# ANTIDEPRESSANT SIDE EFFECTS IN CHILDREN AND ADOLESCENTS

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The controversy over antidepressant prescription for children and adolescents is driven largely, if not entirely, by data from clinical trials sponsored by pharmaceutical manufacturers. How do data from clinical practice compare, with respect to the problem of behavioral toxicity in general, and suicidal behavior in particular? This is a timely question because opposing opinions are sharply drawn, while the information base is really quite limited.

The question of suicide as an SSRI side effect was raised by Teicher et al in 1990, who reported new-onset suicidal preoccupation in six patients taking fluoxetine (FXT) (54). A furor ensued, but it was mitigated by a meta-analysis of large numbers of depressives in clinical trials conducted by the manufacturer of FXT that demonstrated no statistically significant increase in suicide in patients treated with FXT compared to other antidepressants (55). The finding was affirmed by two independent epidemiological studies (Jick et al 1992; Jick et al, 1995). The controversy was kept alive, however, by occasional reports; for example that SSRI's *in general* were more likely to induce "deliberate self-harm" than the older antidepressants (59). In 2000, the Medicines Control Agency (Britain) called for this warning to be added to SSRI package inserts:

> *Whilst the reporting rate of suicidal behavior for all SSRI's has been low in recent years, there continue to be anecdotal case reports of suicidal behavior associated with fluoxetine. Prescribers and patients should be aware that it is general clinical experience that the risk of suicide may increase in the early stages of treatment with any*

*antidepressant. Patients thought to be at risk should be carefully monitored.* (Reuters, 10/18/2000).

In 2003, the focus of the controversy turned to antidepressant treatment in children and adolescents. In that year, an "Expert Working Committee" of the Committee on Safety of Medicines in Britain concluded that: "Paroxetine, venlafaxine, sertraline, citalopram and escitalopram are now contraindicated in pediatric MDD in the under 18s…fluvoxamine…should not be used in this age group…The balance of risks and benefits of fluoxetine in the treatment of MDD in under 18s (sic) appears to be favourable" (Duff, Committee on Safety of Medicines, December 10, 2003). This opinion was impelled, in part, by the occasional reports of SSRI-related suicidal behavior; but more by the weak efficacy data that had accrued, on behalf of the antidepressants listed, in clinical trials. Ironically, FXT was recommended as the *only* SSRI that might be prescribed for depressed children or adolescents.

For some reason – perhaps the sensitivity of the issue, possibly the paucity of available information on the topic – the issue of antidepressant-induced suicidality in young people has not abated. In the US, the Food and Drug Administration convened a series of meetings and initiated a meta-analysis of the information from clinical trials of antidepressants in children and adolescents (http://www.fda.gov/). Data from 25 clinical trials of 9 antidepressants was entrusted to a team of investigators at Columbia who were well-known for their epidemiological studies of suicide in children and youths. They reviewed data from 4555 children and adolescents who had been treated with antidepressants and/or placeboes, and their focus was on the occurrence of suicidal or self-injurious events.

The "events" themselves were responses generated on instruments like the Hamilton Depression Rating Scale, the Childhood Depression Rating Scale or the "Kiddie-SADS," a semistructured interview administered independently to parents and children. A total of 120 events were noted by the Columbia experts as "possible" suicidal behavior among the 4555 subjects in the trials. (This was 22 more than had been identified by the sponsors of the clinical trials.) The risk ratio (RR) generated for drug vs. placebo was reported as:

| | |
|---|---|
| All drugs | 1.95 |
| Venlafaxine (VEN) | 4.97 |
| Paroxetine (PXT) | 2.65 |
| Sertraline (SRT) | 1.48 |
| Citalopram (CTP) | 1.37 |
| Fluoxetine (FXT) | 1.52 |

The only RR that were statistically significant were for "all drugs" and VEN. The FDA report has not, so far, indicated whether one could predict which patients were more likely to develop suicidal behavior on antidepressants. But they conceded that "most of the events occurred in trials with the highest proportion of patients with a history of suicide attempts or ideation at baseline." The outcome of the FDA's deliberations was to recommend a "black box" warning (http://www.fda.gov/bbs/topics/news/2004/NEW01116.html); a recommendation with which not all child and adolescent psychiatrists seem to agree.

Reflecting on the issue, Graham Emslie, a child psychiatrist, and principal investigator in pediatric SSRI trials, wrote: "SSRI's are effective and generally well tolerated in depressed children and adolescents. Indirect evidence supports they have resulted in the decreased suicide rate over the past 10 years. Whether they increase suicidal behavior in some is unclear, and alternative treatments are not readily available" (Emslie, Making Sense of the Research Puzzle – the learning curve and controversy about using SSRI's with pediatric depression, AACAP News, April, 2004, Vol 35, #2).

Emslie's views are shared, it appears, by most child psychiatrists who responded to a recent poll: no fewer than 95% felt that "the potential benefits of SSRI treatment outweigh the risks." In a reader survey in the March, 2004, *Child and Adolescent Psychiatry Alerts*, 40% of respondents agreed that concerns about suicidal ideation were appropriate ("Concerns are

always appropriate"), while only 14% had ever experienced "anything like this in (their) practise" (Child & Adolescent Psychiatry Alerts, May 2004).

The FDA's deliberations naturally generated a great deal of attention in the popular press. Together with the meager statistical support for antidepressant efficacy that emerges when all of the clinical trials are considered together (which was also emphasized by the press), the public view of antidepressant therapy is likely to take a turn towards the negative. Among physicians, one might expect a more cautious approach to antidepressant prescription for children and adolescents.

If greater reluctance to prescribe antidepressant medication were the consequence of the FDA's recommendations, it would clearly represent a reversal of current trends. National prescription survey data in the US indicate that the rate of antidepressant treatment for patients less than 18 years old increased by 9.2% a year from 1998 to 2002 (Delate et al, 2004). The increase was largely accounted for by SSRI's. If fewer children and adolescents were treated with antidepressants, that, presumably, would be a "good thing." Or would it? The data suggest that 2.4% of children and adolescents were prescribed antidepressants in 2002 (Delate et al, 2004). That number would be inappropriate and excessive, though, only if the prevalence of mood and anxiety disorders in young people were *lower* than 2.4%. In fact, data suggest that the prevalence of mood disorders and anxiety in children and adolescents is considerably higher (Ihle et al, 2004; Masi et al, 2004; Saluja et al, 2004; Vila et al, 2004).

The "indirect evidence" to which Emslie alluded was a prescription survey by Olfson and colleagues (2003), that established that a 1% increase in antidepressant prescription to adolescents in any particular geographic region was associated with a corresponding decline in suicide rates (by 0.23 per 100,000 adolescents).

Certainly, this is an issue of no little import. The modern antidepressants are used so widely among children and adults because depression and anxiety are common clinical problems, and physicians believe that the modern antidepressants are "effective and generally well tolerated." If data were to accrue that challenged those assumptions, they would inevitably lead to far-reaching changes in treatment practice. The upshot of the FDA's deliberations has been a "black box" warning about the potential hazards of antidepressant treatment. But "like the medications about which they warn, warnings themselves carry some risk…patients may be so frightened of the potential side effects of an intervention that they refrain from taking a useful medicine from which they would have benefited substantially" (S.F.Colb, http://www.writ.news.findlaw.com/colb/20040421.html).

What, then, do we know about suicidal behavior in children and adolescents who are treated with antidepressants? And to what degree do the realities of clinical practice reflect the data generated from clinical trials?

The first point to emphasize is that SSRI-induced suicidal behavior is a form of behavioral toxicity; and the occurrence of behavioral toxicity associated with antidepressant treatment in children has been recognized for a long time. In Table 1, we list published studies that have addressed the issue, directly or indirectly.

**Table 1. Behavioral Toxicity in Antidepressant Publications**

| Dx | Reference | Symptoms | Frequency | Rate |
|---|---|---|---|---|
| OCD | King et al, 1991 | Self-injury | FXT 6/42 | 14.3% |
| MDD | Emslie et al, 1997 | Manic symptoms | FXT 3/48, PLA 0/48 | 6.3% |
| MDD | Rey-Sanchez et al, 1997 | Anxiety & Nervousness | PXT 1/45 | 2% |
| OCD | March et al, 1998 | Agitation | SRT 13/92 PLA 2/95 | 14% |
| MDD | Abrosini et al, 1999 | Insomnia | SRT 17/53 | |
| | | Agitation | SRT 6/53 | |

| | | | | |
|---|---|---|---|---|
| | | "↑ Depression and/or suicidality" | SRT 3/53 | 49% |
| GAD | Rynn et al, 2001 | Restlessness | SRT 6/11 PLA 3/11 | 55% |
| ADHD | Daviss et al, 2001 | Insomnia | BP 1/24 | |
| | | Irritability | BP 2/24 | 12% |
| OCD | Cook et al, 2001 | Insomnia | SRT 22/137 | |
| | | Hyperkinesia | SRT 16/137 | |
| | | Nervousness | SRT 15/137 | 38.7% |
| MDD | Emslie et al, 2002 | Agitation | FXT 1/109 PLA 0 | |
| | | Hyperkinesia | FXT 1/109 PLA 0 | |
| | | | FXT 2/109 PLA 0 | 3.7% |
| MDD | Wagner et al, 03 | Agitation | SRT 7/185 PLA 2/179 | |
| | | Suicidal behavior | SRT 5/185 PLA 2/179 | |
| | | Aggression | SRT 1/185 PLA 0 | 7% |
| MDD | Branconnier et al, 2003 | Suicidal behavior | PXT 8/63 | |
| | | Mania | PXT 3/63 | |
| | | Psychosis | PXT 2/63 | |
| | | Anxiety | PXT 19/63 | |
| | | Behavior Disturbance | PXT 1/63 | |
| | | Insomnia | PXT 7/63 | 63.4% |
| MDD | Wagner et al, 2004 | Agitation | CTP 2/93 PLA 0/85 | |
| | | ↑ Depression | CTP 1/93 PLA 2/85 | 3.2% |

NOTE: OCD = obsessive compulsive disorder. MDD = major depressive disorder. GAD = generalized anxiety disorder. ADHD = attention deficit/hyperactivity disorder. FXT = fluoxetine. PLA = placebo. PXT = paroxetine. SRT = sertraline. BP = bupropion. CTP = citalopram. ↑ = increased. The symptoms are as described in the papers.

As reflected in Table 1, the literature, from 1991 on, certainly indicates frequent occurrence of behavioral toxicity. The relative rates vary considerably. This degree of variability may reflect subject differences, ascertainment, medication or dose differences. Suicidal behavior is not an infrequent occurrence. No suicides have been reported, however. Indeed, it is difficult to determine, from the publications, just how serious the problems of self-injury and suicidality really were.

We thought that clinical data from our clinics might serve to illuminate the issue, at least to a degree. We also found a high rate of self-injurious behavior and suicidality in 128 children and adolescents treated with antidepressants during the course of the past year. The question we tried to address is, how serious is the problem?

## METHODS & MATERIALS

This was a retrospective side-effects study of children and adolescents treated with antidepressant drugs.

### SUBJECTS

The subjects of this investigation were identified from an office database that tracks demographic variables, diagnosis, medications and other information. They were children and

adolescents who had been treated with one of the following antidepressants:Bupropion (BP), Citalopram (CTP), Escitalopram (ECTP), Fluoxetine (FXT), Fluvoxamine (FVX), Paroxetine (PXT), Sertraline (SRT) or Venlafaxine (VEN)). They had a variety of different diagnoses (Major Depression, Obsessive Compulsive Disorder, Oppositional-Defiant Disorder, ADHD, Tourette's Syndrome, Asperger's Syndrome). They were all outpatients at the NC Neuropsychiatry Clinics in Chapel Hill and Charlotte during a fourteen month period from July, 2003 through August, 2004.

## METHOD

The CNSVS database contains records from more than 2000 patients with neurological and/or psychiatric disorders. The database was scanned for patients whose age was 18 years or younger and who had been treated with one of the antidepressants listed above.

One hundred and twenty eight (128) patients were identified who met those criteria. Their charts were then examined by a research clinician for data concerning the following signs of behavioral toxicity: suicide attempts, threats or ideation, self-injurious behavior, aggression, disinhibition, agitation or extreme emotional instability. The research clinician determined, on the basis of the clinic note, whether these problems pre-dated antidepressant treatment, or if they arose *de novo* after treatment was initiated, or if they increased in intensity/frequency after treatment. The latter two groups were felt to have behavioral toxicity (BT) related to drug treatment. The same charts were also reviewed by the clinicians who had been treating the patents, and they followed the same process, independently. The few differences that occurred between the research associate's chart review and the treating clinicians' were reconciled. The data were then reviewed a third time by the primary author (TG).

The 128 patients were divided into two groups: patients who developed behavioral toxicity following antidepressant treatment (BT), and patients who did not (NBT). The BT group included patients whose behavioral toxicity comprised suicide attempts, threats or ideation, or self-injurious behavior such as cutting (BT-S). The three groups were compared to each other for clinical, diagnostic and cognitive differences. The present clinical status of the patients was then reviewed, by chart analysis, and by conversations with the treating clinicians.

## ANALYSIS

Clinical and Neurocognitive data were analyzed by comparing two groups (BT and NBT) and by comparing three groups (BT' [i.e., BT – BT-s], BT-S and NBT). The tests were the two-tailed t test for independent samples, analysis of variance and the chi square test.

## RESULTS

Of 128 patients whose data were reviewed, 36 (28%) were felt to have developed behavioral toxicity to one or more antidepressants (BT); 92 did not (NBT). Eleven patients in the BT group had overt suicidal or self-injurious behavior (BT-S).

**Table 2. Behavioral Toxicity In 128 Patients**

| CONDITION | NBT | BT | BT-S |
|---|---|---|---|
| N | 92 | 36 | 11 |
| AGE | 13.1+/-2.9 | 13.4+/-2.9 | 13.7+/-2.8 |
| RACE W:B | 82/10 | 34/2 | "10/1" |
| SEX M:F | 58/34 | 20/16 | "5/6" |
| BP | 16 | 6 | 1 |
| PXT | 13 | 7 | 2 |
| SRT | 14 | 10 | 4 |
| VEN | 6 | 6 | 1 |
| FVX | 9 | 4 | 1 |
| FXT | 10 | 9 | 4 |
| ECTP | 20 | 6 | 2 |
| CTP | 5 | 4 | 1 |

In Table 2, we present the distribution of demographic variables and antidepressants in each category. The numbers of antidepressants in the BT and BT-S columns exceed 36 (BT) and 11 (BT-S) because some children had behavioral reactions to more than one antidepressant.

The age, race and gender distributions in the three groups did not differ. The distribution of behavioral toxicity did not differ among the various antidepressants (chi square = 5.48, df 7, NS). Every antidepressant was represented in the BT and the BT-S columns.

In Table 3, the distribution of the various symptoms of behavioral toxicity (i.e., both BT and BT-S groups are represented)is listed, along with the frequency with which they arose for each antidepressant.

**Table 3. Symptoms of Behavioral Toxicity in 36 Patients**

| | BP | CTP | FXT | FVX | ECTP | PXT | SRT | VEN | |
|---|---|---|---|---|---|---|---|---|---|
| Suicidal Ideation | | | x | x | | | x | | 3 |
| Suicide Threats | | x | x | | | | | x | 3 |
| Suicide Attempts | x | | | x | x | | | | 3 |
| | | | | | | | | | |
| Cutting | | | x | | | x | x | | 3 |
| Picking | | x | | | | x | | x | 3 |
| Self-injurious Behavior | | x | x | x | x | | x | x | 6 |
| | | | | | | | | | |
| Irritability | x | | x | x | x | | | | 4 |
| Increased Anger | x | | | | | | | | 1 |
| Violent Thoughts | x | x | | | | | | | 2 |
| Homicidal Ideation | | x | | | | | | | 1 |
| Aggressive Impulses | | | | x | x | | | | 2 |
| Aggression | x | x | x | x | x | x | | x | 7 |
| | | | | | | | | | |
| Depression, Dysphoria | | | | x | x | | | x | 3 |
| Extreme Emotionality | | | x | x | x | x | | x | 5 |
| Nightmares | x | | | | | | | | 1 |
| Temper Outbursts | x | | x | | | | x | x | 4 |
| | | | | | | | | | |
| Hypomania | | | x | | | | x | | 2 |
| Increased Hyperactivity | | | x | x | | | x | x | 4 |
| Increased Impulsivity | | | x | | | | x | x | 3 |
| Disinhibition | x | x | x | x | x | x | x | x | 8 |
| | 8 | 7 | 12 | 10 | 8 | 5 | 8 | 10 | |

Table 4 is a description of the problems that arose in the 36 individuals who experienced behavioral toxicity.

**Table 4. Behavioral Toxicity in 36 Individuals**

| S | CurrMed | BEHAVIORAL TOXICITY |
|---|---|---|
| 7WM | SRT | Increased disinhibition on SRT |
| 9WM | PXT | Cognitive impairment on FVX |
| 9WM | | Suicidal thoughts on SRT, temper outbursts on FXT & SRT |
| 9WM | | Increased aggression, emotional lability, disinhibition on PXT |
| 10WM | DE BP | Suicidal & violent thoughts, extreme emotional instability on VEN |
| 10WM | NOR | Aggression & disinhibition on FVX |
| 11WF | PXT | Cutting & disinhibition on PXT and SRT |
| 11WF | TRZ | Increased aggression & disinhibiton on PXT |
| 11WM | PXT | Intrusive thoughts of vilence & death on BP |
| 12WF | ECTP | Increased aggression on PXT |
| 12WM | IMI | Nightmares, chest pain. Tachycardia on BP |
| 12WM | BP | Disinhibition on CTP, seizure on SRT |
| 12WM | VEN | Suicide threats & disinhibited on CTP, aggressive & disinhibited on PXT |
| 12WM | FXT | Aggressive on FVX |
| 13BF | FVX | Wrote obscenities on school property on CTP |
| 13WF | SRT | Increased irritability of ECTP |
| 13WM | BP | Picking, volatile on VEN |
| 13WM | BP | Picking on PXT, impulsive, hyperactive on FXT & VEN |
| 14WF | ECTP | Cutting on FXT |
| 14WF | ECTP | Violent of ECTP, disinhibited on FXT |
| 14WF | FXT | Suicide ideation on SRT, temper outbursts on FXT |
| 14WM | ECTP | Picking, aggressive on CTP |
| 14WM | CTP | Irritability on FXT |
| 15BF | FXT | Aggression and suicide attempt on ECTP |
| 15WF | VEN | Uncontrollable weeping on FXT |
| 15WM | BP | Hypersensitive, hyperactive, impulsive on SRT |
| 16WF | ECTP BP | Increased anger on BP, jittery on SRT |
| 16WF | VEN | SIB & disinhibition on ECTP |
| 16WM | SRT | Suicidal ideation on FXT |
| 17WF | ECTP MTZ | Aggressive on PXT, disinhibited on SRT |
| 17WF | CTP | Hypomania, cutting, suicidal ideation on SRT |
| 17WF | ECTP | Disinhibited on SRT |
| 17WM | SRT | Violent temper outbursts on BP, increased inpulsivity on VEN |
| 17WM | FVX | Suicide attempt on BP. Suicide threat & SIB on VEN, disinhibited on VEN & WBT |
| 18WF | ECTP | Increased picking on VEN |
| 18WM | SRT | Aggression & SIB on CTP, aggressive on VEN & FXT, emotional instability on ECTP, FVX & VEN, disinhibition on SRT, irritable on BP, hypomanic on FXT |

The column marked “CurrMed” (current medication) is interesting. This represents the medication that the patients were taking at the time of their most recent follow-up visit to the Clinic. No fewer than 34 of the 36 patients were still on medication, and all of them were still on antidepressants. Five of them were taking the same antidepressant that had, on an earlier occasion and at a higher dose, caused an adverse behavioral or emotional reaction. The 34 patients were all doing relatively well, with no further problems, and no anticipated change in their medication regimes.

All of the behavioral reactions were readily controlled by discontinuing the offending agent or lowering the dose. In most cases, the adverse events were dealt with over the telephone. The reactions subsided quickly, with no lasting effects. The three suicide attempts were of decidedly low lethality. No patient had to be hospitalized.

Neither age, nor race, nor gender was predictive of, or especially prone to behavioral toxicity. Neither was diagnosis. The 128 patients had a number of different diagnoses (Table 5). Mood disorders and ADHD were the most frequent. (There were 30 patients whose *only* diagnosis was ADHD. They also had symptoms of anxiety, depression and/or oppositional behavior, but not to a degree sufficient to warrant an additional diagnosis.) There was no difference among the different diagnostic groups in terms of behavioral toxicity in general or suicidality in particular (chi-square 15.03, df 16, NS).

**Table 5. Behavioral Toxicity by Diagnosis**

| | NBT | BT | BT-S |
|---|---|---|---|
| ADHD | 48 | 20 | 5 |
| ODD | 5 | 2 | 1 |
| OCD | 10 | 8 | 2 |
| MAJOR DEPRESSION | 25 | 7 | 3 |
| MOOD DISORDER NOS | 5 | 4 | 0 |
| BIPOLAR DISORDER | 3 | 1 | 1 |
| SCHIZO-AFFECTIVE DIS | 1 | 1 | 0 |
| GEN ANXIETY DISORDER | 15 | 5 | 3 |
| ASPERGER'S SYNDROME | 4 | 3 | 2 |

Regardless of diagnosis, the occurrence of suicidal behavior, self-injury, aggression, disinhibition and extreme emotional instability was very common in all of the patients prior to treatment with antidepressant medications (Table 6). In Table 6, the data are presented for the three groups. (The BT-S patients are not included in the BT group). In fact, suicidal behavior, self-injury and disinhibition were significantly more likely to have been a problem prior to treatment in the patients who developed drug-induced behavioral toxicity following treatments. This was especially true of the BT-S group; no fewer than 10 of the 11 patients who were suicidal and/or self-injurious on antidepressants had been suicidal and/or self-injurious prior to treatment.

**Table 6. Premorbid behaviors in the three patient groups.**

| **Premorbid Behavior** | **BT** | **BT-S** | **NBT** | **chi-square** | **p** |
|---|---|---|---|---|---|
| | N=25 | N=11 | N=92 | | |
| **Suicidal behavior** | 4 | 8 | 12 | 16.4 | <0.001 |
| **Self Injurious behavior** | 10 | 4 | 14 | 6.72 | <0.05 |
| **Aggression** | 13 | 4 | 17 | 1.92 | NS |
| **Disinhibition** | 15 | 2 | 17 | 12.9 | <0.01 |
| **Extreme emotional instability** | 11 | 4 | 15 | 1.13 | NS |

## DISCUSSION

If these data are at all representative of what really happens to children who are treated with modern antidepressants, there is ample reason for concern. There is also cause for re-assurance. The fact that behavioral toxicity occurred so frequently in connection with antidepressant treatment (36 of 128, or 28% of child and adolescent patients) is cause for concern. The fact that behavioral toxicity tended to be mild, transient and easy to manage is cause for re-assurance.

The nature of the behavioral toxicity that occurred (Tables 2 & 3) can be summarized as follows: hyperactivity & disinhibition, 17 occurrences; anger & aggression, 17; dysphoria and extreme emotional reactivity, 13; various forms of self-injurious behavior, 12; and suicide ideation, threats or attempts, 9 occurrences. In terms of the *severity* of the problems, two observations are salient:

1. All of the problems that arose were managed successfully by discontinuing the offending drug or by lowering the dose. At worst, this generated an unscheduled visit to the Clinic; usually, matters were dealt with satisfactorily by phone. There were no injuries of any magnitude, no visits to the Emergency Room, and no hospitalizations.

2. No fewer than 34 of the 36 patients who developed behavioral toxicity continued to be treated with antidepressants after the side effect resolved, usually a different drug, sometimes the same drug at a lower dose. These were not patients for whom the decision to institute antidepressant therapy was made casually. They were all patients with serious problems of behavioral and affective dysregulation, and they needed to take medicine.

Neither demographic nor diagnostic factors predicted behavioral toxicity in general or suicidal behavior in particular. However, patients who had suicidal symptoms prior to antidepressant therapy, or who had been self-injurious or disinhibited, were more likely to have those symptoms after treatment as well. In their cases, drug treatment was associated with recurrence or aggravation of a premorbid problem. Whether the relation is temporal or a causal, we cannot say.

How do these data compare to findings on the matter reported elsewhere? They are largely in agreement. As described in Table 1, virtually all of the published reports on antidepressant treatment in children and adolescents describe the occasional (or frequent) occurrence of behavioral toxicity; indeed, all of the behavioral signs we observed have been described before. The rate of behavioral toxicity in this study is higher than in some published reports, but lower than in others.

Neither the data presented herein nor in the published literature convey any clear impression of why behavioral toxicity or suicidal behavior occurs with modern antidepressants. Nor are we inclined to speculate on the matter, beyond observing that what may happen is that activating antidepressants sometimes evoke emotionality and behavioral disinhibition in individuals who are disposed to emit those behaviors in other circumstances as well. We have, on an earlier occasion, remarked on the paradoxical side effects of SSRI antidepressants (Gualtieri, 1991).

We are not about to suggest that data generated in a study like this are equivalent to data generated in clinical trials. A retrospective chart-review is not the same as a prospective, placebo-controlled trial. But it is hardly a trivial exercise. Our method had the advantage of experienced psychiatrists and psychologists, who knew the patients and their families very well, and who were available to take phone-calls in the evening. Most clinical trials rely on research assistants, with varying degrees of training and experience. Before writing something down in a chart, an experienced clinician filters the information for importance and reliability; this is different from a research assistant checking a box on a rating scale. We also had the advantage of having known the children for a long time before they were treated with antidepressants, and, most important, of having followed them after they were treated.

In spite of these differences, there is broad agreement between our findings and the summary review commissioned by the FDA. Behavioral toxicity, including suicidal behaviors, is not infrequently met with when children and adolescents are treated with modern antidepressants. Patients and families should be warned accordingly.

Nevertheless, we do not agree on all points. Neither the results of this study, our clinical experience, nor our reading of the wider literature leads us to believe that any one modern antidepressant is more or less likely to induce behavior toxicity or suicidal behavior. In fact, similar effects occur in patients treated with bupropion, a modern antidepressant that is not serotonergic at all. We also feel secure in advising patients, and their families, that behavioral toxicity is a transient problem that is readily corrected when the offending agent is removed, or the dose lowered. The problems that arise are not trivial, but nether are they dissimilar to the problems the patients had before and which led us to conclude that antidepressant treatment was necessary. There is no reason to think that antidepressants are dangerous. Still, no drug should

ever be prescribed, to a child, or to an adult, for that matter, unless there are reliable lines of communication to address, promptly, the sudden emergence of untoward effects.

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