Selective Serotonin Reuptake Inhibitor (SSRI) Drugs: More Risks Than Benefits?

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ABSTRACT

Anecdotal reports have suggested that selective serotonin reuptake inhibitors (SSRIs) may cause suicidal or violent behavior in some patients. Because of the publicity surrounding certain events, and the numerous lawsuits that have been filed, a review of benefits and risks is needed.

At most 30% of patients receive a benefit from SSRIs beyond the large placebo effect in certain mental conditions, especially depression, according to a recent meta-analysis of published trials. An equally recent meta-analysis of all SSRI trials submitted to the FDA showed a small benefit for the severely depressed patients only. Many early unpublished trials did not show any benefit.

Adverse effects are common, occurring in up to 75% of subjects. Severe adverse effects may be underreported. Meta-analyses of controlled trials did not include any actual suicides or murders, but only suicidality, some finding, in 1991 and 2007, no evidence even of suicidality. Other meta-analyses using many of the same trials found that suicidality doubled to 1 in 500 on SSRIs compared with placebo or non-SSRI antidepressants, but did not include any actual suicides or murders. The trial designs were devised by SSRI makers to prevent reports of suicides, by eliminating subjects with the slightest trace of suicidal tendencies. Retrospective studies by others showed actual suicides on SSRIs with a relative risk (RR) of 2–3 compared with non-SSRI antidepressants, with an increased incidence of 123/100,000.

Lower doses than the smallest available ones were found to maintain benefits in a majority of patients while reducing risks.

No causal connection between SSRIs and suicide and/or violence has been proved; neither has it been ruled out. Physicians need to be vigilant, and aware of legal precedents that may subject them to enhanced liability when prescribing these drugs.

The Genesis of SSRIs

Fluoxetine (Prozac in the U.S., see Table 1), introduced in 1988 to combat depression, was the fourth selective serotonin reuptake inhibitor (SSRI) on the U.S. market, after being seriously considered by Eli Lilly as an antihypertensive drug. Unlike the earlier "tricyclics" (amitripyline, clomipramine, dothiepin, imipramine, etc.) and other drug classes, SSRIs acted on the brain to raise levels of the neurotransmitter serotonin without raising the levels of norepinephrine. This was thought to be a benefit in treatment of depression, and later anxiety, panic, social phobia, obsessive-compulsive disorder (OCD), and many other conditions.[1] The SSRIs listed in Table 1 are among the most frequently prescribed in the U.S., and compete with the five non-SSRIs shown, and others.

Benefits of SSRIs

A prominent recent meta-analysis of Bridge et al.[2] included 27 trials of SSRIs for three defined mental conditions: major depressive disorder (MDD), OCD, and non-OCD anxiety disorders. Benefits, compared with placebo, were found to be highly statistically significant. For MDD, data from 13 trials showed benefit in 61% vs. 50% on placebo, a gain of 11% absolute (NNT=10), $P<0.001$ for all ages of participants. For OCD, data from six trials showed benefit in 52% vs. 32% on placebo, a gain of 20% absolute (NNT=5), $P<0.001$ for all ages. For non-OCD anxiety, data from 6 trials showed benefit in 69% vs. 39% on placebo, a gain of 30% absolute (NNT=3), $P<0.001$ for all ages. These results represent the maximum expectation of benefit from SSRIs since 22 of the 27 trials were financially supported by SSRI makers, and thus subject to the routinely positive bias of industry-sponsored clinical trials.[3]

Jay S. Cohen, M.D., author of the 2001 book *Over Dose: the Case Against the Drug Companies*, wrote that half his patients did well on fluoxetine, but he noted a high incidence (50%) with side-effects. Cohen also cited a pre-approval study showing that the standard 20 mg per day starting dose helped 65% of patients, while 5 mg helped 54%, so Cohen became one of the pioneers in using lower doses before Lilly made them available.[4] The 1996 *Physicians Desk Reference (PDR)* entry for paroxetine, at least, confirmed that the 17 most common side-effects were dose-dependent.

In four observational cohort studies of four common SSRIs reported by physicians as part of the prescription-event monitoring program in the UK, with more than 10,000 patients in each drug group, only 36% of the physicians reported fluvoxamine as effective, compared with 60% for fluoxetine, sertraline, and paroxetine. These possible benefit rates, which include the placebo effect, parallel the percentage of patients remaining on the drug for 2 months.[5]

Table 1. Commonly Prescribed SSRIs and Other Antidepressants

USA Trade Name	Generic Name
SSRIs	
Celexa	citalopram
Luvox	fluvoxamine
Paxil	paroxetine
Prozac	fluoxetine
Zoloft	sertraline
non-SSRIs	
Effexor	venlafaxine
Remeron	mirtazapine
Serzone	nefazodone
Wellbutrin	bupropion
(UK)	dothiepin

An old trial of placebo for anxious and depressed subjects reduced distress in 43%.[6] Three meta-analyses of the antidepressant literature that appeared in the 1990s independently concluded that two-thirds of the effectiveness attributed to SSRIs is actually placebo effect.[1] In a series of nine controlled studies on hospitalized patients with depression, 57% of those given placebo showed improvement in 2–6 weeks.[7]

A 1998 meta-analysis of 47 trials on antidepressant medication including SSRIs indicated that 75% of the response to them was duplicated by placebo. This meta-analysis was criticized on several grounds. Therefore, Irving Kirsch, Ph.D., of the University of Connecticut, with other authors, obtained data submitted to the FDA on every placebo-controlled clinical trial on the six most widely used SSRIs, and published a meta-analysis on 47 trials, finding a small, clinically insignificant effect.[8] This work was updated in 2008:

> Analyses of datasets including unpublished as well as published clinical trials reveal smaller effects that fall well below recommended criteria for clinical effectiveness. Specifically, a meta-analysis of clinical trial data submitted to the U.S. Food and Drug Administration (FDA) revealed a mean drug–placebo difference in improvement scores of 1.80 points on the Hamilton Rating Scale of Depression (HRSD), whereas the National Institute for Clinical Excellence (NICE) used a drug–placebo difference of three points as a criterion for clinical significance when establishing guidelines for the treatment of depression in the United Kingdom.[9]

Kirsch et al. concluded that the updated findings from 35 carefully vetted trials suggest that, compared with placebo, the four new-generation antidepressants (fluoxetine, venlafaxine, nefazodone, and paroxetine) do not produce clinically significant improvements in depression in patients who initially have moderate or even severe depression. They show statistically significant but clinically minor effects only in the most severely depressed patients. Moreover, the significance of the effect probably is based on a decreased responsiveness to placebo, rather than increased responsiveness to medication. Given these results, the researchers conclude that there is little reason to prescribe new-generation antidepressant medications to any but the most severely depressed patients unless alternative treatments have been ineffective. In addition, they write that the decreased placebo response in extremely depressed patients, combined with a response to antidepressants comparable to that of less severely depressed patients, is a potentially important insight that should be investigated further.

Even these unimpressive findings exaggerated the benefits of antidepressants. In three fluoxetine trials and in the three sertraline trials for which data were reported, the protocol allowed replacement of patients who, in the investigators' judgment, were not improving after 2 weeks. The trials also included a 1–2 week washout period, during which patients were given a placebo prior to randomization. Those whose scores improved 20% or more were excluded from the study. In 25 trials, the use of other psychoactive medication was reported. In most trials, a chloral hydrate sedative was permitted in doses ranging from 500 mg to 2,000 mg per day. Other psychoactive medication was usually prohibited but still reported as having been taken in several trials.[9]

Perhaps such considerations led David Healy, M.D., an SSRI expert, to his conclusion that "...these drugs do not convincingly work…."[10] His evidence came from early unpublished clinical trials whose results were revealed to him at FDA hearings. For fluoxetine, Healy noted four trials with a positive result and four without. For sertraline, only one of five early studies showed benefit.[11,12]

Because of the huge placebo effect, 32–75%, most physicians unfamiliar with the studies revealing this effect are likely, in my opinion, to say that one-third to two-thirds of their patients are improved on SSRIs. This would also explain Dr. Jay S. Cohen's findings on lower doses of fluoxetine.

Adverse Effects of SSRIs

SSRIs reportedly interact with 40 other drugs to cause "serotonin syndrome." This presents as twitching, tremors, rigidity, fever, confusion, or agitation. Serotonin/norepinephrine reuptake inhibitors (SNRIs) also may cause serotonin syndrome by interactions. Most tricyclic depressants do not have these interactions, with the exception of amitriptyline.[13]

In a controlled trial of paroxetine vs. clomipramine sponsored by GlaxoSmithKline, 75% of the subjects had an adverse effect on paroxetine, 21% had a severe adverse effect, and 13% committed a suicidal act (1 in 8).[14] The 1996 *Physicians Desk Reference* (*PDR*) entry for paroxetine lists 17 side-effects with an incidence of ≥5% for approved doses. They are: asthenia, sweating, constipation, decreased appetite, diarrhea (up to 15%), dry mouth (up to 21%), nausea (up to 36%), anxiety, dizziness, nervousness, paresthesia, somnolence (up to 22%), tremor (up to 15%), blurred vision, abnormal ejaculation, impotence, and other male genital disorders. Fully 31 additional side effects with an incidence at least 1% greater than placebo were listed, including uncontrollable yawning. Murder, suicide, and suicidality were *not* included. Nor were they on comparable lists for fluvoxamine, or sertraline.

For fluvoxamine, suicide *attempts* were separately listed as "infrequent." For fluoxetine, suicidal ideation was listed as a voluntary report not proved to be drug related. For sertraline, suicidal ideation and attempt were listed separately as "infrequent." The entry for venlafaxine was: "…the possibility of a suicide attempt is inherent in depression."

Not found in the *PDR* was weight gain, which Cohen lists as a serious side effect.[4]

Typical dropout rates in recent trials are claimed to be 5% (see below), but these must be short trials, or trials with a run-in period. In a meta-analysis of 62 earlier trials with a total of 6,000 subjects, the mean total dropout rate and the proportion of dropouts due to side effects appear comparable to results in general practice: total dropout rates of between 30% and 70% have been reported by 6 weeks, of which some 30%–40% are attributed to side effects and the rest to failure of treatment.[15]

Early findings of severe adverse effects by SSRI makers came to light only after the class was established. Of 53 healthy volunteer studies on fluoxetine, the results of only 12 were openly reported. From 35 healthy volunteer studies on paroxetine, pre-launch, the results of only 14 appeared. From 35 pre-launch healthy volunteer studies on sertraline, only seven appeared. Among the unpublished trials, there was one in which all volunteers dropped out because of agitation (akathisia). In published work on sertraline, data excluded material on behavioral toxicity, including at least one suicide of a

healthy volunteer, and in a different trial, 2 of 20 volunteers became intensely suicidal. This last is consistent with the dropout rate of 5% for agitation alone in actual trials.[16] It is also consistent with Lilly's animal studies, in which previously friendly cats treated with fluoxetine started growling and hissing—an unheeded warning.[1]

Just a year after fluoxetine was introduced, Bill Forsyth of Maui, Hawaii, had taken it for only 12 days when he committed one of the first murder/suicides attributed to any SSRI. In the same year Joseph Wesbecker killed eight others and himself in a Louisville, Ky., printing plant where he worked, after 4 weeks on fluoxetine. Yet as early as 1986, clinical trials showed a rate of 12.5 suicides per 1,000 subjects on fluoxetine vs. 3.8 on older non-SSRIs vs. 2.5 on placebo! An internal 1985 Lilly document found even worse results and said that benefits were less than risks. Such documents were released into the public domain by Lilly as part of the settlement in the Wesbecker case.[17] Fifteen more "anecdotes" of murder/suicide, three with sertraline, were listed by DeGrandpre.[1]

Lilly's denials of a link to murder/suicide on national television and elsewhere cited a sponsored meta-analysis in *BMJ* in 1991, which exonerated fluoxetine as a cause of suicidal acts or thoughts without even mentioning actual murder or suicide.[18] This study included only 3,067 patients of the 26,000 in the clinical trials it utilized. None of the trials had a declared endpoint of suicidality. Some of the trials had been rejected by the FDA. No mention was made that Lilly had had benzodiazepines co-prescribed to minimize the agitation that had been recognized with fluoxetine alone. The 5% dropout rate for anxiety and agitation (akathisia) would have taken out the most likely candidates for suicide.[16] Nevertheless, the 1991 study had its intended effect. For example, in 2006 a 900-page tome entitled *Drug Injury*, which was aimed at attorneys, cited *only* this study, and *only* failed lawsuits concerning SSRIs.[19]

The 2007 meta-analysis by Bridge et al.[2] may be influenced by indirect conflicts of interest that are hard to prove based on the financial disclosures. Their paper pooled excess risk above placebo for "suicidal ideation/suicide attempt" from 27 trials. The excess risk was said to be 0.7% and statistically significant across all indications, but *not* significant within each indication. Of the 27 trials, only five were *not* sponsored by the drug maker, and one of these, the 2004 Treatment for Adolescents with Depression (TADS) study of fluoxetine, had the highest rate of suicidality—7% above placebo. Most of the same trials were used in a meta-analysis by the FDA, which found a statistically significant excess risk of 2% (4% vs. 2% on placebo, 1 in 50 more). Bridge et al. used a random-effects calculation, while the FDA used a fixed-effects calculation. In commenting on the negative findings, Bridge et al. write: "No study [in our meta-analysis] was designed to examine suicidal ideation/suicide attempt as a study outcome, and in fact most trials were conducted in patients who had been carefully screened to exclude youths at risk." No actual murders or suicides associated with SSRI use were reported. Did the designs of the studies preclude detection or reporting?

The Bridge meta-analysis was not just a vindication of SSRIs, as communicated to the *Wall Street Journal* by Gilbert Ross, M.D., Medical Director of the American Council on Science & Health. Ross went further, commenting that the FDA "Black Box warning" (see below) was counterproductive because it was discouraging the use of antidepressants! Ross speculated that the lethal rampage of the Virginia Tech shooter might have resulted from premature cessation of medications.[20]

SSRIs in general have long lifetimes in the body. Fluoxetine and its active metabolite in particular have a half-life of 16 days, according to the 1996 *PDR*. In a reexamination of trials in which suicides or attempts during the inadequate washout period were not blamed on the drug, it was shown that the relative risk (RR) of suicidal acts ranged from 3 for sertraline to 10 for fluoxetine.[21]

A concurrent meta-analysis of 24 trials by Kaizar et al.[22] utilized Bayesian statistics, a valid choice, in my opinion, because data do not have to follow a Gaussian or normal curve to yield valid results, and this method can be used to revise probabilities to determine whether a specific effect was due to a specific cause.[23] They found an association between SSRI use and suicidality with odds ratios of 2.3 (95% confidence interval [CI] 1.3-3.8), when the diagnosis was MDD, not OCD, anxiety, nor ADHD. Non-SSRI antidepressants were said to have no association with suicide. This supports the FDA's findings and requirement, as of October, 2004, for a Black Box warning for all SSRIs, to monitor children and adolescents for suicidality. Kaizar et al. were concerned that there were no completed suicides among 4,487 subjects in the trials; that the trial times were too short at median length of 8 weeks; and that in 10 of the 12 MDD studies, *children and adolescents with an elevated baseline risk of suicide were excluded.* Again, there was no citation of actual suicides associated with SSRIs and no citation of Healy's work.[16,17,24]

Healy reviewed epidemiologic studies that have been cited to exonerate SSRIs.[16] One was analyzed by Healy to show a threefold increase in suicidality compared with other antidepressants.

While "treatment-related activation" has been considered primarily with regard to suicidality, it can lead to harm to others as well as to self. Healy[17] summarized data on "hostile episodes" provided by GlaxoSmithKline from placebo-controlled trials with paroxetine in subjects of all ages: 9,219 on paroxetine and 6,455 on placebo. The rubric of "hostility" was used in the trial to code for aggression and violence, including homicide, homicidal acts, and homicidal ideation, as well as aggressive events and "conduct disorders." No homicides were reported from these trials. Overall, during both therapy and withdrawal, the RR was 2.1 for hostile events. In children with OCD the RR was 17. Separately, in healthy volunteer studies, hostile events occurred in 3 of 271 subjects on paroxetine vs. none of 138 on placebo. In trials of sertraline on depressed children submitted by Pfizer, 8 of 189 subjects discontinued for aggression, agitation, or hyperkinesis (a coding term for akathisia), compared with 0 of 184 on placebo. In clinical practice, the term akathisia has been restricted to demonstrable motor restlessness, but if that is the only effect, it would have been called dyskinesia according to Healy, who cites four studies linking akathisia to both suicide and homicide.[17]

Actual suicides were combined with suicide attempts in a 2005 meta-analysis of 702 trials of SSRIs vs. either placebo or an active non-SSRI control.[25] Studies were rejected if the citation was a review, a result of duplicate publication, too short, crossover, or had no reporting of actual or attempted suicide. The studies meeting the criteria included 88,000 patients. For attempted suicide, the RR was 2.3 for SSRIs vs. placebo (95% CI, 1.14-4.55). The number needed to treat to harm (sometimes called the "reverse NNT") was 1 in 684.[2] There was no difference in actual suicide. Of the 702 trials, 104 failed to report adverse events below a certain pre-set limit of 3%, 5%, or 10% of patients. Only 493 trials reported dropout rates, with a mean of 29%, and the mean follow-up time was only 11 weeks. Thus, there was clearly gross underreporting of adverse effects.

Table 2. Suicides Related to SSRIs or Mirtazapine

Drug	No. Patients	No. Suicides	Incidence/100,000
SSRIs			
Fluoxetine	12,692	31	244
Fluvoxamine	10,983	20	183
Paroxetine	13,741	37	269
Sertraline	12,734	22	173
Total SSRI	50,150	110	219
Mirtazapine	13,554	13	96

Source: British Drug Safety Research Unit, adapted from Healy, 2003[16]

More importantly, because actual suicides are involved, Healy cited a study by Donovan et al.[26] that demonstrated a RR=3.4 (P<0.01) for SSRIs compared with all non-SSRI antidepressants involving 222 actual suicides, of which 41 were among patients who had an SSRI within a month of their suicide.[26] Also the British Drug Safety Research Unit recorded more than 110 suicides in 50,000 patients taking an SSRI, an incidence of 219/100,000 compared with 96/100,000 for the non-SSRI mirtazepine (Remeron), an increase of 123/100,000, or 1 in 813 (Table 2). Thus the RR for actual suicide in patients taking SSRIs was 2.3 (or 2.8 for paroxetine). Even here, though, no murders were listed.[16]

In another study cited by Healy, Jick et al.[27] reported 143 actual suicides among 172,598 patients taking antidepressants. The relative risk of suicide in patients taking fluoxetine was 2.1, compared with those taking the tricyclic antidepressant dothiepin. The risk was not age-dependent.

SSRI makers keep insisting that there will be more suicides if SSRIs are *not* used as frequently as now. But the RR of 2–3 shown in studies is a *net* number that *includes* the number of suicides that may have been prevented, so SSRI use is associated with more suicides, not fewer.

SSRIs Provide 1,600 Anecdotes of Violence

The International Coalition for Drug Awareness in cooperation with the Prozac Survivors Support Group has produced a website on which about 1,600 violent incidents associated with SSRI use are described (www.ssristories.com/index.php). The first column on the type of incident (murder, school shooting, etc.) is a hot link to a publicly available description of the incident, typically a local newspaper article. A selection of 10 entries (rows) is presented here as Table 3.

About 360 suicides are tallied as well as about 400 murder incidents, many of which were multiple murders, each linked to SSRI use (Rosie Meysenburg, personal communication, 2008). As the number of "anecdotes" exceeds 1,600—hardly a small number—the association of SSRIs with murder/suicide, often combined, must be taken seriously.

The SSRI website was searched to find combined murder/suicide incidents attributed to a specific SSRI. There were three for fluvoxamine, four for citalopram, 10 each for paroxetine and sertraline, and 31 for fluoxetine. Where the studies above substantiated suicide from SSRI use, the total on the SSRI website of 48 simultaneous murder/suicide incidents associated with SSRI use ties together SSRIs and murder. Since there were about two murders per suicide, we may infer that the murder rate on SSRIs could be about 250/100,000. Since no clinical trial involving multiple homicides is ever likely to be run, no firmer evidence is likely to be found. Healy noted that much of the evidence for suicide and murder came from the efforts of journalists and lawyers.[12]

Note that the website carries a prominent warning that "withdrawal can often be more dangerous than continuing on a medication."

Nine violent events cited elsewhere—seven court cases of homicide (one attempted) and two assaults—were associated with specific SSRIs: three with paroxetine, three with sertraline, two with fluoxetine, and one with venlafaxine.[17]

Skeptics have cast doubt on whether the prescribed SSRIs were actually taken, especially since many medical records of juveniles were sealed. In the Columbine, Colo., shootings the toxicology report showed "therapeutic" levels of fluvoxamine in one of the shooters. The Red Lake, Minn., shooter had fluoxetine found, according to news items referenced on the website.

A 2004 editorial in *JAMA* by Simon Wessely, M.D., a spokesman for Eli Lilly, and Robert Kerwin, Ph.D,[28] cited only a single paper by Healy[24] as a source of claims of suicidality that have found a receptive media audience. Tellingly, the only study described at length is by Jick et al.[29] on the correlation of SSRI use and "attempted suicide," in which the rates on dothiepin, amitriptyline, fluoxetine and paroxetine were not statistically different. Actual suicides in this study (seven on SSRIs) were not mentioned by Wessely and Kerwin, nor were the 143 suicides in Jick's earlier paper.[27] Jick et al. have been supported partially by GlaxoSmithKline and Pfizer. No study that reported actual suicides on SSRIs was described in detail, let alone refuted. Wessely and Kerwin wrote: "The problem is that depression is unequivocally and substantially associated with suicide and self-harm." True, but this not the *whole* truth.

Table 3. Selected Violent Incidents Associated with SSRI Use

INCIDENT TYPE	DRUG	DATE	LOCATION	ADDITIONAL INFORMATION
School Shooting	Prozac	March 24, 2005	Minnesota	10 dead, 7 wounded: dosage increased one week before rampage
School Shooting	Zoloft	October 12, 1995	South Carolina	15 year old shoots two teachers, killing one: then kills himself
School Shooting	Luvox/Zoloft	April 20, 1999	Colorado	Columbine High School: 15 dead, 24 wounded
School Shooting	Prozac	November 5, 1999	Oregon	Four dead, twenty injured after Prozac withdrawal
School Shooting	Celexa	August 30, 2006	North Carolina	Teen shoots at two students: kills his father
Murder-Suicide	Paxil	August 9, 2001	Wyoming	Jury finds Paxil was cause of murder-suicide
Robbery/Armed	Paxil	August 10, 2003	England	Man cleared of charges due to Paxil withdrawal defense
Murder	Prozac	July 11, 2003	Louisiana	Not guilty by reason of Prozac induced insanity: mother kills daughter
Murder-Suicide	Prozac	September 14, 1989	Kentucky	Nine dead, 12 wounded in workplace shooting
Suicide	Effexor/Zoloft	October 6, 2004	Nebraska	11 year old hangs himself: lawsuit

Source: List of 1,600 violent incidents found at www.ssristories.com/index.php. Accessed Feb 21, 2009.

The legal defense by Lilly, repeated by the media and others, is that any suicides are caused by the condition, depression, not by their drug—whether the violence is associated with short-term drug use, long-term drug use, increased doses, withdrawal, or rechallenge. There is no website, as far as I know, for violent acts committed by persons who never received SSRIs, or for total violent acts; hence the denominator for violent acts is not known. Also unknown is the fraction of potentially violent persons who are treated with SSRIs, or of persons treated with SSRIs who are potentially violent. The published studies on actual suicide, however, compare patients on SSRIs with similar patients on non-SSRI antidepressants or placebo. Children diagnosed with OCD, not depression, also became suicidal on SSRIs, as did healthy volunteers. Actual two- to threefold increases in suicide rates have been demonstrated as well as they could be.[1,11,17] How else could such effects be demonstrated? Who would submit, and what institutional review board or human subjects committee would approve a study explicitly designed to show whether assaultive, homicidal, or other violent behavior increases in subjects prescribed the study drug?

Denial by SSRI makers of culpability for these risks continues to this day. Whether physicians' acting on the Black Box warnings of 2004 and 2007 for all SSRIs will diminish the incidence of murders and suicides is not yet known.

200 SSRI-related Lawsuits

Following the introduction of fluoxetine in 1988, only a year passed before an early user committed multiple murders and suicide; many other examples followed. More than 200 lawsuits have been begun by users of SSRIs and victims' families charging wrongful death or failure to warn; these have had mixed outcomes. There is now legal precedent for SSRIs as a cause of murder, and the maker of the SSRI is potentially liable for damages, according to David Healy.[10-12]

Eli Lilly responded with total denial to the lawsuits claiming a link between fluoxetine and violence. Several claims were settled out of court with secret details and no admission of guilt. The Australian David Hawkins was freed from a murder charge by a finding of temporary insanity caused by using sertraline. Tim Tobin of Wyoming won $6.4 million from SmithKline Beecham when a jury found that a murder/suicide committed by Donald Schell was attributable to use of paroxetine.[1] There are four other homicide cases in which the SSRI was deemed to have contributed, resulting in a suspended sentence in one case and an insanity verdict in another. One case of homicide, with a guilty verdict and a life sentence, followed a judicial ruling that akathisia was associated with SSRI use, but that a causal relationship with homicide could not be argued; thus the link of an SSRI with homicide was disallowed. This was in direct conflict with the findings of the four trials cited above.[17]

The SSRI website was searched to find murders related to a specific SSRI whose perpetrators were acquitted based on temporary SSRI-induced insanity. There were two cases with sertraline, four cases with paroxetine, and four cases with fluoxetine. So a precedent has been established for legal recognition that an SSRI can be a cause for murder, and that the drug maker can be found liable for damages. The notices of suicidality for the SSRIs found in the PDR or package inserts before 2004 did not really warn of actual suicide or murder.

The Black Box warning of 2004 about possible suicide in children under 18 years of age did not cover adults or murder at any age, so potential liability for the SSRI makers still exists. In 2007 the warning was extended to persons under age 25 years. David Healy was quoted as saying that the warning was overdue, and that the risk was not likely to disappear above age 25.[30] This was shown by the trials from GlaxoSmithKline on paroxetine cited above.

Conclusions

Antidepressants are extraordinarily difficult to assess for risks or benefits in trials.

At most, 11%–30% of patients with depression or related conditions who take SSRIs actually benefited beyond the placebo effect on normal doses. Of the perceived benefit, 32%–67% can be attributed to the placebo effect.

Adverse effects, mostly dose-dependent, will appear in up to 75% of patients on normal doses. Of these, studies suggest that suicidality will be observed in an additional 2%–13% (1 in 50 to 1 in 8) of patients on normal doses, beyond what is seen on placebo or many non-SSRI antidepressant drugs. This is sufficiently frequent that a typical prescribing physician should observe examples in routine practice.

The actual suicide rate could be about 123/100,000 (1 in 813) higher in patients on SSRIs than in those on tricyclics or placebo. Studies show that many more suicides are *attempted* on normal doses of SSRIs beyond what is seen on placebo or many non-SSRI antidepressant drugs.

Available data suggest that actual murders may be committed at about the rate of 250/100,000 (1 in 400) SSRI-treated patients beyond what is seen on placebo or many non-SSRI antidepressant drugs, and that many more murders will be attempted on normal doses as well. While correlation does not prove causation, and results of court trials are not medical science, the data for suicide are solid, and the association of murder with *simultaneous* suicide is very suggestive.

Now that there is a stronger Black Box warning, physicians who ignore it may be liable for damages; the warning primarily protects the manufacturers of SSRIs.

There is obviously great peril in drawing conclusions about causation from press reports or court decisions. While manufacturers have a vested interest in exonerating their drugs, plaintiffs have an interest in blaming it, and defendants in exonerating themselves. We need careful, independent analysis of existing study data. In addition to randomized controlled trials, evidence from basic science (neuropharmacology) and challenge/dechallenge/rechallenge investigations needs to be sought. Both the public and individual patients are imperiled by an incorrect answer to the pressing questions about these widely prescribed drugs.

Future studies may show lower levels of murder and suicide with close supervision, and with better matching of this drug type to patient type.

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