DrugSafetyResearch

Special Report

Antidepressant Drugs and Suicidal/Aggressive Behaviors

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Executive Summary

Antidepressant Drugs and Suicidal/Aggressive Behaviors

This is a study of adverse event reports of suicidal and aggressive behaviors in children and adults associated with the six most commonly prescribed antidepressant drugs. The target drugs are: sertraline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), amfebutamone (Wellbutrin, bupropion), and venlafaxine (Effexor).

Key Findings:

- Reports of death, disability and other serious events associated with six antidepressant drugs increased by 41% from November 1997 through December 2002. In that interval, the Food and Drug Administration (FDA) received 44,026 reports about all types of adverse events that identified as a suspect one of the six most commonly prescribed antidepressant drugs.

- Overall, the proportion of adverse events reported in children less than 18 years of age was about the same as expected from the medical use of antidepressants in this population group. Children accounted for 5.2% of all reported adverse events and 4.8% of all doctors' office visits in which antidepressant drugs were mentioned.

- Among all ages, the six target drugs were suspected of triggering 3,309 episodes of suicide, attempted suicide, or hostile, violent or other abnormal behaviors. A total of 353 cases were in children under 18 years of age.

- Suicidal/aggressive behaviors were reported in children at more than twice the expected rate given the drugs' medical use in this age group. Suicidal/aggressive behaviors were also reported more frequently in children when compared to other types of adverse events, which were reported in similar proportions in both adults and children.

- An additional 544 cases involved the suspicion that an antidepressant drug was linked to another disorder of mood, potentially dangerous feelings of euphoria, grandiosity or mania. Of these cases, 72 were reported in children. Like suicidal/aggressive behaviors, mania/euphoria was also reported more than twice as frequently as expected in children.

- Taken together, suicidal/aggressive behaviors and mania/euphoria describe potentially dangerous changes in mood or personality suspected of being associated with the six target drugs. In children, such reports accounted for 24% of all reported adverse events.

- No specific drug emerged as unusually toxic or especially safe. The percentage of adverse events reported for each target drug was similar to its medical use, based on the results of a companion study.

- The FDA or the manufacturer has previously warned doctors that clinical trials in children showed unexpectedly high numbers of suicidal or hostile behaviors for two of the target drugs, paroxetine (Paxil) and venlafaxine (Effexor). However, these data showed similar results for the two drugs with warnings about risks in children, compared to those without such warnings.

Conclusions

The higher than expected numbers of suicidal and aggressive behaviors observed in some clinical trials of antidepressants in children also can be seen in spontaneous adverse event data, and add substantial additional evidence to the case. The data show that suicidal/aggressive behaviors are reported in both adults and children, but more than twice as often in children. Finally, while two drugs now carry warnings about this risk, similar risks were reported for the four drugs without warnings. Findings from these adverse event data should be interpreted in context with other scientific evidence, and with consideration of the limitations outlined below.

Limitations

Reporting of drug adverse events in the U.S. is entirely voluntary for consumers and health care professionals, and only a small fraction of all events are ever reported to the FDA. Drug manufacturers must report all serious adverse events of which they become aware (typically from consumers or health care professionals) but are not required to monitor safety systematically. The reporting of an adverse event typically establishes that an observer suspected the drug was responsible, but does not in itself establish that the drug caused the event reported. Variation in adverse event reporting rates can occur for reasons unrelated to the safety of the target drug.

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Contents

Section 1: Introduction and Background

The Issue

On June 10, 2003, the British drug regulatory agency warned doctors and patients that paroxetine "must not be used for the treatment of children." [1] In a press statement, British drug regulators said "New data, received within the last two weeks, has been evaluated and considered….It shows that there is an increase in the rate of self harm and potential suicidal behavior when Seroxat [paroxetine] is used for depressive illness."

Apparently reacting to the British action, the U.S. Food and Drug Administration (FDA) issued its own safety alert nine days later.[2] The statement was, however, filled with uncertainty and qualifications. It identified the same issue as "possible safety concerns" and urged patients "to avoid sudden discontinuation of paroxetine." But the agency did state "FDA is recommending that Paxil not be used in children and adolescents for the treatment of MDD [major depressive disorder]." But as to suicidal and self injurious behavior, the agency said that it was "reviewing reports of a possible increased risk." In fact, however, both the British and U.S drug agencies had received copies of the same study from paroxetine's manufactuer, GlaxoSmithKline, in mid-May and were reacting differently to the exact same evidence. [3]

In August 2003 Wyeth Pharmaceuticals issued a similar public warning for its antidepressant, venlafaxine. [4] In a letter to doctors and other health care professionals, Wyeth revealed "increased reports among patients on Effexor [venlafaxine] XR vs. placebo, of hostility and suicide-related adverse events, such as suicidal ideation and self-harm." The company said that venlafaxine (and its extended release form, Effexor XR) "have not been and are not now recommended for use in pediatric patients." While such manufacturer warning letters are typically issued at the request of and in coordination with the FDA, the companies have the legal authority and may act independently to warn of newly discovered drug risks. The Wyeth analysis and warning differs from that for paroxetine in another subtle but potentially important regard. Wyeth, in analyzing the data, combined "hostility" and related aggressive behaviors with suicidal behaviors while GlaxoSmithKline's analysis was limited to suicidal behaviors.

As a result of Wyeth's action, two of the six best-selling antidepressant drugs had warnings against use in children. But what about the other antidepressants, in particular the other four major drugs, sertraline, fluoxetine, amfebutamone and citalopram?

The FDA answered this question, in part, on October 27, 2003, when it issued an unusual public health advisory, "Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD)." [5] What was unusual about the advisory was that the FDA was unable to make up its mind about the subject. On one hand it said, "The data do not clearly establish a relationship between the use of these drugs and increased suicidal thoughts or actions by pediatric patients." On the other hand, it said "it is not possible at this point to rule out increased risk." But still the agency issued the warning "to alert physicians to reports of suicidal

thinking (and suicidal attempts)." If the agency found itself unable or unwilling to interpret the risk it is not clear how much a vague press release was going to assist physicians in assessing this newly disclosed risk.

While the FDA was unable to decide about the other antidepressants, the British once again took action. On December 10, 2003, the British drug regulatory agency declared that six antidepressant drugs "are not suitable" to treat depression in children. [6] The British noted that other drugs had excesses of suicide-related behaviors, specifically sertraline, fluoxetine, and venlafaxine. [7] Even if there was ambiguity in the risks the British agency was also concerned that efficacy had not been demonstrated in children for depression for any drug except fluoxetine, which it continued to allow for use in children for this purpose.

In January 2004 the FDA revealed that it had detected "a signal of increased risk" in four of the seven drugs studied, and possibly in a fifth.[3] But the agency said it was going to re-request and analyze the data still again.

Nevertheless, all this activity was based on clinical trials data submitted to the U.S. and British regulatory agencies. This study addresses the same issues using the second major source of drug safety data, reported adverse events.

The Data

This is a study of suicidal, hostile or aggressive behaviors in children who were taking one of the six most commonly prescribed antidepressant drugs. The core data are adverse event reports submitted to the FDA. For context and perspective, it also includes data on two documented adverse effects of antidepressant drugs: movement disorders and potentially dangerous mood elevation, often described medically as euphoria, mania or hypomania.

In the United States the reporting of adverse events associated with prescription drugs is purely voluntary for those who experience these events or observe them in the course of medical practice. However, pharmaceutical companies must report to the FDA the adverse events associated with their drugs of which they become aware—even though they have no obligations under law to seek out or search for adverse events that do not come to their attention spontaneously. [8]

The FDA in turn publishes for public research use extracts of all the adverse event reports that it has received.[9] Personally identifiable information is first removed, and the event narrative is replaced with a list of standard medical terms that best describe the event that occurred. The existence of an adverse event report does not in itself establish that the drug caused the event. However, in most cases it indicates that an observer (a health professional, patient or family member) suspected that that drug was responsible.

The target drugs for this study were previously identified as those which doctors use most commonly in a separate study using a large government survey of outpatient medical care. [10] The drugs are:

- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Fluoxetine (Prozac)
- Citalopram (Celexa)
- Amfebutamone (Wellbutrin, bupropion)
- Venlafaxine (Effexor).

Section 2: Adverse Event Reports in Context

The data for this study are drawn from a master file of 956,511 adverse event reports submitted to the FDA from November 1997 through December 2002. All reports identifying a trade name, chemical or generic name of one of the six target drugs were initially extracted.

The following kinds of reports were excluded from this analysis:

1. Reports in which the target drug was listed as being given in concomitant therapy, rather than being specifically identified as a primary suspect, secondary suspect, or interacting drug.

2. Any report of an event occurring in a child under 12 months of age that was assumed to be a complication of administering the drug to the mother, or a report that specifically stated it was such a complication.

3. All reports with a medical term indicating the event was the result of medication error or accidental overdose.

4. Only the last, best case report was included, excluding any previous reports about the same adverse event.

A total of 44,026 adverse events were identified as meeting the study criteria outlined above. (Table 1) This included 3,242 deaths, 1,980 cases of disability and 16,365 cases of other serious outcomes such as hospitalization, an episode described as life threatening, or as requiring medical intervention to prevent permanent harm. Of these reports, 1,647 occurred in children, including 69 deaths, 51 cases of disability and 722 cases with another serious outcome. In 12,284 cases, no age was provided for the person injured. Among those cases for which age was provided, 5.2% occurred in children.

Nine out of ten of these reports were prepared by drug manufacturers, who collected the information from the original sources, selected what they deemed relevant, and gathered additional information as they saw fit. The other reports were submitted directly to the FDA. These results are similar to those seen for all reported adverse events.

Since it is known that only a fraction of all adverse events are reported to the FDA, [11] from these data it is reasonable to estimate that hundreds of thousands of persons experienced injury associated with antidepressant drugs, and thousands died. The large toll of injury is expected given that antidepressant drugs are so widely used and

Table 1. Number and Type of Reports

	Adverse Event Reports, No. (%)					
All Reports	All Ages*		Adults		Children	
Total (n =)	55,518		35,684		1,917	
Cases	44,026	(79)	30,095	(84)	1,647	(86)
Previous Reports	7,942	(14)	5,589	(23)	270	(14)

	Adverse Event Unique Cases, No. (%)					
Report Source	All Ages*		Adults		Children	
Total (n =)	44,026		30,095		1,647	
Healthcare Prof	19,224	(44)	11,452	(38)	980	(60)
Consumer	10,673	(24)	7,297	(24)	242	(15)
Foreign	7,953	(18)	6,803	(23)	150	(9)
Study	583	(1)	518	(2)	36	(2)
Other	184	(<1)	88	(<1)	17	(1)
None Stated	5,409	(12)	3,937	(13)	222	(13)
Outcome Group						
Total (n =)	44,026		30,095		1,647	
Death	3,242	(7)	2,583	(9)	69	(4)
Disability	1,980	(4)	1,588	(5)	51	(3)
Serious (non-fatal)	16,365	(37)	12,680	(42)	722	(44)
Other	22,439	(51)	13,244	(44)	805	(49)
Who Prepared	44,026		30,095		1,647	
Manufacturer	39,872	(91)	27,185	(90)	1,453	(88)
FDA	4,154	(9)	2,910	(10)	194	(13)
Target Drug**						
Total (n =)	47,257		32,734		1,803	
Sertraline	14,872	(31)	8,394	(26)	579	(32)
Paroxetine	8,225	(17)	6,087	(19)	409	(23)
Fluoxetine	4,757	(10)	3,703	(11)	226	(13)
Citalopram	6,700	(14)	5,050	(15)	216	(12)
Venlafaxine	6,421	(14)	4,580	(14)	186	(10)
Amfebutamone	6,282	(13)	4,920	(15)	187	(10)

* Includes reports with no age stated.

** Reports naming 2 target drugs are counted twice

have such substantial toxicity that in clinical trials for depression from 15 to 21 percent discontinued treatment because of intolerable side effects. [12]

Trends Over Time

Given the rapid increases in the medical use of antidepressants from 1998 to 2001 in both adults (up 33%) and children (up 114%), [13] it is revealing to check whether the increased exposure to the drugs led to similar growth in adverse event reports.

Figure 1. Adverse Event Cases Over Time

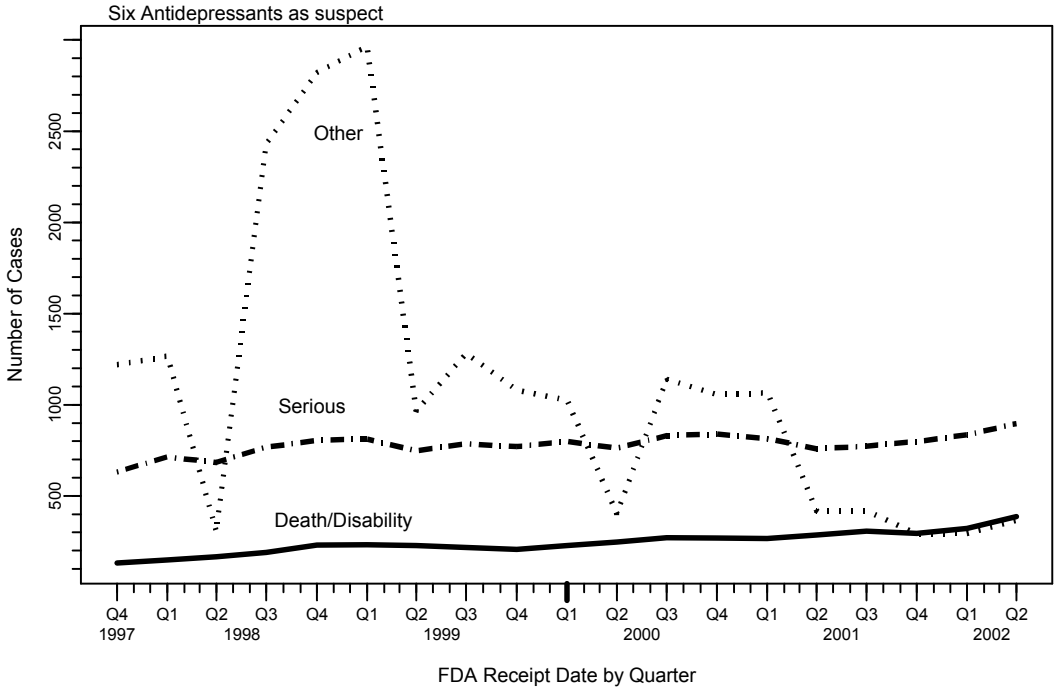
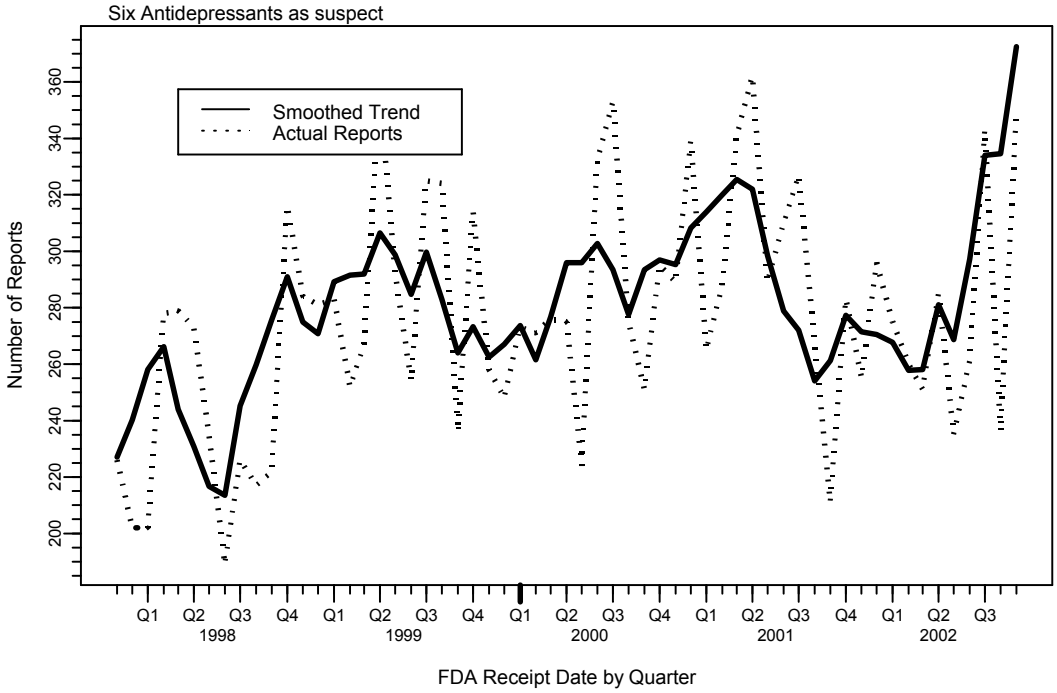


Figure 1 shows that the overall report totals were influenced by large fluctuations in "other" reports that were not serious or for which no outcome was listed. This illustrates, as noted before, that the volume of reports can be influenced by factors unrelated to the safety of the drug. The volume of reports about events that were not serious can be influenced by several factors: a) direct-to-consumer advertising campaigns provide an 800 number to report adverse events; b) after three years the FDA permits manufacturers to stop submitting adverse event reports about non-serious events; [14] c) FDA periodically gets ahead of the report processing backlog for non-serious reports, which are a lower priority.

A more accurate picture of the adverse event report time trend comes from limiting the focus to reports of events that are serious, and for which the manufacturer has not previously warned doctors and patients. These are called expedited reports. These events are the principal focus of the adverse event reporting system and must be sent to the FDA within 15 days. [8]

Figure 2 shows that the volume of these expedited reports fluctuated, but increased over the time period, growing by approximately 50% over the five-year period. These expedited reports are those most likely to contain a signal to the manufacturers about new adverse events about which doctors and patients have not been warned.

Figure 2. Signal to Manufacturer: Expedited Reports



Patterns of Adverse Events and Medical Use

Table 2 demonstrates that patient characteristics of those experiencing a reported adverse event closely represent the medical population for which the target drugs are prescribed, according to the companion study and confirmed in other reports. [15] [16] For example the mean age of 46.5 years (SD +/ -18.4) of those injured by adverse events is only slightly younger than the mean of 47.6 years (SD +/- 18.2) for all those prescribed antidepressants. The percentage of females is also similar in the two groups; the adverse events occurred in a population that was 67% female and the drugs were prescribed to a patient population that was 69% female.

The total number of medications taken by the patient populations was also similar, a mean of 2.9 medications for the adverse event group, compared to 3.0 medications for the overall population taking antidepressant drugs. Overall, those experiencing a reported adverse event were slightly younger, and slightly more likely to be male, but the differences were small. These data demonstrate that adverse events reported for these drugs did not notably affect a population subgroup that could be identified.

Table 2. Comparison of Reported Adverse Events with Medical Use

Age	Adverse Events	Medical Use (Surveys)
mean years	46.5	47.6
+/- std dev	18.4	18.2
Age Group (percent)	Percent	
Adult	94.8	95.2
Adolescent (13-17)	3.5	3.2
Child (6-12)	1.5	1.6
Children (1-17 yrs)	5.2	4.8
Sex (percent female)	67.0	69.0
Number of Medications	Number	
mean	2.9	3.0
+/- std dev	2.6	1.8
Target Drug (percent total)**	Percent	
Sertraline	31.4	24.5
Paroxetine	17.4	22.8
Fluoxetine	10.0	22.1
Amfebutamine	13.4	10.6
Citalopram	14.1	10.1
Venlafaxine	13.5	9.6

** Calculated for 6 target drugs from 2 government health care surveys

** Percentages may not add to 100% because of rounding

Results for Specific Drugs

The volume of reports for each of the six target antidepressant drugs does not as closely resemble the medical use of these drugs, as do the patient characteristics. In particular, sertraline accounts for a seeming excess (31.5% of reports but 24.4% of medical use) and fluoxetine for only about half the volume expected (10% versus 22.1%). In statistical terms, the relationship between medical use and adverse event report volume was modest (Pearson's r = 0.52). However the volume of reports for individual drugs was heavily influenced by fluctuations in non-serious or "other" reports noted in Figure 1. When the analysis was confined to serious, disabling and fatal events, the relationship between the volume of adverse event reports and the drugs' medical use was much closer. (Pearson's r = 0.83) From these data alone, there did not appear to be marked differences between the six target drugs in toxicity as reflected in the more serious adverse event reports. [17]

In conclusion, these overall adverse event data show that the patient population experiencing reported adverse events had similar characteristics to the overall patient population in which the six target drugs were prescribed. This means that adverse events

associated with the target drug were not confined to a particular, vulnerable subgroup (such as the elderly or young children). In addition, this suggests that this particular group of adverse event reports were largely but not entirely free of influences unrelated to the safety of the drugs. The notable exception was changes in the volume of non-serious reports. While adverse event data typically provide an accurate profile of the toxic properties of the target drug, it is essential to scrutinize the data for influences that may be unrelated to the safety of the drug.

Section 3: Suicidal/Aggressive Behavior and Other Key Events

Obstacles to Case Identification

The accurate and unbiased identification of cases of suicidal or aggressive behavior is problematic in both clinical trials and adverse event data. As the FDA noted in its own report, [3] the clinical trials in children were not designed to measure this kind of event, but rather to gauge accurately changes in the severity of depression, obsessive compulsive disorder or attention deficit disorder. No side-effect checklist was used, but instead a vague question was posed to the patient, "How have things been?" Events also could be overlooked in the large numbers of dropouts that occur in antidepressant trials.[12]

Even if the events were reported, the manufacturers might code them differently. In the case of paroxetine, for example, many cases of suicidal behavior were initially categorized as "emotional lability," and the excess of suicidal behaviors did not emerge until this error was corrected.[3] The same manufacturers were also preparing and coding the large majority of adverse event reports as well, but may not have followed the same procedures used in the clinical trials, or even used the same medical dictionary.

The greater weight given to adverse event trials comes in part because the trials are intended to be "double blind." Even if the methodology is flawed, placebo patients and patients taking the target drug are treated identically in the trial. However, in the case of antidepressant drugs, it is known that the blind is compromised because of the distinctive pattern of some adverse events. [18]

An additional layer of complication occurs not only because the event under study was not clearly defined, but also because little agreement exists whether a distinctive event associated with the drug exists, or is merely a product of underlying mental disorder. Those who have reported individual cases of suicide and self-harm under a variety of circumstances [19] [20] [21] often report a component of violence, or violent thoughts or feelings about others. Finally, any specific "adverse event" typically is part of a broader medical problem that involves a larger number of events that are more moderate in character. For example, drug-induced, life-threatening damage to the liver is a rare event; but liver-toxic drugs capable of inducing acute liver failure also produce frequent cases of less severe liver damage from which the body can recover without long-term injury. A causal relationship between a drug and a narrowly-defined adverse event might not be apparent but be obvious using a broader definition.

A final obstacle occurs because in these reports the full case narrative has been replaced by one or more medical terms from a standard dictionary used worldwide for drug regulation. [22] The FDA initially selected the medical terms when the reports were received; events were not independently classified for this study.[23]

Case Definitions for This Study

This study uses a broad selection of medical terms expected to identify the case of interest, despite differences in manufacturer coding practices or the language used by the health care professional or other observer. Furthermore, as Wyeth did in its evaluation of venlafaxine, this study includes terms describing violent, hostile or aggressive behaviors. The specific medical terms and their frequency in the overall data and among children are shown in Table 3.

Inspection of Table 3 reveals that the majority of cases correspond to relatively unambiguous medical terms such as non-accidental overdose, completed suicide, suicidal ideation, aggression, hostility and abnormal behavior. Note that this is a tally of report terms and not cases; one case might feature several of these terms.

Another related disorder is medically described as manic, hypomanic and euphoric moods. While this mood disorder typically involves feelings of inflated self esteem and grandiosity, the bipolar mood disorder is also associated with paranoia, psychosis and violence. [24] The manic/euphoric behavior also differs from suicidal/aggressive behaviors in being a documented adverse effect of antidepressant drugs. [25-28] Agreement is higher about the characteristics of this disorder and the number of possible medical terms describing it is far smaller.

Together, these two adverse events likely address a primary concern of parents: Are antidepressant drugs capable of inducing a marked mood or personality change involving self-harm, violence and or other potentially dangerous behaviors?

To provide an additional perspective, this study also grouped together all medical terms describing tremor, convulsions, and other disorders of muscle movement. The specific terms and how frequently they were mentioned in these reports are described in Appendix 1. The strength of this category is that tremors and other movement disorders are well documented adverse effects of antidepressant drugs. Tremor in particular occurs in more than 10% of cases in clinical trials and seldom in placebo. [26] In addition, it is by definition, a chemical reaction to the drug rather than a variation in amore ephemeral and difficult to measure change in mood. The limitation of this category is the very large number of terms (53) that might describe a movement disorder. This is mostly a result of the large number of near synonyms in the medical dictionary used to classify adverse events. (For example, muscle spasm, muscle cramp, muscle rigidity and dystonia.)

Table 3. Reaction Term Mentions for Two Adverse Events*

Suicidal Behavior /Aggression

Suicidal Behavior	Total**	Adults	Children
Non-accidental overdose	891	699	69
Completed suicide	848	664	43
Suicidal ideation	815	547	55
Suicide attempt	758	541	76
Intentional self-injury	88	50	15
Self mutilation	22	14	5
Depression suicidal	19	15	0
Self injurious behavior	15	8	4
Aggression/Hostility			
Aggression	672	438	84
Abnormal behavior	443	284	62
Hostility	274	146	39
Anger	246	165	22
Mood swings	187	148	9
Akathisia	119	76	9
Murder	114	66	12
Personality change	92	65	8
Impulsive behavior	38	21	12
Homicidal ideation	31	17	3
Disinhibition	28	13	7
Violence-related symptom	23	17	2
Antisocial behaviour	15	9	1
Impulse-control disorder	14	8	4
Belligerence	6	4	1
Manic/Euphoric			
Mania	469	285	44
Euphoric mood	130	87	11
Hypomania	86	76	5
Bipolar disorder	70	43	15
Bipolar I disorder	46	28	4
Elevated mood	16	10	1
Grandiosity	9	5	1

* Target drug named as suspect. Each report may contain several terms

** Includes cases with no age given

Section 4: Results and Findings

Suicidal/Aggressive Behaviors

A total of 3,309 cases of suicidal/aggressive behavior in patients of all ages were identified among the 31,742 reports for which age information was provided.[29] This accounts for 10.2% of all reports of adverse events of all types. This total includes 848 cases identified as "completed suicides." The remainder was suicide attempts of various types, or aggressive or violent behaviors. The large number of events shows that these behaviors are an important and substantial portion of these drugs' overall adverse event profile.

Among cases of suicidal/aggressive behavior more than twice as many as expected were reported in children less than 18 years of age. For all other reported adverse events, 4.6% occurred in children, but for cases of suicidal/aggressive behavior 10.7% occurred in children (chi-square 225.4 $p < .001$). (Table 4)

A total of 353 reports of suicide/aggression in children occurred. Examined over time, the number of events increased from 52 in 1998 to 98 in 2002. This 88% increase parallels the rapid growth in medical use reported in the companion study.

The results change little using another approach to calculate the expected number of cases of suicide/aggression in children. Based on the medical use of these drugs we would expect that 4.8% of reports of suicidal/aggressive behavior would occur in children, since that was the proportion of all medical use of the target drugs that occurred in this age group. However, 353 cases (10.7%) occurred in children when only 158 (4.8%) would be expected.

Mania/Euphoria

The results for mania/euphoria were similar to those for suicidal/aggressive behaviors except that the number of cases was substantially smaller. A total of 544 reports of mania/euphoria were identified or 1.7% of all types of adverse events among persons of all ages. Mania/euphoria was reported less frequently than suicidal/aggressive behaviors even though mania and hypomania are more accepted side effects of antidepressant drugs.

Among cases of mania/euphoria, 72 (13.2%) occurred in children. However, only about 27 cases (5%) would be expected based on the percentage of all other types of adverse events reported in children. (chi-square 78.2 $p < .001$) The results are similar using the alternative approach basing the expected values on overall medical use of the target drugs.

Table 4. Selected Adverse Events vs All Other Events in Children and Adults*

	No. Events,%		No. Other Events,%		Statistical Significance
Suicidal Behavior/Aggression					
Total	3309		28433		chi-sq = 225.4 p < .001
Children < 18	353	(10.7)	1294	(4.6)	
Adults	2956	(89.3)	27139	(95.4)	
Mania/Euphoria					
Total	544		31198		chi-sq = 78.2 p < .001
Children < 18	72	(13.2)	1575	(5.0)	
Adults	472	(86.8)	29623	(95.0)	
Movement Disorders					
Total	5400		26342		chi-sq 67.3 p < .001
Children < 18	402	(7.4)	1245	(4.7)	
Adults	4998	(92.6)	25097	(95.3)	
All Other Adverse Events					
Total	23398		8074		chi-sq 244.6 p < .001
Children < 18	942	(4.0)	705	(8.7)	
Adults	22456	(96.0)	7369	(91.3)	

* Cases where target drug named as a suspect

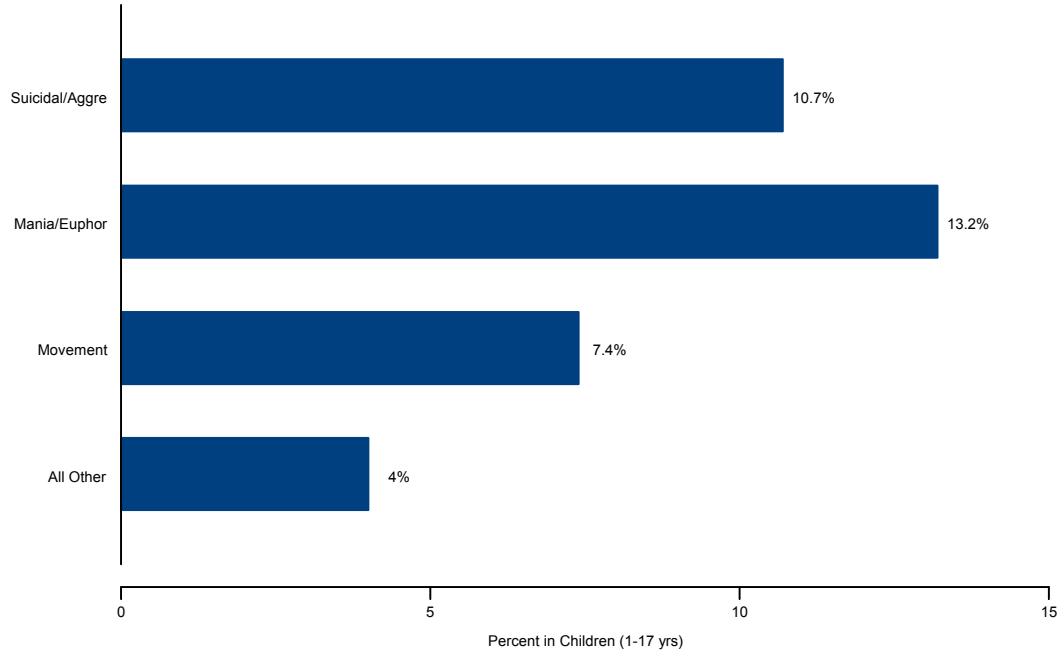
Movement Disorders

For tremors, convulsions and a wide variety of other muscle movement disorders, the numbers of cases were far larger. A total of 5,400 cases were identified, accounting for 14% of all reported adverse events. Among these events 402 (7.4%) occurred in children and 1,245 (4.7%) of all other types of adverse events occurred in children. While these events were also more likely to be reported in children compared with adults the differences were smaller. (chi-square 67.3 p < .001).

Differences among the types of adverse events are illustrated in Figure 3.

Using statistical measures that take into account both the number of cases of interest and the size of the difference between the observed and expected values, we conclude that the evidence is strongest that suicidal/aggressive behaviors are reported more frequently in children, and weakest that movement disorders occur more frequently.

Figure 3. Percent of Adverse Events Occurring in Children



Warning versus Non-Warning Drugs

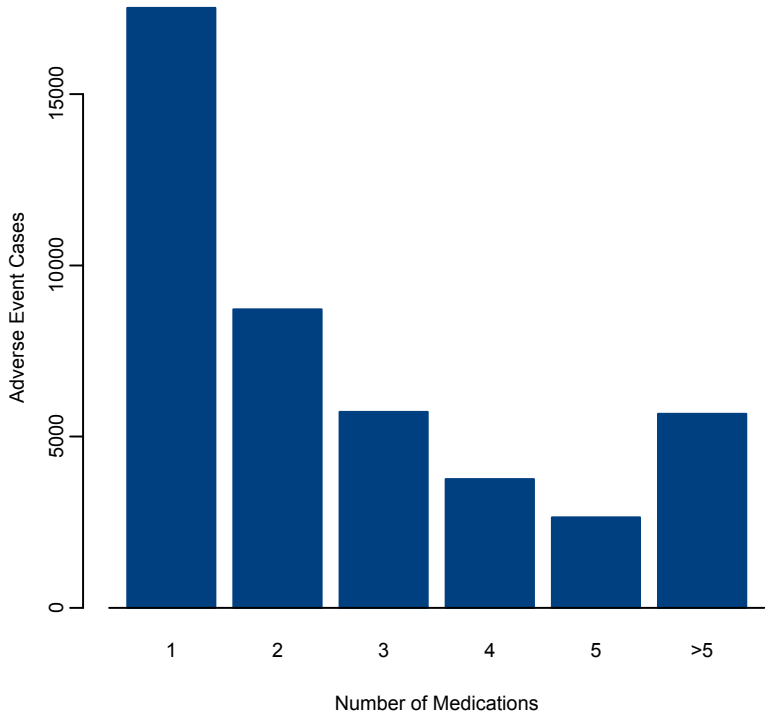
As noted earlier, warnings have been issued for suicidal or suicidal/hostile behaviors for paroxetine and venlafaxine based on excesses of such events seen in clinical trials in pediatric patients. But for the other four target drugs (sertraline, fluoxetine, citalopram, and amfebutamone) no such warnings have yet been provided.

This study also examined whether the adverse event reports for the two warning drugs provided evidence that they posed greater risks to children than did the other four target drugs. The data showed that there was no distinguishable difference between the warning and non-warning drugs in the unexpectedly large numbers of reports of suicidal/aggressive behavior. For drugs with warnings, 11% of suicidal/aggressive behavior cases occurred in children, compared to 10.3% for the drugs without warnings. (NS $p = .569$) This small difference (11% vs 10.3%) likely occurred by chance.

Section 5: Effects of Other Drugs

A special feature of clinical trials is that they typically prohibit the co-administration of other psychoactive drugs (except sedatives) that might confound the effect of the drug under study. In the real world of medical treatment, however, multiple drug use (polypharmacy) occurs in a majority of cases. Similar patterns of polypharmacy are seen in the adverse event data. (Figure 4)

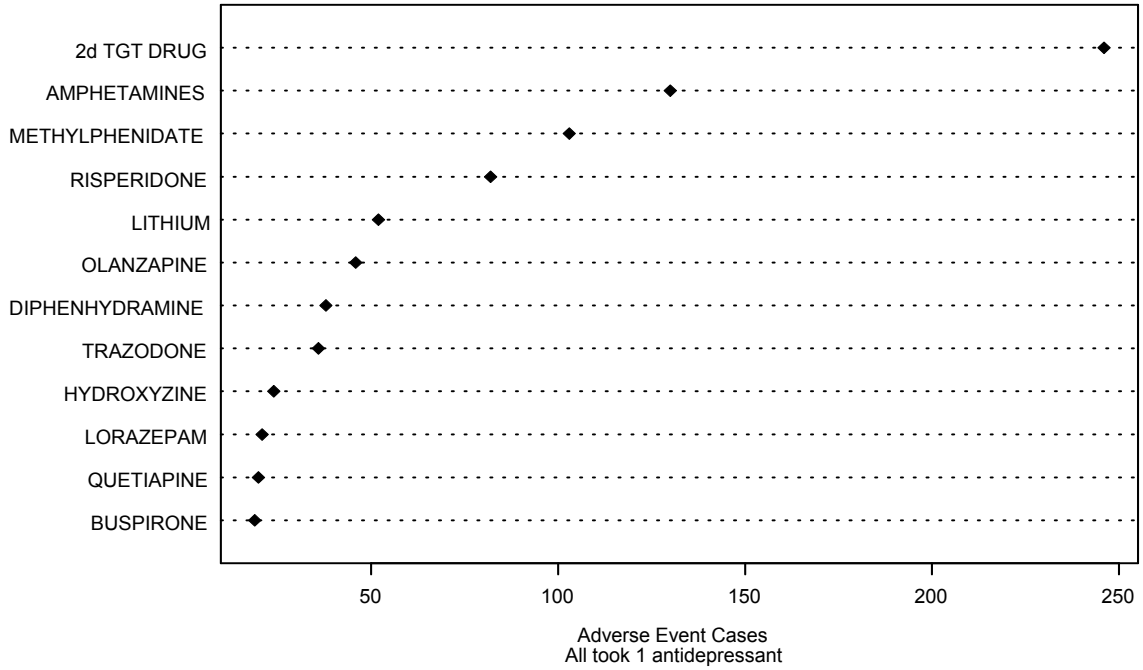
Figure 4. Number of Medications Listed (All Ages)



As might be expected, adults experiencing adverse events were taking more medications (mean 3.3 drugs SD +/- 1.7) than were children (mean 2.1 SD +/- 2.8). But for medications affecting the central nervous system (CNS), polypharmacy was similar in children and adults. Among children, 35% with a reported adverse event were taking two or more CNS drugs, compared to 37% among adults.

Figure 5 shows the other CNS medications given most frequently to children who experienced a drug adverse event while taking antidepressant drugs. It also reflects another factor identified in the companion study of medical use. It showed that antidepressant drugs were frequently prescribed not only for the treatment of depression, but also for attention deficit and other conduct disorders, often in combination with a stimulant drug or an antipsychotic drug.

Figure 5. Other CNS Medications in Children



An additional issue is whether the frequent use of multiple CNS medications might help cause or contribute to any of the three adverse events--suicidal/aggressive behaviors, movement disorders or mania/euphoria. In theory, the adverse events might result in part from synergistic or additive effects of multiple medications, or from interactions, rather than being toxic properties of the target drugs alone.

These data provided no evidence to support the hypothesis that use of multiple medications played a significant role in the three adverse events under study. The number of medications prescribed in overall medical practice was similar to the number of medications listed in adverse event cases. (Table 2) This proved true for both adults and children. In addition, no statistically significant difference was seen between the number of medications taken by children experiencing reported episodes of suicidal/aggressive behaviors or movement disorders, and the number taken by those who did not. However, this approach and these data lacked statistical power to examine the possibility that particular drug-drug combinations might increase the risk of certain adverse events. As other investigators have noted, [30] little scientific information exists about the safety or benefits of CNS drug combinations in the treatment of attention deficit and conduct disorders or depression.

Section 6: Conclusions and Comment

For the six target antidepressant drugs, these data show a growing volume of adverse event reports of suicidal and aggressive behavior in children, a change roughly in proportion to the rapidly increasing medical use of antidepressants in this age group. Clear evidence was seen that these events are reported more frequently in children than in adults. However, completed suicides (rather than attempts and other behaviors) were not reported more frequently in children.

These post-market surveillance data confirm and extend previous findings in clinical trials that have led to warnings about paroxetine and venlafaxine, where the use in children is not now recommended. [2 4] This means that a signal has now been seen in the two major sources of drug safety information, pre-marketing clinical trials and post-market surveillance.

However, little difference in risk could be detected among the six target drugs. In fact, the proportion of cases occurring in the two drugs with warnings was similar to that for the four drugs for which no warnings have been published.

Limitations

Adverse event data have important limitations that should be considered in assessing the scientific and regulatory significance of these findings. These data come from spontaneous, voluntary reports rather than from systematic comparisons between treated and untreated patients. Furthermore, the reporting of an adverse event does not establish that the suspect drug caused it—only that it was a suspect. If each of the 44,065 cases were investigated in greater depth, it is certain that unbiased investigators would identify cases where a relationship between the drug and a reported adverse event was unlikely. In numerous additional cases alternative factors would be identified that might have contributed to or caused the event. On the other hand, it is also known that only a fraction of the adverse events that occur are ever reported, and some studies show doctors seldom report even the serious adverse events they observe. [31]

Despite these limitations, adverse event data remain a primary source of information supporting major regulatory decisions about the fate and appropriate use of approved drugs. Reported adverse events were instrumental in the safety withdrawal of troglitazone, cisapride, and cerivastatin, and in triggering major warnings about potentially lethal risks of felbamate, pemoline and nefazodone.

Adverse event data continue to be influential for two reasons. First, for most relatively rare adverse events, little or no other information is available. Second, in case after case, toxic properties of drugs are first signaled and initially identified in these data. Rare is the case where a strong signal was seen in these data and then discovered to be unfounded in more systematic scientific study.

Finally, these data were screened for evidence of unusual influences that might have distorted the results. None were found. Report source, volume, type, age and

gender were similar to the values seen in all reported adverse events or derived from medical use.

Contrast with Clinical Trials

Many regulators and scientists believe that clinical trial data can be relied on (often without question) because they come from controlled, double blind studies, and that uncontrolled data are of limited value and cannot be trusted. In the case of suicidal and aggressive behaviors, information is available from both primary sources of drug safety information.

In the present case, however, clinical trials information also has important limitations. First, as a group the trials were generally unable to detect the treatment effect being measured directly, with 13 of 15 trials not showing a statistically significant benefit. [3, 6] As the FDA noted, this does not prove that no benefit exists, but it does mean that any benefits that might be detected by a larger experiment must be very small.

Using these same, generally unsuccessful trials to measure suicidal behaviors is especially problematic. As the FDA noted, the studies had no common definition or protocol procedure to identify these behaviors, and some cases were clearly miscoded. [3] The FDA's approach,a reanalysis of pooled data from unsuccessful trials, runs a great risk of Type II statistical error—designing an experiment without the capacity to distinguish between a positive and negative outcome.

Confounding by Indication

The debate about whether antidepressant drugs may trigger suicidal and violent behaviors in adults (or children) has raged for over a decade. In court and elsewhere, defenders of antidepressant drugs say that such behaviors are only to be expected in patients with depression or other mental disorders and the drug is being unfairly blamed. When the adverse event that may be attributed to the drug is also a symptom of the underlying disorder the problem is called confounding by indication. In the current controversy, this very argument has been raised. [32]

However, in this case suicidal/aggressive behaviors have been seen in substantially greater numbers of patients treated with both paroxetine and venlafaxine, compared to otherwise similar patients who took a placebo. Across even more trials, such events are uncommon among patients taking a placebo.

In the present case, the large volume of adverse event reports over time continues to send a signal that such events are real and seen frequently.

Reported More Frequently in Children than in Adults

The principal new finding of this study is evidence that reports of suicidal/ aggressive and manic/euphoric behaviors are reported more frequently than expected in children. In this evidence it is impossible to tell whether such events *occur* more

frequently in children possibly because their underlying moods are more volatile, or whether they are *reported* more frequently because many parents observe their children carefully and might identify behaviors that seem out of character. These data provide no tools for distinguishing the two factors and it seems likely both may be involved.

Strength of these Reports

Those pursuing further study of the safety of antidepressant drugs in children should also be aware that just how the events of interest are defined will have a major influence on the outcomes of future studies. Is the focus narrowed to actual, completed suicides? Suicidal behaviors, which can be extended to non-fatal overdoses? Other forms of self-harm can be related to causes other than suicide. [24] What about aggression, hostility and violence towards others? Wyeth included some such cases in its analysis and warning, [4] but the FDA apparently plans to exclude them.[3] And none of the other analyses have yet included mania/euphoria, which was included in the present analysis.

The core issue that ought to concern parents is whether antidepressant drugs are capable of inducing a substantial personality change leading to destructive or violent behaviors with potentially life long implications for the child.

The evidence from this study shows that among children 24% of all reported adverse events included these unexpected and potentially dangerous personality or mood changes. When combined with clinical trials evidence, these data raise serious questions about the safety of antidepressant drugs for the treatment of depression in children.

Appendix 1. Reaction Term Mentions for Movement Disorders

	Mentions in Case Reports, No.,%		
Movement Disorders	All Ages**	Adults	Children
Tremor	1,906	1,423	92
Convulsion	1,643	1,119	122
Grand mal convulsion	585	472	55
Difficulty in walking	312	255	13
Muscle twitching	408	269	44
Dyskinesia	354	273	31
Dysarthria	247	210	13
Hypertonia	276	209	13
Gait abnormal	231	175	5
Balance disorder	262	211	5
Ataxia	200	158	9
Muscle cramp	193	146	2
Extrapyramidal disorder	233	170	15
Muscle spasms	183	134	7
Muscle rigidity	212	177	13
Other (38 terms)	1,530	1,155	102

* Terms mentioned in suspect drug cases

** Includes reports giving no age

Notes

(1) Department of Health UK. Seroxat Must Not Be Used for the Treatment of Children. *Medicines and Healthcare products Regulatory Authority (MHRA)* 2003; Available at: URL: http://www.mhra.gov.uk/news/2003/seroxat10603.pdf. Accessed December 29, 2003.

(2) Food and Drug Administration. FDA Statement Regarding the Anti-Depressant Paxil for Pediatric Population. Rockville, MD: U.S. Food and Drug Administration; 2003 Jun 19.

(3) Laughren T. Background on Suicidality Associated with Antidepressant Drug Treatment. Rockville, MD: U.S. Food and Drug Administration, Center for Drug Evaluation and Research; 2004 Jan 5.

(4) Wyeth Pharmaceuticals. Dear Health Care Professional (venlafaxine). 8-22-2003. Collegeville, PA, Wyeth Pharmaceuticals.

(5) Food and Drug Administration. FDA Issues Public Health Advisory Entitled: Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD). *U S Food and Drug Administration* 2003 October 27. Accessed December 29, 2003.

(6) Medicines and Healthcare products Regulatory Authority. Selective Serotonin Reuptake Inhibitors(SSRIs): Overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. *Medicines and Healthcare products Regulatory Authority* 2003; Available at: URL: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverview_101203.htm. Accessed December 29, 2003.

(7) The agency, the Medicines and Healthcare products Regulatory Agency (MHRA), did not distinguish between statistically significant and non-significant findings.

(8) Center for Drug Evaluation and Research. Guidance for Industry: Postmarket Safety Reporting for Human Drug and Biological Products Including Vaccines. Rockville, MD: US Food and Drug Administration; 2002.

(9) FDA Quarterly Extract from Adverse Event Reporting System. Springfield, VA: US Department of Commerce, National Technical Information Service; 2001.

(10) Moore TJ. Medical Use of Antidepressant Drugs in Children, 1998-2001. Washington, D.C.: Drug Safety Research; 2004 Jan 10.

(11) Graham D. Final Report: Liver Failure Risk with Troglitazone. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2000 Dec 19.

(12) Kirsch I, Moore T, Scoboria A, Nicholls S. The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration. *Prevention & Treatment* 2002 July 15;5 Available at: URL: http://journals.apa.org/prevention/volume5/toc-jul15-02.htm.

(13) Moore TJ. Medical Use of Antidepressant Drugs in Children, 1998-2001. Washington, D.C.: Drug Safety Research; 2004 Jan 10.

(14) Food and Drug Administration. Granting Waivers Under 21 CFR 314.90 for Post Market Safety Reporting Requirements Under 21 CFR 314.80 (MAPP 6004.1). Rockville, MD: Food and Drug Administration; 2004.

(15) Moore TJ. Medical Use of Antidepressant Drugs in Children, 1998-2001. Washington, D.C.: Drug Safety Research; 2004 Jan 10.

(16) Olfson M, Marcus SC, Pincus HA, Zito JM, Thompson JW, Zarin DA. Antidepressant prescribing practices of outpatient psychiatrists. *Arch Gen Psychiatry* 1998 April;55(4):310-6.

(17) While overall report volume is similar, differences in specific kinds adverse events exist in clinical trials data and may exist in adverse event data. Paroxetine, for example, appears to have more withdrawal effects as a result of its shorter half life.

(18) Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002 April 10;287(14):1807-14.

(19) Glenmullen J. *Prozac Backlash*. New York: Simon & Schuster; 2000.

(20) Healy D. Emergency of antidepressant induced suicidality. *Primary Care Psychiatry* 2000;6(1):23-8.

(21) Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990 February;147(2):207-10.

(22) MedDRA MSSO. *Introductory Guide: MedDRA Version 5.1*. Reston, VA: MedDRA Maintenance and Support Services Organization (MSSO); 2002.

(23) Food and Drug Administration. Coding Principles for Postmarketing Adverse Drug Reactions. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2002 Feb 7.

(24) Task Force on DSM IV. *Diagnostic and Statistical Manual of Mental Disorders*. IV ed. Washington, DC: American Psychiatric Association; 1994.

(25) Eli Lilly and Co. Prescribing Information for Prozaz (fluoxetine hydrochloride). 2003. Indianapolis, IN, Eli Lilly and Co. 2003.

(26) Pfizer I. Prescribing Information for Zoloft (sertraline hydrochloride). 2003. New York, NY, Pfizer Inc. 2003.

(27) GlaxoSmithKline. Prescribing Information for Paxil (paroxetine hydrochloride). 2003. Research Triangle Park, NC, GlaxoSmithKline.

(28) Wyeth Pharmaceuticals. Prescribing information for Effexor (venlafaxine hydrochloride). 2003. Philadelphia, Wyeth Pharmaceuticals.

(29) This total counts each adverse event case once even if more than one of the terms shown in Table 3 occurred on the report.

(30) Zito JM, Safer DJ, dosReis S et al. Rising prevalence of antidepressants among US youths. *Pediatrics* 2002 May;109(5):721-7.

(31) Scott D, Rosenbaum S, Waters W, Colt AAL. Rhode Island Physicians' Recognition and Reporting of Adverse Drug Reactions. *Rhode Island Medical Journal* 2004;70:311-6.

(32) Mann J, Emslie G, Beardsless W, Fawcett J. Preliminary Report of the Task Force on SSRIs and Suicidal Behavior in Youth. Nashville, TN: American College of Neuropsychopharmacology; 2004 Jan 21.