Professor David Healy

The dangers of Cipramil (citalopram)

The SSRI that caused the deaths of Shane Clancy and Sebastian Creane
Re. SHANE CLANCY

I have been asked by James MacGuill to prepare a report for the inquest on Mr Clancy to cover the effects of the antidepressant drug citalopram, which Mr Clancy had been taking for some weeks prior to his death.

I am in receipt of Mr Clancy’s medical records from the Carlton Clinic (2 pages), along with post-mortem and toxicology reports. I have discussed his medical history with his mother Leonie Fennell.

In this report I will deal primarily with the effects of citalopram with some attention to Mr Clancy’s case, but I am not attempting to establish at this point the precise cause of Mr Clancy’s death.

Background

My professional experience with antidepressant medications and selective serotonin reuptake inhibitors ("SSRIs," dates back more than twenty five years. My post-doctoral thesis, conducted from 1980 to 1985, was on serotonin reuptake mechanisms in patients. I was an early prescriber of serotonin reuptake inhibiting drugs following their launch in Britain and have had extensive experience with them, including zimelidine (Zelmid), fluvoxamine (Luvox), fluoxetine (Prozac), sertraline (Zoloft), citalopram (Cipramil/Celexa) and paroxetine (Paxil/Seroxat).

I am a Professor of Psychiatry at Cardiff University, and a former secretary of the British Association for Psychopharmacology. I have published over 20 books on psychiatry, mostly linked to psychopharmacology, including the standard histories of the antidepressants, antipsychotics and mood-stabilizers, and books on the use of these drugs that have been translated into several different languages and are now in their 5th edition. I have also authored 50 chapters in books on similar issues, over 150 peer-reviewed articles and over 250 other pieces, for the most part dealing with aspects of psychopharmacology.

I have been invited to talk at close to 300 international meetings on all continents – again largely on the issue of psychotropic drugs and in particular the antidepressant group of drugs. I have lectured about SSRIs and their ability to induce suicidality in some patients at dozens of Universities and professional associations around the world, including Harvard Medical School, Department of Epidemiology, Columbia University, Yale, University of Toronto, British Association of Psychopharmacology, Royal College of Psychiatrists, European College of Neuropsychopharmacology, Irish College of Psychiatrists, International Society of Pharmacoepidemiology, American Psychiatric Association, Hungarian Psychopharmacology Annual Meeting, Instituto Superiore de Sanitate in Rome and Tokyo University.

I have been a consultant to most of the SSRI manufacturers including Eli Lilly and Company, Pfizer and SmithKline Beecham (now GlaxoSmithKline). I have conducted clinical trials, given lectures, and chaired symposia for these companies. Years before ever being asked to be an expert witness for any plaintiffs, I was
asked by Eli Lilly (the maker of Prozac) to provide my expert opinion regarding then-pending Prozac litigation related to a homicide/suicide case in Louisville, Kentucky.

Among the journal publications dealing with SSRIs and suicide and company manipulation of clinical trial data in relation to this issue are the following:


“Antidepressant Induced Suicidal Ideation,” Human Psychopharmacology, Vol. 6, 329-332 (1991);

“The Fluoxetine and suicide controversy: a review of the evidence,” CNS Drugs 1:223-231 (Mar. 1994);

“Suicide in the Course of the Treatment of Depression,” Journal of Psychopharmacology 13: 94-99 (1999);

“A failure to warn,” International Journal of Risk & Safety in Medicine, 151-156 (1999);

“Emergence of antidepressant induced suicidality,” Primary Care Psychiatry, 6, 23-28 (2000);

“Modeling suicide risk in affective disorders,” European Psychiatry 16, 400-405, Boardman A, Healy D (2001);

The dilemmas posed by new and fashionable treatments. Advances in Psychiatric Therapy 7, 322-327 (2001);

“Antidepressants and Suicide: Risk-Benefit Conundrums,” J Clin Neurosci, 28(5):3331-337 (2003);

“Lines of Evidence on SSRIs and Risk of Suicide, Psychotherapy and Psychosomatics,” 72:71-79 (2003); and

“The Interface between authorship, industry and science in the domain of therapeutics,” British Journal of Psychiatry 182, 22-27, Healy D, Cattell D (2003);

“Association between suicide attempts and selective serotonin reuptake inhibitors; systematic review of randomised controlled trials,” British Medical Journal, Volume 330 (19 February 2005);


“Antidepressant drug use and the risk of suicide,” International Review of Psychiatry 17, 163-172. Healy D, Aldred G (2005);


I have reviewed virtually every study, both published and unpublished conducted on the most popular SSRIs (Seroxat, Zoloft and Prozac). I have reviewed hundreds of thousands of pages of internal company documents concerning these drugs and dozens of depositions of company employees, scientists, academics, experts and regulatory personnel.

I practice clinically treating both inpatients and outpatients, who are depressed and anxious, of all ages, using a full range of treatment methods.

Since 1997, I have been involved in a series of cases involving suicide or homicide on SSRI drugs. Two American SSRI civil cases that have gone to trial, the Forsyth case (Prozac) and the Tobin case (Seroxat). I have reviewed documents and prepared reports in other US civil cases, Berman, Cassidy, Lown, Prior & Blowers (Prozac), Miller, Motus & Witzczak (Zoloft), Coburn, Tucker, Van Dyke, Turek and Collins (Seroxat), and in a set of cases involving dependence on Paxil in both the United States and United Kingdom.

I have been consulted on and declined to offer a view on or else offered a view that the drug was not involved in precipitating violence or suicide in over 100 other cases involving SSRI antidepressants. This work was almost entirely done without charge.

I have offered reports for inquests on approximately 10 individuals who have committed suicide following intake of one or other of the major SSRI drugs. This work did not aim at claiming the drug caused the problem in individual cases but rather at establishing a general causation case and indicating the likely possibility that drug treatment might have been a factor, leaving it to the discretion of the coroner to take this evidence into account if indicated. This work was done pro bono.

I have testified in one US criminal case, Pittman, involving Zoloft, and two UK criminal cases involving Prozac, one involving Seroxat, one involving Citalopram, and reviewed documents and prepared reports in two Australian criminal cases, Hawkins, involving Zoloft, and Bentley, involving Effexor.

I have been involved in 2 Canadian cases linked to the patenting of Zyprexa, 2 US cases involving suicide on Zyprexa, 1 securities case involving Forrest Pharmaceuticals, who marketed Citalopram in the US, and a series of cases linked to birth defects in mothers taking Seroxat.

Citalopram & Suicide:
Citalopram is one of the Selective Serotonin Reuptake Inhibiting (SSRI) group of drugs, which include drugs such as Prozac and Seroxat. It is used primarily for the treatment of depression and anxiety.

There is substantial evidence that the SSRI group of drugs in general can induce suicidality in patients who would not otherwise be at risk of suicide. The evidence for this claim stems from careful clinical observation of patients in whom suicidality appears to emerge on treatment, where it clears up when treatment is discontinued reappears on the reintroduction of the same SSRI agent or another SSRI agent. This evidence is supported from clinical trials in patients where the rate of suicidal acts and completed suicides in patients being treated with SSRIs compared to placebo is 2½ times greater on the active agent than it is on the placebo (see references above).

This evidence is further supported by clinical trials of SSRI agents in patients who are anxious or who are being treated for other disorders than depression, in which there is a significant excess of deaths on SSRI or other antidepressants compared to placebo. The significant point about this is that these other conditions show a very low natural rate of suicide or suicidal acts but in these conditions also the rate of suicides and suicidal acts is doubled on the SSRI. This appears to be true for both adults and children.
The evidence of this doubling of suicides and suicidal acts escaped attention of clinicians, academics and regulators for many years as a number of pharmaceutical companies making SSRIs have handled the data regarding suicides and suicidal acts in ways that would appear to be both unscientific and unethical. Data has been miscoded so that suicides and suicidal acts on the active agents have disappeared or have been coded under the heading of placebo when these suicides or suicidal acts did not happen on placebo. I have a series of books and articles on these issues most notably a book published by New York University Press – Let Them Eat Prozac.

The data for suicides and suicidal acts in placebo controlled trials of antidepressant drugs is laid out in Table 1 below; this table has been drawn from figures submitted to the Medicine’s and HealthCare Regulatory Agency review of antidepressants and suicide published in December 2004.

These figures give a relative risk of completed suicides of 2.62 where the 90% Confidence Interval (C.I.) is 1.05, 6.54, and the 95% CI 0.88, 7.79

The relative risk for completed suicides and suicidal acts combined is 2.80 with a 90% C.I of 2.10, 3.90, and 95% C.I. of 1.88, 4.15

There is no reason to think there are significant differences between citalopram and other drugs from the group such as fluoxetine (Prozac) or paroxetine (Seroxat), other than on factors not relevant to this case such as the greater propensity of one or other of these drugs to cause dependence and withdrawal.

Table 1: MHRA Expert Working Group Suicides & Suicidal Acts with data on Paroxetine from GSK May 06 analysis (minus the results for intermittent brief depression).  

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>1/1320</td>
<td>1/0622</td>
<td>11/1320</td>
<td>5/0622</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0/2648</td>
<td>1/2088</td>
<td>06/2648</td>
<td>1/2088</td>
</tr>
<tr>
<td>Total C &amp; E</td>
<td>1/3968</td>
<td>2/2710</td>
<td>17/3968</td>
<td>6/2710</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2/4186</td>
<td>2/3396</td>
<td>24/4186</td>
<td>10/3396</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>5/2618</td>
<td>0/0388</td>
<td>09/2349</td>
<td>3/0388</td>
</tr>
<tr>
<td>Sertraline</td>
<td>4/7169</td>
<td>0/5108</td>
<td>20/7169</td>
<td>8/5108</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>4/6153</td>
<td>0/2962</td>
<td>25/6153</td>
<td>8/2962</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1/8058</td>
<td>0/5266</td>
<td>17/8059</td>
<td>4/5266</td>
</tr>
<tr>
<td>Total</td>
<td>17/32,153</td>
<td>4/19,830</td>
<td>119/32153</td>
<td>30/19,830</td>
</tr>
</tbody>
</table>

These figures do not stand in isolation. They come supplemented with convincing clinical reports of individuals becoming suicidal on these drugs, where the problem clears up when the drug is discontinued, and reappears when the original drug or a related drug is introduced. There are a greater number of clinical reports of this type for Prozac and Seroxat than for citalopram but this is likely to be an artefact of the sequence in which these drugs were introduced to clinical practice - the adverse effect had been clearly described by the time citalopram came into use and there was less need to outline further cases.

The combination of these clinical reports and the figures above show that, pretty well beyond a shadow of doubt, antidepressant drugs including citalopram have the capacity to lead patients to commit suicide or a suicidal act who would not have done so had they not been on treatment. Treatment appears to have the capacity to disturb

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the balance of an individuals mind and this raises the question as to whether the disturbance was such that it makes a verdict of suicide inappropriate.

A further point of note is that in clinical trials of healthy volunteers with these agents healthy volunteers who can be presumed to be at no risk of suicide have become suicidal on SSRIs.

Citalopram & Violence:
The possibility that psychotropic drugs including antidepressants might be linked to violence has been recognized for over twenty years². This issue has come to the fore in recent years with reports in several instances of mass-shootings that the shooter was on an antidepressant, and subsequent legal actions that ended in settlements or verdicts against the maker of the antidepressant. These include the Fentress (Prozac - fluoxetine) and Tobin (Seroxat - paroxetine) trials³. There have been verdicts in homicide cases (Hawkins – Zolof – Zolof – sertraline), - or attempted murder (Bentley – Efexor - venlafaxine) that have also implicated the antidepressant being taken.

In general the risks posed by antidepressants in this domain have been thought to be mediated through an activation syndrome and this in turn it is thought can lead on to violence to others or to self (suicide or suicidal acts). Up to 1/4 of patients put on antidepressants may get worse during the first weeks of treatment, although not all of these will have a treatment-induced worsening⁴.

The risks stemming from treatment-related activation have been viewed primarily in terms of possible increases in the risk of suicide among a subgroup of patients who react adversely to treatment. This possibility has in recent years led regulatory authorities to warn doctors about risks of suicide in the early stages of treatment with antidepressants, at times of changing dose, and during the withdrawal phase of treatment.

Some regulators, such as the Canadian regulators, have also referred to risks of treatment-induced activation following initial antidepressant use leading to harm to others⁵. The labels for all antidepressants in the United States as of August 2004 note that “anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness) impulsivity, akathisia, hypomania and mania have all been reported in adult and pediatric patients, being treated for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric”⁶.

While this wording in both the Canadian and American labels for antidepressant drugs stemmed from a series of hearings on the adverse effects of antidepressants in children, it applies to the use of citalopram in adults also.

Violence to others has been much less adequately studied than suicides and suicidal acts. After the introduction of Seroxat and Prozac, a series of studies by the Drug Safety Research Unit in Southampton gave the following figures for violence for these two drugs, which are both closely related to citalopram.

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⁶ Taken from the most recent Zoloft label, posted 8th July 2005. www.fda.gov/cder/drug/infopage/sertraline/default.htm
Table 2: Drug Safety Research Unit's Prescription Event Monitoring Studies of Paroxetine & Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine N = 13,741 First 6 months of treatment</th>
<th>Paroxetine N = 13,741 Overall</th>
<th>Fluoxetine N = 12,692 First 6 months of treatment</th>
<th>Fluoxetine N = 12,692 Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression</td>
<td>18</td>
<td>36</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>0.13%</td>
<td>0.26%</td>
<td>0.16%</td>
<td>0.38%</td>
</tr>
<tr>
<td>Assault</td>
<td>7</td>
<td>19</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>0.05%</td>
<td>0.14%</td>
<td>0.08%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Murder</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>56</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>0.19%</td>
<td>0.41%</td>
<td>0.24%</td>
<td>0.47%</td>
</tr>
</tbody>
</table>

These figures suggest that 1 in 250 people taking one of these drugs might be involved in a violent episode, and that approximately 1 per 1000 may be involved in an episode of relatively clearcut violence.

Data from rates of violence in all placebo controlled trials for all antidepressants of the type laid out in Table 1 are not available. The only agent for which presumably complete data is available is Seroxat (paroxetine). This is laid out in Table 3. In this table violent or potentially violent episodes were coded under the rubric of "hostility".

There is no reason to doubt that the clear increase in the risk of violent episodes in patients taking paroxetine shown in Table 3 below does not occur to the same extent and probably to a comparable extent with other agents of similar type.

Table 3: Hostility Events in Paroxetine Placebo Controlled Trials.

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine Events/Patients</th>
<th>Placebo Events/Patients</th>
<th>Odds Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>60/9219</td>
<td>20/6455</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td>0.65%</td>
<td>0.31%</td>
<td>(1.27, 3.48)</td>
</tr>
<tr>
<td>Depression</td>
<td>20/3799</td>
<td>8/2402</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>0.53%</td>
<td>0.33%</td>
<td>(0.70, 3.58)</td>
</tr>
<tr>
<td>OCD</td>
<td>19/737</td>
<td>5/470</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td>2.58%</td>
<td>1.06%</td>
<td>(0.91, 6.45)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16/3823</td>
<td>7/3404</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>0.42%</td>
<td>0.21%</td>
<td>(0.84, 4.84)</td>
</tr>
<tr>
<td>PMDD</td>
<td>5/760</td>
<td>0/379</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.66%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PMDD = Pre-menstrual Dysphoric Disorder

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8 It may be open to the Court to request the relevant data from Lundbeck the makers of citalopram but this risks introducing considerable delay into the proceedings and also uncertainty in that there may be difficulties establishing how the extent to which Lundbeck have genuinely attempted to assist the Court.
For a number of reasons it has not been possible to produce clinical reports exploring issues of homicidality or violence on antidepressants to the same extent as has happened in the case of suicidality. But it is of some note that an increased propensity to violence has been noted/reported in healthy volunteer studies involving sertraline\textsuperscript{10} and paroxetine.

I can also report that I have had clinical experience of two men, with no prior history of violence, who became homicidal after a week on citalopram where the problem cleared up once treatment had stopped

\textbf{Mechanisms of Induction of Suicide & Violence:}

There is evidence that the excess of suicidal acts found in clinical trials of SSRIs are produced by an induction of agitation/akathisia, in addition to emotional blunting and/or drug-induced psychotic decompensation.

\textbf{A) Agitation/Akathisia}

The evidence that SSRIs cause agitation comes directly from company clinical trial programs, where approximately 5\% of patients have dropped out for reasons of agitation. Rates of drop-out for agitation are significantly greater than for placebo.

The best descriptions of this drug induced state come from its first description in the 1950s following the use of the drug reserpine in patients being treated for raised blood pressure. Reserpine induced states characterised as follows: “increased tenseness, restlessness, insomnia and a feeling of being very uncomfortable” (Achor et al 1955), “the first few doses frequently made them anxious and apprehensive... they reported increased feelings of strangeness, verbalized by statements such as ‘I don’t feel like myself’.. or ‘I’m afraid of some of the unusual impulses that I have’” (Faucett et al 1957).

Comparable reports can be found in trials of healthy volunteers taking SSRI drugs.

The fact that SSRIs cause akathisia has been conceded by company reviewers, by regulators and by DSM-IV and a link between akathisia and suicide has been recognized by DSM-IV and company reviewers.

The critical point here is how can companies answer the question of how their drug could cause agitation severe enough to lead to drop-outs from clinical trials at up to 5\% - in addition to all the less severe forms of agitation caused – without leading some individuals to suicide or violence.

Events such as these in clinical trials of antidepressants have commonly been coded under headings such as agitation, emotional lability and hyperkinesis (overactivity), and only rarely to akathisia. In clinical practice the term akathisia has sometimes been restricted to states of demonstrable motor restlessness, but by definition it cannot be a simple motor disorder or it would be classified as a dyskinesia\textsuperscript{11}. There is good evidence that akathisia can exacerbate psychopathology in general\textsuperscript{12}, and a consensus that it can be linked to both suicide and violence\textsuperscript{13}. A link between akathisia and violence, including homicide, following psychotropic drug use has previously been reported\textsuperscript{14}.


\textsuperscript{14} Lane RM (1998) SSRI-induced extrapyramidal side effects and akathisia: implications for treatment. J. Psychopharmacology 12: 192-214

Substantial evidence from SSRI clinical trials shows that these drugs can trigger agitation. Approximately 5% of patients on SSRIs in randomised trials drop out of the trial because of agitation against 0.5% developing agitation while on placebo. The current data sheets for SSRI antidepressants specify that the drugs can cause akathisia and agitation and warn about developing suicidality in the early phase of treatment, on treatment discontinuation as well as in the wake of a dose increase in the course of treatment. In addition in the United States, these warnings explicitly apply not only to depressed patients but also to people being treated for anxiety, smoking cessation or pre-menstrual dysphoric disorder (PMDD). In Canada, in addition to suicide, warnings specify an increased risk of violence.

B) Emotional Blunting

The evidence that SSRIs cause emotional blunting lies in the fact that these drugs are used to treat a wide variety of anxiety states and that many of these drugs advertise themselves as anxiolytic antidepressants. An anxiolytic effect is by definition an instance of emotional blunting. The term blunting is applied when the degree of this effect gets to the extent that an individual perceives it to be excessive.

This action of SSRIs is in fact abundantly supported by randomized placebo-controlled trial evidence. This clinical trial evidence is supplemented by a growing body of case studies, which make it clear that the emotional blunting SSRIs produce, the fear reduction, can proceed too far and become an abnormal absence of fear that has consequences for behavior. In addition to the above in their phase 1 healthy volunteer studies, company monitors have regularly recorded the occurrence of mood change on SSRIs, and coded this to emotional lability. Discontinuing treatment rapidly leads to a restoration to normal.

The significance of this is that such an effect can be expected to make an individual less sensitive to the consequences of their actions than they would be in the normal course of events – making it possible to act without fear of the consequences, or not to be inhibited by any moral consideration of the consequences of an action.

C) Psychotic Decompensation.

Since the first administration of imipramine to patients, it was also noted that patients at risk of psychotic decompensation became worse on this drug. This has been a regular feature of the testing of SSRIs, with for example in the case of Prozac, numerous early reports from hospital studies of patients with schizoaffective type disorders becoming markedly worse on this drug at what was probably a greater rate than for other drugs or patients. Having reviewed trials from the clinical trial databases of Prozac, Seroxat and Lustral/Zoloft, I can state that at present all SSRIs that I have reviewed have caused psychotic decompensation in some patients. This happens at a higher rate with SSRIs than occurs on placebo. This data has not been published. This problem clears up on discontinuation of the SSRI.


17 Fluoxetine Project Team Meeting Minutes August 1978. Exhibit 30 in Forsyth Vs Eli Lilly; Fluoxetine Project Team Meeting Minutes July 23rd 1979
These drug-induced states often resolve once the medication is removed. However, the full dimensions of treatment-induced psychotic or manic reactions have yet to be mapped\textsuperscript{18}. It has recently been estimated that these drug-induced manic or psychotic states may account for up to 8% of admissions to psychiatric facilities\textsuperscript{19}.

The development of a psychotic episode or of command hallucinations has traditionally been linked to both violence and suicide. The labels for most SSRIs now concede a causal relationship to psychosis, and to hallucinations.

A proportion of these cases with superficially manic or psychotic reactions and unrecognised confusion may be delirious states reflecting organic brain disturbances rather than a functional psychosis or mania. Delirium has traditionally been an absolute defence against murder, where psychosis and mania may not be.
