians and patients falsely believe that the drug "doesn't take effect" for weeks when it fact it can have adverse effects with the first dose.

The development of severe stimulating adverse drug reactions in depressed patients in the absence of a corresponding beneficial effect is a prescription for disaster that the drug company has hidden from view. Physicians and patients needed this information.

(7) SKB committed various other individual acts of negligence that are noted and documented in the body of this report.

(8) Paxil's efficacy was marginal. Physicians and patients need to know both the relative lack of efficacy and the relative frequency of adverse effects in order to make an informed risk/benefit assessment. The effectiveness assessment was largely based on two very limited tests, the Hamilton Depression Scale (Ham-D) and the Clinical Global Inventory (CGI). Because of the high drop out rate due to adverse effects and lack of efficacy, patients dropped out too early to allow meaningful conclusions to be drawn.

(9) SKB failed to act on the known fact that SSRIs tend to share the same adverse reaction profile, including the production of stimulation and akathisia. Instead, it tried to cover up this similarity, falsely encouraging physicians and patients to believe that Paxil is safer than Prozac and other drugs in the same class.

(10) SKB emphasized the short-acting nature of Paxil as a pure benefit, when in fact it causes special hazards, such as the potential for interdose withdrawal.

(11) SKB representatives were discussing with at least one FDA official the possibility of future employment in the pharmaceutical industry. This could encourage leniency on the part of the FDA official. The same FDA official helped SKB manipulate their suicide data to their advantage.

[redacted]

E. Bibliography

Breggin, P. and Breggin, G. (1994), Talking Back to Prozac, New York: St. Martin's Press.

Breggin, P. (1997). Brain-Disabling Treatments in Psychiatry: Drugs, Electroshock and the FDA, New York: Springer Publishing Company.

Breggin. (2001). The Antidepressant Fact Book, Cambridge Massachusetts: Perseus Books.

Glenmullen, J. (2000). Prozac Backlash, New York: Simon & Schuster.

Lipinksi, Jr., J., Mallaya, G., Zimmerman, P., and Pope, Jr. H. (1989, September). Fluoxetine-induced akathisia: Clinical and theoretical implications. Journal of Clinical Psychiatry, 50, 339-352.

Public Citizen (1990, May 23). Re: Citizens petition for revision of fluoxetine (Prozac) labeling. Letter to David Kessler, Commissioner, Food and Drug Administration. Washington, DC: Public Citizen Health Research Group.

Rothschild, A. and Locke, C. (1991, December). Reexposure to fluoxetine after serious suicide attempts by three patients: The role of akathisia. Journal of Clinical Psychiatry, 52, 491-493.

Teicher, M., Glod, C., and Cole, J. (1990, February). Emergence of intense suicidal preoccupation during fluoxetine treatment. American Journal of Psychiatry, 147, 207-210.

Teicher, M., Glod, C., and Cole, J. (1993). Antidepressant drugs and the emergence of suicidal tendencies," Drug Safety 8(3):186-212.

Under penalty of perjury of the laws of the State of California, I submit this declaration to the court and arbitrator, and further believe the foregoing to be true and correct to the best of my knowledge and recollection. Executed: Bethesda, MD.

DATE: July 21, 2001

Peter R. Breggin, M.D.
Declarant

Attached Appendices:
(a) Summary and Annotated Resume of Peter R. Breggin, M.D.
(b) Bibliography of Peter R. Breggin, MD.
(c) Peter Breggin, M.D., Trial Testimony Accepted in Court.