SPECIAL REPORT PART II

How GlaxoSmithKline Suppressed Data on Paxil-Induced Akathisia: Implications for Suicidality and Violence

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This is the second in a series of *Special Reports* on previously suppressed data concerning the selective serotonin reuptake inhibitor (SSRI) antidepressant Paxil (paroxetine) and its capacity to cause violence and suicide. The data were contained in a report that I wrote as a medical expert for a product liability suit against the manufacturer of Paxil, *Lacuzong v. GlaxoSmithKline* (GSK).[1] After taking Paxil 10 mg for 3 days, Mr. Lacuzong drowned his two children and himself in a bathtub. The case was eventually "resolved" without the details of the settlement being made public. The drug company denied all allegations.

My product liability report was based on numerous sources, most notably a 3-day trip to the drug company offices to examine its internal files concerning how Paxil was researched, developed, and marketed. Until these *Special Reports*, the information in these files had not been made public.

Since the publication of my first special report concerning how the manufacturer of Paxil hid and manipulated data concerning Paxil-induced suicide (Breggin, 2006), the FDA and the drug company, GlaxoSmithKline, have issued statements confirming that depressed adults of all ages taking the antidepressant have an increased rate of suicidality compared to depressed adults taking placebo (Kraus, 2006). These adults 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%). This meta-analysis of placebo-controlled clinical trials also focused on *young adults* who were prescribed Paxil for anxiety disorders as well as depression. In this broader diagnostic group, young adults (ages 18–24) who were given Paxil were also at increased risk for suicidality. Summarizing these data, Paxil increased suicidality in depressed adults of all ages and also in young adults with depression, dysthymia, panic disorder, generalized anxiety disorder, and obsessive compulsive disorder.

The rates of Paxil-induced suicidality will be much higher in actual clinical practice where the drug exposure typically lasts much longer than 4–6 weeks, patient monitoring is much less thorough, multiple drugs often exacerbate adverse drug reactions, and many patients are already suicidal.

By admitting that Paxil causes suicidality in adults, the FDA and GlaxoSmithKline confirmed observations I have been making in my publications and trial testimony for more than a decade (e.g., Breggin, 1997, 2001; Breggin & Breggin, 1994). The FDA and the drug company released their results within weeks after the publication of my initial special report in *EHPP*, which showed that the drug company had been suppressing the relevant data for many years (Breggin, 2006).

My first *Special Report*, "Court Filing Makes Public My Previously Suppressed Analysis of Paxil's Effects," described how recent court proceedings made my product liability report available to the public despite previously successful efforts by GSK to suppress it. My initial *Special Report* provided excerpts from my product liability analysis concerning how the drug company manipulated data concerning Paxil-induced suicidality. For example, GSK's analysis of suicidality left out two attempted suicides and two completed suicides on Paxil, and exaggerated the number of suicidal acts on placebo. The company also reduced the apparent significance of suicide-related events by providing separate analyses of overdose, suicide attempt, and suicidality. It is more useful and meaningful to combine all suicide-related activities into one category, suicidality.

For *Special Report Part II*, I have excerpted sections from my product liability report concerning how the drug company hid both the rates for Paxil-induced akathisia and the relationship between akathisia and suicidality. Akathisia is a drug-induced inner agitation or dysphoria that causes a person to feel compelled to move about. The painful feelings associated with akathisia have been compared to torture and often make people feel as if they are going "crazy." People who suffer from akathisia often voice dramatic descriptions such as "electricity streaming through my veins," "horrible jagged feelings inside my head" or "something pinching my nerves all over my body." These vivid, desperate descriptions can be mistaken for delusions or hallucinations (American Psychiatric Association, 1994, 2000; Breggin, 1997).

When the FDA initially approved Paxil in December 29, 1992, it had already been reported that SSRI antidepressants tend to induce extremely high rates of akathisia. For example, Lipinski, Mallaya, Zimmerman, and Pope (1992) described five cases and, based on a review of the literature, they estimated that Prozac (fluoxetine) causes akathisia in 9.7%–25% of patients.

Since the 1970s, studies of neuroleptic-induced akathisia have demonstrated that akathisia causes severe emotional disturbances, including aggression, suicidality, and a worsening of psychosis (van Putten, 1975; van Putten & Marder, 1987; Breggin, 1983, 1997). In the early 1990s, clinical reports began to link Prozac-induced akathisia to severe, acute, and obsessive suicidality (e.g., Rothschild & Locke, 1991; Teicher, Glod, & Cole, 1990).

In 1994, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*, 1994, pp. 744–746) attempted to sum up the available clinical and research data concerning drug-induced akathisia. It stated, "Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts." It also linked akathisia to "worsening of psychotic symptoms or behavioral dyscontrol." The manual focused on neuroleptic-induced akathisia but made clear that the same problems are associated with SSRI antidepressant-induced akathisia: "**Serotonin specific reuptake inhibitor antidepressant medications** may produce akathisia that appears to be identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia."[2]

Because it was already known that SSRI-induced akathisia causes suicidality, violence, and overall mental deterioration, it was beholden on GSK to conduct a careful analysis

of Paxil-induced akathisia. It was also beholden on the company to look for a link between Paxil-induced akathisia and mental or behavioral abnormalities. Instead, GSK went to extreme lengths to hide the fact that Paxil causes akathisia and that the some Paxil akathisia cases were associated with suicidality.

SSRI antidepressants can cause suicidality and violence through means other than akathisia, including drug-induced agitation, depression, and mania. Patients who were previously depressed can be pushed into states of agitated depression or manic-like reactions (Breggin, 2003). The stimulating effects of SSRIs, from akathisia and agitation to mania, are responsible for causing some of the most severe mental and behavioral aberrations.

Some progress has been made by the Food and Drug Administration (FDA) in warning about the risks associated with SSRI stimulation or activation (reviewed in Breggin, 2005). The agency now requires antidepressant labels to carry several warnings related to overstimulation and akathisia including the following:

> **Clinical Worsening and Suicide Risk:** Patients, their families and caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, and other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. (FDA, 2005a, p. 2)

The FDA also requires antidepressant labels to carry a black box warning about the increased risk of suicidality in children who take these drugs (FDA, 2005a). Although specific warning about the increased risk of suicidality in *adults* who take these antidepressants is not required, the FDA has issued a Public Health Advisory about the potential danger in adults (FDA, 2005b). The data disclosed in this *Special Report* should lend scientific weight to the FDA's concerns and encourage a specific label warning about the increased risk of suicidality in adults taking SSRI antidepressants such as Paxil.

The following excerpts from my product liability report dated July 21, 2001, focus on akathisia. In addition to examining how GSK manipulated or suppressed data concerning akathisia, these findings confirm a link between Paxil-induced akathisia and suicidality. The data also confirm that these severe reactions can occur beginning with the first dose of the drug and that they often occur within the first few days of the initial exposure.

My product liability report can be found in its entirety on my website, www.breggin.com. It covers numerous additional concerns about how GSK researched, developed, and marketed Paxil.

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

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; 2000) describes akathisia in the context of neuroleptic drugs, but [as noted in the *DSM-IV*] the clinical manifestations are

the same when akathisia is induced by SSRI antidepressants. The *DSM-IV* observes that akathisia includes the following symptoms:

> [S]ubjective 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 are 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) [most recently in Breggin 2003] in regard to psychiatric drugs in general and specifically the SSRIs of which Paxil is a member. Teicher et al. (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 also 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 (now GSK) as a preferred term from the U.S. and non-U.S. studies. 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. (Preferred terms are the words used to describe specific adverse effects, such as akathisia, agitation, or mania. They are selected from a codebook provided by the FDA. If akathisia is not listed by the company as a preferred term in its plan or protocol for a study, then investigators will code or list akathisia as something else, such as agitation. Almost any term is less threatening than akathisia.)

Remarkably, akathisia does not even appear as an investigator's term on any U.S. reports that I located. It appears only as an investigator's term in about one dozen non-U.S. reports, whereas symptoms attributable to akathisia abound in the summaries of the U.S. reports of adverse drug reactions. From this it must be concluded that SKB not only removed akathisia 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 in 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.[3] They should have been put in the label as a premarketing finding involving multiple cases (p. 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, although 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 other 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), which 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." It quickly became apparent, however, that Prozac-induced akathisia was common

and 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 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 Rothschild 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.[4]

IV. Reanalysis of Preferred Terms in U.S. Trials

In addition to akathisia, Paxil commonly causes a variety of related symptoms of central nervous system stimulation (CNS), 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 & Breggin, 1994; Breggin 1997 [and more recently, Breggin 2003]). 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 (see previous) 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 3 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 reanalysis of several categories of 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). A total of 49 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 (see previous), these cases are most likely akathisia. Consistent with the Lacuzong case, 21 occurred in the first 1 to 3 days. Another 11 occurred in 4 to 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 to 3 days. Another 9 occurred in 4 to 5 days; 8 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. In all, 23 of 91 reports occurred in the first 1 to 3 days. Another 15 occurred in 4 to 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 in the United States, a few cases of akathisia were reported using the investigator's term akathisia in the non-U.S. Phase II–III studies (for Aropax, another brand name for 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 eight patients diagnosed with akathisia, only four were identified by patient number [and therefore could be traced back to their detailed clinical reports]. Of the four 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 four identified patients, one did not have onset data. Of the seven 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 to 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 five 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 five patients who successfully committed suicide on Paxil, all were diagnosed with CNS-related AERs (Adverse Event Reports) before suicide. Of those five cases, at least two presuicide diagnoses (40%), agitation and motor akathisia, were related to stimulation and/or akathisia. All of them had CNS adverse drug reactions.

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

1. 1.13.126 "severe insomnia"
2. 2206.005 light-headedness, drowsiness, malaise
3. 2406.149 "restlessness (agitation)"
4. 6.47. 003 vertigo
5. 7124–012 motor akathisia. "mild hyperkinesia"

VI. Rapid Onset of Adverse Drug Reactions (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 adversely 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. (p. 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).

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 to 2 days of the start of treatment. Five adverse events occurred at the 10 mg dose, none of which were in the 1- to 2-day period.

(2) Anxiety and Suicide From Non-U.S. Phase II and 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, 3 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.

NOTES

1. Formerly known as SmithKline Beecham (SKB).

2. Bold in original. All quotes from p. 745. The same points are made in identical language in the more recent edition (American Psychiatric Association, 2000, p. 801).

3. EPS (extrapyramidal symptoms) include a broad array of drug-induced neurological reactions, including akathisia.

4. The NDA (new drug application) contains all documents pertaining to the drug approval process, including all clinical trial data, evaluations of safety and efficacy, proposed advertising and marketing materials, the proposed label for the drug, and communications with the FDA.

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