

Fluvoxamine as a cause of stimulation, mania and aggression with a critical analysis of the FDA-approved label ¹

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1. Introduction

Health professionals often rely upon government approved labels for medications as a reliable source of information in determining potential adverse drug reactions. This can lead these professionals to under-estimate the hazards associated with drugs. As an illustration of the need for greater caution and skepticism, this article will examine the label for Luvox (fluvoxamine) as approved by the U.S. Food and Drug Administration (FDA). It will compare the contents of the label to the known risks of fluvoxamine-induced stimulation, mania and aggression in children and adults. The intention is to alert health professionals to the need for approaching government-approved drug labels with more scientific sophistication, especially in regard to evaluating the risks of medications.

In the spring of 1997, fluvoxamine was approved in the United States for the treatment of obsessive-compulsive disorder in children (aged 8–17) and for adults. Fluvoxamine, manufactured by Solvay Pharmaceuticals, Inc., was the first Selective Serotonin Reuptake Inhibitor (SSRI) to be approved for any purpose in children. Controlled clinical trials involving children are required for a drug to be approved for use by children under the age of eighteen.

The potential for fluvoxamine to cause stimulation, mania and violence became a public health issue in the United States after the student Eric Harris committed multiple murders and suicide on April 20, 1999 at Columbine High School in Littleton, Colorado (described in detail in [5]). Harris had been taking fluvoxamine for approximately one year. According to the manufacturer's report [45] to the Food and Drug Administration (FDA), Eric Harris had a "therapeutic blood level" of fluvoxamine at the time of his autopsy.

Eric Harris was born on April 9, 1981. He had recently reached the age of seventeen at the time he began to take fluvoxamine. In regard to drug testing for FDA approval, this put him one-year within in the pediatric category for FDA studies (under age 18). Eric had reached the age of eighteen just eleven days before he committed the violence on April 20, 1999. When it was revealed that Eric Harris had been

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taking fluvoxamine, psychiatric experts and the media gave little credence to any causal connection between fluvoxamine and violence [5]. Indeed, the FDA-approved label² for the drug seemed to give little or no indication that the drug could cause a person to commit catastrophic violence.

This report will use the case of Eric Harris and the Luvox label as an example of how critically important data can be obscured or omitted even, on a government-approved drug label.

2. The psychopharmacological nature of fluvoxamine

Fluvoxamine is a Selective Serotonin Reuptake Inhibitor (SSRI). In the United States, other drugs in this same class include Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine) and, more recently, Celexa (citalopram).

Unlike other SSRIs, at the time fluvoxamine was prescribed to Eric Harris, it had not been approved for depression in children or adults but only for obsessive-compulsive disorder. However, textbooks available in 1998 and 1999 without any apparent exceptions included fluvoxamine among the SSRI antidepressants (e.g., Silver et al. [42], for example in their table on p. 926). Fluvoxamine under different trade names was officially approved as an antidepressant in European countries, including Great Britain (*British National Formulary*, 1995).

When observations are made in clinical practice and in the scientific literature concerning the impact of SSRIs, including fluvoxamine, these drugs are typically treated as a single category or class of pharmacological agents. It is generally recognized that an adverse mental or behavioral reaction, such as mania or psychosis, that is observed in regard to one SSRI is likely to be found with the other SSRIs. Thus, Marangell et al. [32] in the American Psychiatric Press *Textbook of Psychiatry* observe, "All SSRIs have a similar spectrum of efficacy and a similar side-effect profile" (p. 1035). Similarly, Borg and Brodin [3] wrote that "... There seems to be little difference between the SSRIs with respect to frequency and severity of adverse effects" (p. 66). An extensive review compared SSRIs, including fluvoxamine, and concluded in its summary: "Overall, the adverse-effect profiles of the different SSRIs are comparable" [21, p. 938]. As a relevant exception, these authors note that fluvoxamine produced a higher rate of adverse reactions (see below).

Therefore, like most textbooks and reviews, this report draws upon data generated about the class of SSRI antidepressants, while also citing scientific literature specifically about fluvoxamine. It will be found that, to the extent that fluvoxamine does differ from other SSRIs in regard to adverse drug reactions (ADRs), it differs in the direction of *more* frequent and severe ADRs.

3. Understanding antidepressant-induced Central Nervous System (CNS) stimulation, mania and aggression

Mania is at one end of a stimulant continuum that often (but not always) begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progresses toward more severe agitation, aggression, and varying degrees of mania. When central nervous system stimulation becomes severe, convulsions may result.

²The term "label" here is used in the FDA sense, comprising not only the physical label attached to the drug but also the data sheet supplied with it; under European legislation the equivalent term is "packaging text".

While the Luvox label avoids any implication that the drug has a stimulant profile of adverse reactions, SSRI stimulation is well-recognized by informed experts who often refer to it by the euphemism “activation”. (e.g., discussion in [29, pp. 9–10]; see also [4–6] for detailed discussions of the stimulant profile of fluoxetine and other SSRI’s). This stimulant continuum will be documented in many reports in the following review.

3.1. Confirmation of antidepressant-induced mania in the DSM-IV

The American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (1994)* was published several years after the advent of SSRI antidepressants and makes clear that all antidepressants can cause mania. *The DSM-IV* makes multiple references to the fact that antidepressants can cause mania. It states, for example, that “. . . Symptoms like those seen in a Manic Episode may be due to the direct effects of antidepressant medication. . .” (1994, p. 329). Similarly, it observes that “Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication. . .” (1994, p. 331). References to antidepressant-induced mania and mood disorder can also be found elsewhere in the manual (e.g., at pp. 332 [note at bottom of table], 334, 336, 337, 351, 371, and 372).

3.2. The nature of a drug-induced manic episode

For simplicity, the following description of the nature of manic episodes will be drawn entirely from the *DSM-IV*. Of special interest to the case of Eric Harris, mania is characterized by “increased involvement in goal-directed activities” (p. 328). Therefore the individual, even when psychotic, does not lack the capacity to plan and carry out inappropriate or destructive aggressive actions. To the contrary, individuals undergoing mania often feel driven to carry out elaborate plans, however bizarre, destructive or doomed they may be.

It is remarkable that the official diagnostic manual provides so many references to antidepressant-induced mania and mood disorders.

The observations in the *DSM-IV* are made by individual committees of specialists in the particular area, in this case adverse effects of antidepressant drugs. The committees then attempt to reach a consensus among experts within the profession. Therefore, the capacity of antidepressants, including all the SSRIs, to cause mania cannot be considered anything but a generally accepted scientific consensus, a recognized fact, within the field.

This description of the nature of manic episodes, will for the sake of simplicity also be drawn entirely from the *American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Of special relevance to the case of Eric Harris is the fact that mania is characterized by “increased involvement in goal-directed activities” (p. 328). Therefore, the individual does not lack the capacity to plan and carry out inappropriate or destructive aggressive actions. On the contrary, individuals undergoing mania often feel driven to carry out elaborate plans, however bizarre, destructive, or doomed they may be.

Aggression is also specifically mentioned in the *DSM-IV* as a feature of manic behavior. It is noted that “antisocial behaviors may accompany the Manic Episode”, “Ethical concerns may be disregarded even by those who are typically very conscientious”. . . . “The person may become hostile and physically threatening to others” and “physically assaultive”, and “The mood may shift rapidly to anger or depression” (p. 330).

Antidepressant-induced aggressive behavior can occur without the individual meeting the complete diagnostic criteria for a manic episode that is not drug induced. Again according to the *DSM-IV* (1994, pp. 370 and 375), an individual can suffer from a Substance-Induced Mood Disorder with manic features “if the predominant mood is elevated, euphoric, or irritable”. In clinical practice and in the literature, antidepressants commonly cause one or more of these events – elevated, euphoric or irritable mood – qualifying the patient for a diagnosis of Substance-Induced Mood Disorder with Manic Features. Based on clinical experience and reports in the literature, an Antidepressant-Induced Mood Disorder often progresses from “irritability” to outright aggression. I have been a medical consultant in many cases in which individuals have developed an SSRI-induced Mood disorder with manic features and aggression (see www.Breggin.com for descriptions of cases).

The label and the promotional materials from Solvay give no indication that the drugs, by commonly inducing mania, can induce very destructive activities, including aggression and violence.

3.3. Confirmation of SSRI-induced manic-like episodes and aggressive behaviour in children and young people

As already noted, Eric Harris was in the pediatric age group when he began taking Luvox and had just reached adulthood when taking the drug at the time he perpetrated the school shootings. Therefore, this analysis will deal with scientific data concerning SSRI-induced abnormal behaviors in children and adults, beginning with children:

3.3.1. Clinical trials and epidemiological reports

A surprising number of clinical trials confirm that SSRIs, including fluvoxamine, cause a high rate of mania in children and young people. Fluvoxamine, according to the label for the drug as found in the *Physicians' Desk Reference (PDR)* [38], causes a 4% rate of mania in children under the age of 18 versus a 0% rate for similar children on placebo. This extremely important fact is not integrated into other sections of the label, such as under the *Pediatric Use* heading. Thus, the busy doctor searching for information specifically about children would not find it. Furthermore, the seriousness of this high rate and the danger associated with mania is not adequately emphasized.

A controlled clinical trial found that fluoxetine caused a 6% rate of mania in depressed children and youngsters age 7–17 [15]. The reactions were severe enough to cause the children to be dropped from the trials. By contrast, none of the depressed youngsters who took placebo developed mania. Therefore, the mania was caused by the fluoxetine rather than by the mental condition of the children.

University of Pittsburgh researchers took a retrospective look at medical charts of children and young men age 8–19 who had taken fluoxetine [25]. They found that an extraordinary 23% of fluoxetine-treated young people developed mania or “manic-like” symptoms. Another 19% of this group developed drug-induced hostility and aggression, including a “grinding anger with short temper and increasing oppositionalism”.

A team of Yale doctors found that 50% of children and young people aged 8–16 developed two or more abnormal behavioral reactions to fluoxetine, including aggression, loss of impulse control, agitation, and manic-like symptoms [39]. The effects lasted until the fluoxetine was stopped.

Another research study from Yale described a number of youngsters (6 of 42 or 14% in their cohort) who became aggressive and even violent while taking fluoxetine [27]. The authors hypothesized that fluoxetine was causing the aggressive behavior by means of “drug-induced activation” (stimulation) or “a specific serotonergic-mediated effect on the regulation of aggression”.

This report by King et al. from Yale is particularly relevant because it provides a direct window into the development of the kind of mentality that led Eric Harris to become a school shooter. A child described in their report actually developed nightmares about becoming a school shooter and then began to lose track of “reality” concerning these events. In reading the relevant excerpt from their report, it is useful to bear in mind that the child’s reaction occurred long before any of the well-known school shootings took place and therefore was not inspired by them:

Thirty-eight days after beginning the protocol, F. experienced a violent nightmare about killing his classmates until he himself was shot. He awakened from it only with difficulty, and the dream continued to feel “very real”. He reported having had several days of increasingly vivid “bad dreams” before this episode; these included images of killing himself and his parents dying. When he was seen later that day he was agitated and anxious, refused to go to school, and reported marked suicidal ideation that made him feel unsafe at home as well (p. 180).

The child was hospitalized for three days and then for 17 days. He gradually improved. Then three weeks after his last hospitalization, his local physician – not one of these investigators – decided to put him back on fluoxetine. He became acutely suicidal until the fluoxetine was stopped a second time.

This individual report is important for a variety of reasons:

- (1) It took place in a controlled clinical trial. Therefore, the investigators did not know if the child was taking fluoxetine at the time that these abnormal reactions erupted.
- (2) Entirely new symptoms related to violence developed on the drug (this stage is called challenge).
- (3) The symptoms terminated after stopping the drug (called dechallenge).
- (4) Some of the symptoms resumed on starting the drug again (called rechallenge).
- (5) The symptoms cleared for a second time after the drug was again stopped, demonstrating dechallenge for a second time.³

Of note, this child developed agitation and anxiety, two symptoms produced by fluvoxamine at a high rate.

Nevertheless, the label for Luvox gives no hint that SSRI’s have been linked so frequently to manic-like behaviour, suicidality and violence.

3.3.2. Examples of case reports

There are many case reports of SSRI-induced mania in the literature. Here are two examples involving aggressive behavior.

A single case study of a 17-year-old youngster taking fluvoxamine [43] provides a window into what happened to Eric Harris. The youth in this case was mildly retarded when he became depressed and anxious, and was started on a 50 mg dose of fluvoxamine. After a single dose, he developed “increasing agitation and insomnia”. Then, “In the next 24 hours, he displayed auditory and visual hallucinations, a fearful mood, and paranoid delusions involving statements that ‘the devil will get me’”. He required hospitalization and was treated with an antipsychotic drug. The authors believe that fluvoxamine caused the acute psychosis.

In another case report, Bastani et al. [1] describe a person who had previously been treated for OCD with paroxetine. On fluvoxamine she became suicidal and had to be hospitalized. In the hospital her

³The process of challenge-dechallenge-rechallenge is discussed in [4].

fluvoxamine dose was increased from 50 mg per day to 150 mg per day whereupon her condition worsened and she began to experience auditory hallucinations. The fluvoxamine was discontinued and she recovered within twenty-four hours, confirming that the fluvoxamine had caused the depression and psychosis.

In another single case study, this time involving paroxetine, Oldroyd [36] describes the case of a sixteen-year-old who became manic, including “angry outbursts”, after three weeks on the drug.

SSRI-induced mania and psychosis are becoming such recognized entities that animal research is being conducted with the aim of unraveling their biochemical mechanisms [48].

3.4. Confirmation of SSRI-Induced manic-like episodes and aggressive behaviour in adults

The previous section of this paper focused on children because of their special vulnerability and because Eric Harris was just turning 17 at the time he began to take fluvoxamine. This section will deal with adults.

3.4.1. Epidemiological and clinical trial data

Ebert et al. [14] attempted to develop a rate for severe mental aberrations caused by fluvoxamine. They carried out a prospective study of 200 inpatients over a total of 8200 treatment days on fluvoxamine. Fourteen patients (17%) developed “hypomania according to *DSM-IV* criteria”. More ominously, three patients (1.5%) “developed a reversible change of mental status with insomnia, agitation, confusion and incoherent thoughts”. This occurred in the absence of more frank toxicity.

These three patients became potentially violent and suicidal. One, a 35-year old man, developed “agitation” and “restless legs” that progressed to “insomnia, confusion with acoustic hallucinations and paranoid ideas”. He recovered after fluvoxamine was stopped. Another patient, a 38-year-old man, developed “agitation and insomnia” that progressed to “aggressiveness, incoherent thoughts, confusion, acoustic hallucinations and paranoid ideas”. He also cleared up when fluvoxamine was stopped. The third patient, another 35-year-old man, developed “insomnia” and then became “agitated with restless legs, and severely depressed with suicidal ideas”. He was “incoherent with confusion and paranoid ideas”. He too recovered in a few days after stopping fluvoxamine.

The authors summarize that the syndrome consists of “insomnia, confusion, incoherent thoughts, agitation, hallucinations and paranoid ideas” and that it “should be recognized”. They observe that it is especially frequent in combination with other drugs and describe it as “rare and reversible”. But were these severe reactions actually “rare”? According to Ebert et al.’s own data, these reactions were extremely frequent. Adding up the 14 hypomanic patients and the 3 psychotic and aggressive patients, there were at least 17 severe psychiatric reactions among 200 patients, pointing to an extraordinary rate of 8.5%. (According to the FDA, a rate of 1% for an adverse drug reaction is defined as “frequent” or “common”.)

Peyre et al. [37] reviewed the histories of 189 patients treated with fluvoxamine and found a rate of 2.5% for “manic switches”, that is, the development of mania during treatment for major depression. The rate of 2.5% is two and one-half times higher than that reported for adults in the labelling text for fluvoxamine.

Howland [23], from the University of Pittsburgh School of Medicine, found 11 cases of SSRI-induced mania among approximately 184 patients treated at the university clinic and hospital. Several observations from the Howland report are especially relevant to this case.

- (1) Four of the mania cases involved paroxetine and sertraline. Fluvoxamine is similar to paroxetine and sertraline in being a short-acting SSRI.
- (2) The 11 cases occurred in a population of 184 patients, indicating a very high rate of 6% for drug-induced mania from antidepressants.
- (3) The episodes were “generally quite severe” (p. 426).
- (4) Eight of the 11 patients became psychotic and 4 were so agitated that they had to be put in seclusion, even though they were probably receiving additional medication to control their mania.

Sertraline is especially similar to fluvoxamine in regard to its relatively short duration of action. Healy [20] recently conducted a randomized double-blind crossover study comparing the effects of sertraline to those of a non-SSRI antidepressant (reboxetine) in a group of health volunteers. Many of the 20 individuals developed adverse mental and neurological effects while taking the sertraline and two became severely disturbed. Case A, a 30-year-old woman, became “withdrawn, was ruminating over impulsive, disinhibited things she had done, was tearful and not herself”. In addition, “. . . Her diary records impulsiveness, irritability, over-sensitivity as well as marked suspicion”. In a “trance-like” state she became obsessed with killing herself and almost threw herself beneath a car or train. Case B, an otherwise peaceful 28-year-old woman, experienced severe road rage and actually grabbed a teenage boy and threatened to “deck him”. On the SSRI, she felt “aggressive and fearless”. While emotionally disturbed and out-of-control (disinhibited), the two individuals nonetheless felt and appeared emotionally “blunted”.

The mixture of apathy and disinhibited aggressiveness found in Healy’s study is confirmed elsewhere, specifically in regard to fluvoxamine. Hoehn-Saric et al. [22] reported on “Apathy and Indifference in Patients on Fluvoxamine and Fluoxetine”. They describe “apathy, indifference, loss of initiative, or disinhibition (with or without sedation or hypomania)” observed in five patients.

3.4.2. Examples of case reports

Many case reports in the scientific literature concern the capacity of SSRIs to cause mania, often in association with irritability and aggression. Christensen [9], for example, reported on the case of a 32-year-old man who developed his first manic episode while taking paroxetine. He became psychotic and “threatened his parents with physical harm” (p. 1400).

Some case reports specifically cite fluvoxamine as the causative agent (e.g., [8,13,35]). Dorevitch et al. [13] describe three cases of fluvoxamine-induced mania. Each case was recognized quickly and the drug was reduced in dose or stopped so that potentially disastrous outcomes were avoided. Had the patients been more secretive or the monitoring less effective, the results could have been tragic. In the first case, “the patient was hospitalized in a full-blown manic state, which included euphoric mood, grandiosity, loose association, and auditory hallucinations”. In the second case, the potential for violence is more apparent. The patient “became euphoric, displayed increased energy, and began cleaning the ward, singing, and kissing other patients. In addition, he was very irritable and anxious, exhibiting psychomotor agitation and describing fears that people were out to kill him”. In the third case, “he experienced motor hyperactivity; a decreased need for sleep; an increased ability to concentrate; and excessive social, sexual, and artistic prowess. Examination revealed an euphoric mood, grandiosity, logorrhea (excessive talking), and a very argumentative disposition”. Manic patients who are “argumentative” can become very aggressive when thwarted. Dorevitch et al. make the point that these patients became manic on fluvoxamine but not on other antidepressants (p. 1456).

In an article entitled “Violent Acts Associated with Fluvoxamine”, Okada and Okajima [35] describe three cases of aggressive and violent behavior induced by fluvoxamine. On fluvoxamine 150 mg/day day,

a 32-year-old woman became “irritable and aggressive, and she expressed impulsive violence during her disagreements with her husband and mother”. She improved after her fluvoxamine was reduced (but not stopped). The addition of fluoxetine did not worsen her condition. The authors stress this point later in the report when they point out that in one case “fluoxetine [fluoxetine] did not elicit the aggressive behavior that treatment with fluvoxamine did”. A 29-year-old woman on 150 mg/day of fluvoxamine became nervous and irritable and then “impulsively violent” on fluvoxamine and was admitted to a psychiatric hospital. She improved with discontinuation of the drug and treatment with other medications. A 28-year-old woman on 150 mg/day of fluvoxamine “exhibited signs of irritability and aggressive behavior, expressing violence toward her mother” on fluvoxamine. She improved when her fluvoxamine was stopped and other medications instituted. They concluded, “However, we wish to draw attention to the emergence of paradoxical effects such as impulsivity and aggressive behaviour induced by fluvoxamine”. *This report alone should have led to a specific postmarketing upgrade of the FDA-approved label citing reported cases of violence without mania caused by fluvoxamine.*

4. Inadequacies of the Luvox labelling with regard to mania

The Luvox label in the USA makes the following statement:

In a ten week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions compared to none of the 63 placebo patients.

Why would the United States FDA approve a drug for children that causes such severe adverse reactions at such a high rate in children? The answer may lie in the following statement in the label under the heading *Pediatric Use*: “The adverse event profile observed in that [pediatric] study was generally similar to that observed in adult studies with fluvoxamine (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION)”. If the FDA was convinced by the drug company that the adverse reaction profiles for children and adults were similar, then the FDA might have failed to grasp the necessity of requiring the drug company to conduct extensive clinical trials on children (see ahead for further discussion).

How similar in fact was the adverse event profile for children and adults? The rate of mania in the adult studies was 1% and in the child studies 4%. A 400% higher rate of mania – one of the most potentially dangerous psychiatric adverse reactions – is in fact a very noteworthy difference.

The 4% rate of drug-induced mania in the pediatric population is found in the Precautions section and not in any later references to children in the label. A doctor who turned directly to the *Pediatric Use* section would be reassured that there are *no* special dangers in regard to giving the drug to children, whereas there is in reality a documented fourfold increase in the risk of drug-induced mania. The cross-reference (see above) in the *Pediatric Use* section does not lead the reader back to the 4% mania rate.

In yet another section, headed *Other Adverse Events in OCD Pediatric Population*, additional information is given about the 57 children treated with fluvoxamine (PDR, 1998, p. 2893). The label repeats the earlier assertion that there is no great difference between fluvoxamine effects in adults and children: “In pediatric patients ($N = 57$) treated with fluvoxamine tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2”. The label then goes on to say that a number of adverse reactions not listed in Table 2 did in fact occur in “two or more of the pediatric patients and were more frequent with [fluvoxamine] than with placebo”. These reactions include several related to a deteriorating psychiatric condition with the potential for over-stimulation, mania and violence: abnormal thinking, emotional lability, hyperkinesia, and manic reaction.

As in the *Pediatric Use* section, there is no reference to the *Precautions* section with its all-important disclosure of an extraordinary 4% rate of mania in the drug-treated children compared to 0% mania in the control group of similar children.

By scattering these observations in two different places and by utterly omitting them from the most obvious place, *Pediatric Use*, the label effectively minimizes the true dangers of psychiatric adverse reactions in the pediatric population.

Meanwhile, the actual rates for mania as reported from studies of routine clinical practice (reviewed above) showed a much higher frequency of occurrence for mania in children and adults than indicated in the label. These findings were not incorporated into a revised Luvox label.

5. Failure to disclose the stimulant profile

Like other SSRI's, fluvoxamine has a dangerous stimulant profile. Mania is simply the extreme manifestation of this profile. Unfortunately, the stimulant profile is not readily apparent in the Luvox labelling text.

As already noted, mania is described in the *Precautions* section. It also appears as "manic reaction" in the section headed *Nervous System* under "Adverse reactions" (PDR, 1998, p. 2894) where it is listed as one of the frequently reported reactions. As we have noted above, in FDA-parlance "frequent" means 1% or more.

Also under the heading *Nervous System* a variety of other stimulant or stimulant-like effects are described. Under the *Frequent* category, the following are listed: hyperkinesis, manic reaction, and psychotic reaction. Under the *Infrequent* category, the following typical stimulant psychiatric effects are listed: hostility, emotional lability, euphoria, psychosis, hallucination, delusion, depersonalization, and paranoid reaction. Also in this *Infrequent* category, several typical stimulant neurological effects are cited, including convulsion, delirium, twitching, akathisia, dystonia, and dyskinesia. I have reorganized the above list to make more obvious the connection between many of the stimulant-like adverse reactions. Not all are specifically stimulant in nature, but in fact all of these can be found in lists of adverse effects of stimulants.

Seizures are noted to occur in 0.2% of fluoxetine-treated patients, sufficient to require the observation to find a place in the *Precautions* section. Seizures are an expression of extreme CNS over-stimulation.

In Table 1 in the Luvox labelling ("Adverse Events Associated with Discontinuation of Treatment in OCD and Depression Populations") under the heading *Nervous System*, stimulant adverse reactions dominate the profile. These stimulant reactions include insomnia (4%), nervousness (2%), agitation (2%), anxiety (1%) and dry mouth (1%). All of these are typical stimulant effects except for somnolence (4%). Typical of the SSRIs, while the dominant profile is stimulatory, somnolence can also result.

In Table 2 ("Treatment-Emergent Adverse Event Incidence Rates by Body System in Adult OCD and Depression Populations Combined") the stimulant profile is further confirmed. Under *Cardiovascular*, the single adverse reaction cited is palpitations (3%). Palpitations are consistent with over-stimulation. Under the heading *Nervous System* in the chart, the pattern is clear: there is a listing of insomnia (21%), dry mouth (14%), nervousness (12%), tremor (5%), anxiety (5%), hypertonia (2%), agitation (2%) and CNS stimulation (2%). Several other listed reactions, including decreased libido, depression, palpitations and sweating are also commonly caused by drugs with stimulant effects. In the label, the drug company states that causation has not been proven in regard to these reports. However, the data demonstrate a stimulant profile, confirming the likelihood that the events are indeed drug related.

The tables in the Luvox label list a 2% rate of agitation compared to 1% for placebo, and this figure has been used in advertisements and promotion. This unlikely result is created in part by dividing or fragmenting agitation into a variety of other symptoms, so as to reduce the rate for any given one. For example, several categories in Table 2 of the label can be viewed as aspects of agitation, including nervousness (12%), anxiety (5%) and CNS stimulation (2%). Combining agitation (2%), nervousness, anxiety and CNS stimulation into one category called “stimulation” results in a total figure of 21% instead of 2%. Again, it is more informative to speak of an overall stimulant profile rather than to present the individual expressions of stimulation as if they were unrelated.

In advertisements published in professional journals, the company produced additional data that were omitted from the labelling for the drug. Luvox advertisements appearing in the *American Journal of Psychiatry* in 1999 note the following rates in children comparing fluvoxamine and placebo:

	Fluvoxamine	Placebo
Agitation	12%	3%
Hyperkinesia	12%	3%
Depression	5%	0%

These rates are not given in the Luvox label. The label merely states that the rates are 5% or more and twice those recorded with placebo. In the *Adverse Reactions* section it is stated that “In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhoea, flatulence, hyperkinesia, rash*”. The “above rule” refers to a parenthetical statement, “(incidence of 5% or greater and at least twice that for placebo)”.

An overall rate of 12% is far more ominous than a rate of 5% or more. A rate of 5% for depression is also especially striking when compared to 0% for placebo. Yet these data, while presented in Luvox advertisements is not to be found in the Luvox label.

Combining these data with others in the label, including the 4% rate of mania in the pediatric trials, the stimulant profile of fluvoxamine appears to be even more extreme in children than in adults. The label seems to indicate that the rates in Table 2, unless otherwise indicated, are similar for children and adults. Those “similar” rates from Table 2 relate to nervousness (12%), anxiety (5%) and CNS stimulation (2%). These rates can however be added to elevated rates for stimulant-like effects in children, i.e., agitation (12%) and hyperkinesia (12%). The total for all stimulant-like effects in children then becomes a huge 43%.

Even taking into account the potential overlap of more than one stimulant ADR in a particular individual, the cumulative rate of stimulation in children will remain very high. It will continue to exceed greatly the rate of stimulation in adults obtained by the same methods of calculation as in children (43% versus 21%).

In short, by scattering the stimulant profile data over various sections of the label, by leaving some critical data out of the text, and by never acknowledging the existence of the stimulant profile, Solvay Pharmaceuticals, Inc. effectively created a label that obscures or omits the most important dangers of Luvox. Clinicians know that stimulant drugs and stimulant-like drugs cause many serious adverse psychiatric reactions, including mania with paranoia and violence; but clinicians are not likely to gather from this label that fluvoxamine has a primarily stimulant profile of adverse reactions.

The label for Luvox should have contained a special table for children. As an example, I have constructed Table 1: Rates for Fluvoxamine-induced psychiatric ADRs in children. A table such as this would bring together the data scattered throughout the existing label with additional data found in the advertisements. It would provide much better information for physicians and consumers in evaluating

Table 1
Rates for Luvox-induced psychiatric ADRs in children*

ADR	Luvox	Placebo
A: Rates exceeding those found in adults		
Mania	4%	0%
Agitation	12%	3%
Depression	5%	0%
Abnormal thinking	4% at least	Less than 4%
Emotional lability	4% at least	Less than 4%
Hyperkinesia	12%	3%
B: Rates similar to those found in adults		
Asthenia	14%	6%
Somnolence	22%	8%
Insomnia	21%	10%
Nervousness	14%	10%
Tremor	11%	6%
Anxiety	5%	1%
CNS stimulation	2%	1%
Taste perversion	3%	1%
Decreased libido	2%	1%
Abnormal ejaculation	8%	1%
Impotence	2%	1%
Anorgasmia	2%	0%
Hypertonia	2%	1%

*This table was constructed based on available data reported by Solvay Pharmaceuticals. It does not reflect higher rates reported in the scientific literature for many of these ADRs. It provides one example of the type of table needed in the Luvox label in order to make the adverse reaction profile for children more readily understandable.

the risk/benefit ratio. The current label fails to bring this critical information together in a readily understandable fashion.

Doctors and consumers need to know that children taking fluvoxamine are exposed, even in very short-term drug-company sponsored trials, to very high rates of drug-induced depression, agitation, and hyperkinesia.

Furthermore, as I have described in various books [4–6] and numerous forensic reports (www.breggin.com), the combination of agitation and depression adds up to an “agitated depression”. *Agitated depression is one of the most dangerous conditions in psychiatry and is frequently the specific disorder associated with drug-induced violence and murder.* The combination of fluvoxamine-induced agitation and depression, even without mania, could account for Eric Harris’s disturbed mental state.

6. Conducting very small paediatric trials

According to the Luvox label only 57 children received fluvoxamine in the pediatric trials for OCD. The trials lasted 10 weeks but the drug would be used for months and even years.

Food and Drug Administration [16] officials and other experts have become increasingly concerned about the inadequacy of the relatively small trials used for drug approval. In that context, they defined “small” as comprising some 3,000–4,000 subjects, very different from the 57 involved in the pediatric trials for fluvoxamine.

Writing in the *Journal of the American Medical Association* on behalf of the FDA, David Kessler declared in 1993 that:

Even the large, well-designed clinical trials that are conducted to gain premarket approval cannot uncover every problem that can come to light once a product is widely used. . . . If an adverse event occurs in perhaps one in 5000 or even in 1000 users, it could be missed in clinical trials but pose a serious safety problem when release to the market.

Writing in *Goodman and Gilman's Pharmacologic Basis of Therapeutics*, Alan Nies [34] makes a similar point:

Since only a few thousand patients are exposed to experimental drugs in more or less controlled and well-defined circumstances during drug development, adverse drug effects that occur as frequently as 1/1,000 may not be detected prior to marketing. Postmarketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects (p. 77).

Thomas Laughren, the Group Leader for Psychiatric Drugs in the FDA reviewed in 1992 the standards and limitations or problems inherent in using clinical trials to determine adverse drug effects. After describing the small size and short duration of the premarketing clinical trials, Laughren concluded:

It is important to acknowledge this limitation of the typical development programs and to recognize that careful postmarketing surveillance is the most feasible method for detecting the more infrequent adverse events occurring with the use of a new drug.

Unfortunately, the vast amount of postmarketing data found in the literature has not influenced the manufacturer of fluvoxamine to increase the warnings about fluvoxamine-induced abnormal behavior including mania and violence.

Given that 1,000 or more patients in clinical trials are inadequate to the task of detecting adverse drug reactions, how and why did the FDA approve fluvoxamine for children on the basis of a mere 57 child subjects in the clinical trials? The label indicates that the drug company took the position that the safety profiles for children and adults were similar. As a result of this claim, the FDA probably failed to demand more rigorous testing in children.

However, the safety profiles for children and adults were dissimilar in significant ways. The rate for mania was four-times greater in the child group than among the adults (4% versus 1%). The rate for agitation was six-times higher in the child group (12% versus 2%). The rate for depression was at least two and a half times higher for the child group (5% versus 2%) and, as earlier discussed, was probably much higher than that. Finally, the rate for hyperkinesia in the children was at least twelve times higher (12%) in the child group than the adult group (no figures were provided but the rate was probably below 1%).

Based on these huge discrepancies involving dangerous psychiatric ADRs of great importance to the mental health of children, the pediatric and adult ADR profiles were very dissimilar. The FDA should have required extensive testing on children in order to more accurately estimate the frequency and severity of ADRs in children.

7. Spontaneous Reports to the FDA

The FDA's Spontaneous Reporting System (MEDWatch) is one of the most important methods for detecting emerging adverse drug reactions after a drug has been approved and put onto the market. Some pharmaceutical companies have tried to minimize the importance of this reporting system in establishing causality. However, the FDA uses it to establish causality, and has drawn on its data to take regulatory actions such as upgrading labels and removing drugs from the market [4].

Making use of procedures established under the *Freedom of Information* legislation, I obtained the FDA's complete file of adverse reactions reported to the FDA from 11.3.97 through 10.13.99. The total number of reports was 441 (with a few duplicates). While no one case report can necessarily be used to determinate causation, overall patterns can be critical to understanding the kind of harmful effects that the drug tends to produce. Therefore, I evaluated the kinds of ADRs reported to the FDA by dividing the reports of adverse psychiatric events into three categories.

I located 65 reports that could be coded into the category of Stimulation. These reactions varied along a continuum from agitation and anxiety to mania. In the category of Depression, Suicide, Self-Injury, and Apathy, I coded 34 reports, nine of which overlapped with the stimulant category (26%). Under the category Anger, Aggression and Violence, I coded 10 cases, five of which overlapped with the stimulant category (50%). The high number of stimulant ADRs and the large overlap of Anger, Aggression and Violence ADRs with stimulation (50%) supports my analysis that the manufacturer of Luvox has failed to communicate the stimulant-like dangerous effects associated with fluvoxamine.

Similarly, the Committee on Safety of Medicines of Great Britain [10] found a significant numbers of reports from physicians concerning fluvoxamine-induced tremor, agitation, anxiety, and convulsions, all of which fit a stimulant profile. They issued a warning not to give fluvoxamine to patients with a history of epilepsy.

8. Problems associated with shorter half-life

According to the manufacturer, Luvox has a half-life of 15.6 hours. When a half-life is less than 24 hours, inter-dose withdrawal is a distinct possibility as the blood levels of the drug fall below half their peak before the passage of 24 hours. Particularly when the individual awakens in the morning, perhaps as much as 24 hours after the last dose, the blood level can be considerably reduced, leading to morning withdrawal symptoms.

Drug blood levels that rise and fall in rapid cycles will cause rapidly fluctuating biochemical imbalances in the brain. The brain simply cannot adjust to such rapid changes. In regard to a psychoactive substance, this will cause unstable moods. In adolescents such as Eric Harris, who might normally have somewhat labile moods, the problem is likely to be exacerbated.

Nowhere in the label however does Solvay Pharmaceuticals, Inc. warn about or even mention the hazards associated with a shorter half-life. The drug company does not describe any withdrawal risk and does not mention the possibility of inter-dose withdrawal occurring between doses with this short-acting drug.

Although the company has given no recognition to the problem, the dangers of withdrawal symptoms from short-acting SSRIs has reached headline proportions. The front page of the October 1999 issue of *Clinical Psychiatry News* reports on "Discontinuation Symptoms Linked to SSRI's Half-Life" (Sherman, 1999). In their 1997 review, Zajecka et al. [49] stated, "The short half-life SSRIs appear to be more commonly associated with acute discontinuation symptoms compared with longer half-life agents". In a section on fluvoxamine, these same authors described studies that have demonstrated high rates of withdrawal reactions including some "associated with significant impaired function" (p. 294).

Withdrawal, like toxicity, can involve increased irritability and aggression (e.g., [2,12,40]). These effects can confuse patients, leading them to believe that they have a "need" for the medication when they are actually undergoing withdrawal reactions between doses or when they cease to take the product.

I was recently the medical expert in a Paxil withdrawal suit filed in San Jose, California on August 19, 2000 as a "Complaint for Injunctive Relief Under Business and Professions Code" (*Nguyen & Farber*,

plaintiffs vs. SmithKline Beecham Corporation, Case No: CV791998). The manufacturer of Paxil, Glaxo SmithKline was accused of negligence in not recognizing the dangers of withdrawal from Paxil. Paxil, like Luvox, is a short-acting SSRI. The drug company and the plaintiffs subsequently “resolved” the suit and the drug company upgraded its label to include a section of withdrawal symptoms. The new Paxil label lists “agitation” and “anxiety” as possible withdrawal effects. These are, of course, relevant to Eric Harris’s experience. Yet Luvox, a very similar drug, has not placed similar information about withdrawal in its label.

9. Evidence of increased risks as compared to other SSRI’s

Evidence is accumulating that fluvoxamine is more dangerous than other SSRIs. An epidemiological study in Great Britain advanced evidence “. . . that fluvoxamine compares unfavourably with fluoxetine, sertraline and paroxetine, both in terms of reported effectiveness and the incidence of adverse events” [31, p. 235]. These data were derived from the Prescription-Event Monitoring (PEM) system. The category of “malaise/lassitude” was the most frequent psychiatric ADR reported for fluvoxamine. Numerous cases of hypomania and mania were also reported for this drug.

Similarly, Grimsley and Jann [21] carried out a large-scale review of published clinical trials and concluded that, overall, SSRIs have similar patterns of adverse effects. However, they cite an important exception: fluvoxamine has a less favourable profile for adverse effects, including some of the more serious ones that have been cited in this report:

“When pooled data from several controlled studies involving 22 patients were used, the frequencies of adverse effects reported with fluvoxamine treatment were much higher: nausea and vomiting (37%), sedation (26%), dry mouth (26%), headache (22%), constipation (18%), agitation (16%), insomnia (15%), dizziness (14%), tremor (11%), and sweating (11%)” (p. 937).”

Several of the above adverse reactions (agitation, insomnia, tremor and sweating) are typical stimulant qualities. As already documented, they can be warning signs of impending violence and mania.

Interestingly, the authors cite a study [24] pointing to electrical brain wave studies that “predicted that fluvoxamine possessed predominantly stimulant-type properties” (p. 938). This indicates that there were early warnings that fluvoxamine would turn out to have particularly stimulating effects.

10. Conclusion

An examination of the FDA-approved label for Luvox (fluvoxamine) illustrates how critical information about adverse effects can be buried, scattered, or omitted, even from an officially approved text, making a medication seem much more safe than it really is. The risks associated with prescribing fluvoxamine to children are scattered throughout the Luvox label in four different sections. They are not compiled or pulled together in the text. It would take hours for a physician or other health care provider to pore over this label in order to extract the information on children. In addition, the safety profile for children is based on a mere 57 children treated with fluvoxamine in controlled clinical trials.

In the case of Luvox, the basic stimulant profile of adverse reactions is difficult to ascertain from reading through the label. Furthermore, children are described as incurring similar risks to adults when in fact children are much more at risk for serious psychiatric adverse drug reactions to fluvoxamine, including mania, agitation, hyperactivity and depression. In addition, a growing literature on the severity and frequency of fluvoxamine-induced mania, including the production of aggression and violence, has been omitted from the label.

Finally, the hazards associated with fluvoxamine's short half-life, especially withdrawal and inter-dose withdrawal, are unmentioned, despite a growing literature on the subject of SSRI withdrawal symptoms.

Health professionals need to be aware that reading of a drug label will not necessarily provide them with all of the most important information that they need in order to evaluate the risk/benefit ratio of the medication. The labels are often organized in a manner that makes it difficult or impossible to make an overall assessment of the more serious risks. As in the case of the Luvox (fluvoxamine) label in the United States, even a thorough reading may not provide the necessary information if the company has failed to test adequately for adverse drug reactions, if the label obscures the information contained in it, omits data otherwise available to the company, or fails to keep pace with the scientific literature.

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