

31st March 2010

CONFIDENTIAL

Cathal Louth
Carrymore
Dublin Road
Arklow
Co Wicklow

Dear Mr Louth

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 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:

“The Marketing of 5-Hydroxytryptamine: Depression or Anxiety?” British Medical Journal, (1991), 158, 737-742;

“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):3331-3337 (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);

“The association between suicide attempts and SSRIs: A systematic review of 677 randomized controlled trials representing 85,470 participants,” *British Medical Journal* 330, 396-399. Fergusson D, Doucette S, Cranley-Glass K, Shapiro S, Healy D, Hebert P, Hutton B (2005);

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

“Antidepressants and violence: Problems at the interface of medicine and law,” *PLoS Medicine* 3, Sept, DOI: 10.1371/journal.pmed.0030372 Healy D, Herxheimer A, Menkes D (2006);

“Manufacturing Consensus. Culture, Medicine and Psychiatry,” 30, 135-156. DOI 10.1007/s11013-006-9013-3, Healy D (2006);

“The Antidepressant Tale: Figures Signifying Nothing?” *Advances in Psychiatric Treatment* 12, 320-328, Healy D (2006); and

“Did regulators fail over selective serotonin reuptake inhibitors,” *BMJ* 333, 92-

95. Healy D (2006).

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 & Witczak (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)¹.**

Drug	Suicides / No Patients	Placebo Suicides	Suicidal Acts / No Patients	Placebo Suicidal Acts
Citalopram	1/1320	1/0622	11/1320	5/0622
Escitalopram	0/2648	1/2088	06/2648	1/2088
Total C & E	1/3968	2/2710	17/3968	6/2710
Fluvoxamine	2/4186	2/3396	24/4186	10/3396
Mirtazapine	5/2618	0/0388	09/2349	3/0388
Sertraline	4/7169	0/5108	20/7169	8/5108
Venlafaxine	4/6153	0/2962	25/6153	8/2962
Paroxetine	1/8058	0/5266	17/8059	4/5266
Total	17/32,153	4/19,830	119/32153	30/19,830
Suicide & Act Total			136/32,153	30/19,830

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 the balance of an individual's 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:

¹ MHRA (2004) Report of the CSM Expert Working Group on SSRIs.
<http://www.mhra.gov.uk/news/2004/SSRIfinal.pdf> (accessed 29.8.05)

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 – Zoloft – 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 1/4th 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.

² Herrera JN, Sramek JJ, Costa JF, Roy S, Heh CW, Nguyen BN (1988) High potency neuroleptics and violence in schizophrenia. *J Nervous and Mental Disease* 176: 558-561. Schulte JR (1985) Homicide and suicide associated with akathisia and haloperidol. *Am J Forensic Psychiatry* 6: 3-7. Rampling D (1978). Aggression: a paradoxical response to tricyclic antidepressants. *American J Psychiatry* 135: 117-118.

³ Healy D (2004). *Let Them Eat Prozac*. New York University Press, New York.

⁴ Cusin C, Fava M, Amsterdam J, Quitkin F, Reimherr F, Beasley C, Rosenbaum J, Perlis R (2007). Early symptomatic worsening on treatment with fluoxetine in major depressive disorder: prevalence and implications. *J Clin Psychiatry* 65, 52-57.

⁵ http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/zoloft_2_hpc-cps_e.html. Accessed May 19th 2006.

⁶ Taken from the most recent Zoloft label, posted 8th July 2005. www.fda.gov/cder/drug/infopage/sertraline/default.htm

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.

**Table 2: Drug Safety Research Unit⁷:
Prescription Event Monitoring Studies of Paroxetine & Fluoxetine**

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

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 type⁸.

⁷ Inman W, Kubota K, Pearce G, Wilton L (1993). P.E.M report number 6. Paroxetine. *Pharmacoepidemiology & Drug Safety* 2: 393-422. Edwards JG, Inman WH, Wilton L, Pearce GL, Kubota K (1997). Drug safety monitoring of 12692 patients treated with fluoxetine. *Human Psychopharmacology* 12, 127-137. First published as P.E.M. Report no 5, 1993.

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.

**Table 3:
Hostility Events in Paroxetine Placebo Controlled Trials⁹.**

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

PMDD = Pre-menstrual Dysphoric Disorder

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 sertraline¹⁰ 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

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.

⁹ http://www.gsk.com/media/par_current_analysis.htm. Appendix 2. Seroxat Article 31 Response. Accessed May 12th 2006.

¹⁰ Healy D (2000). Emergence of antidepressant induced suicidality. Primary Care Psychiatry 6: 23-28.

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 hyperkinesia (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 dyskinesia¹¹. There is good evidence that akathisia can exacerbate psychopathology in general¹², and a consensus that it can be linked to both

¹¹ Cunningham Owens DG (1999) A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs. Cambridge, Cambridge University Press.

¹² Duncan EJ, Adler LA, Stephanides M, Sanfilippo M, Angrist B (2000) Akathisia and exacerbation of psychopathology: a preliminary report. *Clinical Neuropharmacology* 23: 169-173.

suicide and violence¹³. A link between akathisia and violence, including homicide, following psychotropic drug use has previously been reported¹⁴.

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 behavior¹⁵. In addition to the above in their phase 1 healthy volunteer studies, company monitors have regularly

¹³ American Psychiatric Association (2000) Diagnostic and Statistical Manual IV TR. American Psychiatric Association, Washington D.C. Lane RM (1998) SSRI-induced extrapyramidal side effects and akathisia:

implications for treatment. *J. Psychopharmacology* 12: 192-214

¹⁴ Siris SG (1985) Three cases of akathisia and "acting out". *J Clin Psychiatry* 46: 395-397.

Herrera JN, Sramek JJ, Costa JF, Roy S, Heh CW, Nguyen BN (1988) High potency neuroleptics and violence in schizophrenia. *J Nervous and Mental Disease* 176: 558-561. Schulte JR (1985)

Homicide and suicide associated with akathisia and haloperidol. *Am J Forensic Psychiatry* 6: 3-7.

¹⁵ Hoehn-Saric R, Lipsey JR, McLeod DR: Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol* 1990; 10:343-345; Wilkinson D. Loss of anxiety and increased aggression in a 15-year old boy taking fluoxetine. *Journal of Psychopharmacology* 13, 420 (1999) Reply by Healy D. *J Psychopharmacology* 13, 421 (1999).. Garland EJ, Baerg EA (2001). Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J Child & Adolescent Psychopharmacology* 11, 181-186.

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 drug¹⁶. 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 patients¹⁷. 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.

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 mapped¹⁸. It has recently been estimated that these drug-induced manic or psychotic states may account for up to 8% of admissions to psychiatric facilities¹⁹.

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.

¹⁶ Healy D (1997). *The Antidepressant Era*. Harvard University Press, Cambridge, Ma.

¹⁷ Fluoxetine Project Team Meeting Minutes August 1978. Exhibit 30 in Forsyth Vs Eli Lilly; Fluoxetine Project Team Meeting Minutes July 23rd 1979

¹⁸ Wilens TE, Biederman J, Kwon A, Chase R, Greenberg L, Mick E, Spencer TJ (2003) A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *J Child & Adolescent Psychopharmacology* 13: 143-152.

¹⁹ Preda A, MacLean RW, Mazure CM, Bowers MB (2001) Antidepressant associated mania and psychosis resulting in psychiatric admission. *J Clinical Psychiatry* 62: 30-33. Nakra BR, Szwabo P, Grossberg GT (1989) Mania induced by fluoxetine. *Am J Psychiatry* 146: 1515-1516. Hersh, CB, Sokol, MS, Pfeffer C (1991) Transient psychosis with fluoxetine. *J Am Acad Child Adolesc Psychiatry* 30: 851-2; Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, Cohen BM, Tohen M (1994) Antidepressant-associated mania: a controlled comparison with spontaneous mania. *Am J Psychiatry* 151: 1642-5. Narayan, M, Meckler L, Nelson JC (1995) Fluoxetine-induced delusions in psychotic depression. *J Clin Psychiatry* 56: 329.

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.

Mr Shane Clancy & Citalopram:

At present I am not aware of any dispute regarding whether Mr Clancy had citalopram. He appears to have suffered adverse effects from his intake of this drug. These may have included his complaint about a swollen throat – this is consistent with an SSRI induced dystonia. There is testimony from his family that he was suffering adverse behavioural consequences from citalopram before the events of August 15th /16th. Finally his toxicology levels appear to confirm that he definitely had citalopram.

This is not a report on whether citalopram caused Mr Clancy to commit suicide or to kill xxxxxxx xxxxxx but certain features of his case are worth noting.

First, the condition that led to Mr Clancy being put on citalopram appears to have been his first episode of a nervous disorder. I do not have any record to indicate prior treatment. The index problem appears to have begun in the wake of a relationship break-up.

A first consultation with a primary care practitioner on July 18th recorded a number of symptoms of a possible depressive disorder. At this consultation a link was apparently between Mr Clancy's unhappiness and the break-up of his relationship with xxxxxxx xxxxxxx and advice was given to this effect.

He was subsequently seen 9 days later by Dr McManus who offered a script for citalopram on July 27th. Four days later was noted to have contacted the practice complaining of a swollen tongue.

After an overdose on August 5th, Mr Clancy returned to the clinic and there is a further note on August 7th, recording a suicide attempt on citalopram, antibiotics and paracetamol. The prescription of citalopram was continued in a lower 10 mg dose.

A week later on August 15th/16th Mr Clancy appears to have taken his own life and that of xxxxxx xxxxxxx and also assaulted xxxxxx xxxxxxx and xxxxx xxxxxx.

By all accounts Mr Clancy took the breakup of his relationship with xxxxxx xxxxxx to heart. There was at least one suicidal act prior to going on citalopram, although the recording of this in the medical notes suggests it was seen as relatively trivial. There were also suicidal thoughts prior to going on citalopram, but again these were not given much weight in the medical records.

While there was a suicidal act and suicidal thoughts were also present, a homicide-self-destructive episode of this type is vanishingly rare following the break-up of a relationship.

To explain such an event without reference to the drugs he was being treated with, we have to posit that either Mr Clancy committed a crime of passion or that he had a psychotic disorder. In the case of crimes of passion, these classically involve the killing of another rather than both killing and self-destruction.

There are no suggestions from the medical records that Mr Clancy had a psychotic disorder of the acute and transient or delusional disorder types. The indications are that he was depressed and if so the likely psychosis would be a depressive psychosis. Depressive psychoses in this age group are vanishingly rare.

In any population of 100,000 people from these islands, there are only 4-5 new cases of depressive psychosis per year and of these few if any go on to violence. Reviewing the last 200 cases of depressive psychosis that have arisen in North West Wales, not one to the best of my knowledge has gone on to violence. Depression in general is not linked to violence.

In considering the possibility that citalopram may have played a part in this case, there are two factors to consider; one is whether this case has features consistent with a treatment induced problem and the second is whether a citalopram induced problem is a more or less likely explanation than the alternate explanations.

From the figures provided above, it would appear that a citalopram induced problem is more likely than any alternate explanation.

As regards the features typical of an SSRI induced self-destructive act or act of violence, these include the following. The onset of problems should occur relatively soon after exposure to the drug – with hours, days or weeks, unless there is a change of dose or a question of withdrawal from the drug. Broadly speaking the higher the dose of the drug the likelier there is to be a problem – in this case the key dose is the drug level within the body rather than simply the dose taken by mouth. Ideally the person should demonstrate problems on the drug prior to any act of violence or self-harm – someone reported to be doing well on the drug is not likely to proceed to treatment induced disturbances of behaviour unless the original description is wrong or another factor supervenes.

In this case, Shane Clancy's problems have a temporal relationship to drug intake that is consistent with a treatment induced problem. While there were suicidal thoughts prior to taking citalopram, his acts after starting it were of a different order to those beforehand and were consistent with later events.

The toxicology report confirms that Mr Clancy had taken citalopram at the time of his death. Post-mortem toxicology reports are unreliable as to the level of drug intake at the time of death. Accordingly it is not possible to take the levels recorded in Mr Clancy after his death as indicative of an overdose.

In the event that Mr Clancy's post-mortem citalopram levels are accurate rather than an artefact of post-mortem redistribution, a further issue arises, namely the degree to which he was a rapid or slow metabolizer of this drug. A proportion of people metabolise this and other antidepressants slowly and can end up with elevated plasma levels of the drug, making them effectively overdosed. If prone to adverse reactions to the drug, the levels recorded for Mr Clancy, if in fact these also applied while he was alive, would make an adverse reaction more likely.

When considering these issues, I have worked from the material available to me noted above. There may be other evidence that casts doubt on whether Mr Clancy had difficulties while on citalopram, or evidence suggesting he had other serious difficulties prior to going on citalopram, and if so I would be happy to consider how these factors might affect the substance of this report.

Citalopram, Suicide and Homicide

In order to return a verdict of suicide as I understand it it should be clear that the individual did intend in their right mind to kill themselves. An individual involuntarily intoxicated with LSD who jumps from a high building could quite reasonably be regarded as not intending to kill themselves in the ordinary sense of that word. In such circumstances a verdict other than suicide is commonly returned, such as death by misadventure or an open verdict.

In my opinion in a similar fashion citalopram can induce thoughts that are alien to the individual concerned so that it becomes difficult to state with confidence even when a person has clearly taken their own life that they intended to do so in the ordinary sense of that word, opening up the question of an open verdict or verdict of death by misadventure. The data on treatment induced akathisia, emotional blunting and psychotic decompensation noted above are all consistent with a diminution of what is commonly termed mens rea.

Such a verdict receives support in this case from the fact that after his suicide attempt both Mr Clancy's doctor and his family failed to identify citalopram as a source of his problems. The explicit message from his doctor and implicit message from his family was that he should continue on treatment. These messages may have over-ridden any intimation he had that the drug was making him worse.

Assuming the issue of whether Shane Clancy killed xxxxxx xxxxx is not in dispute, we can apply the same perspective to the question of whether this might

have been considered a murder had Mr Clancy survived and could be charged with an offence.

As far back as the 17th century, Britain's Lord Chief Justice Hale stated that "if a person by the unskilfulness of his physician or the contrivance of his enemies, eat or drinketh such a thing as causeth such a temporary or permanent frenzy, as aconitum or nux vomica, this puts him into the same condition, in reference to crimes as any other frenzy, and equally excuseth him"²⁰.

The not guilty by virtue of a frenzied state referred to here primarily referred to delirious states, stemming from physical or other disorders, and only secondarily to what later came to be termed not guilty by virtue of insanity or psychiatric illness. Delirium refers to states induced by a fever, or toxic metabolism, or by a toxic agent such as a drug. Delirious states as instanced by the disordered mental states accompanying a high fever or delirium tremens can offer an absolute defence against murder and provides a basis for a not-guilty verdict, on the basis that the capacity to form intent could not have been present.

There is a contrast between a delirious state of this sort and what is often thought of as an insanity defence. An insanity defence only emerged in the 19th century with the recognition that in addition to the disordered mental states that might accompany physical illness, there could be abnormal mental states that were not linked to fevers or poisonings. Such insanities were dominated by delusional beliefs that would commonly persist after the event and the persistence of this form of insanity required committal of the affected individual to a secure mental hospital in order to protect the public.

As the insanity defence evolved, so also did considerations of deliria or other abnormal physical states and the contribution these might make to a not guilty verdict. The main development lay in the evolution of what came to be termed an automatism. The classic states that are regarded as producing automatisms include sleepwalking and epilepsy, states that lead to behaviours that are outside ordinary conscious control.

An automatism in this context is classically defined as follows: A transient non-recurrent mental malfunction caused by an external factor, whether physical or psychological, that the mind of an ordinary person would be not likely to have withstood and which produces an incapacity to control his or her acts.

In my opinion there are several grounds to think that Shane Clancy's behaviour is appropriately described either as delirious or as resulting from an automatism.

²⁰ Hale M (1736/2003) *Historia Placitorum Coronae*. Vol 1 Lawbook Exchange. Clark New Jersey, Chapter 4, Concerning the Defect of idiocy, madness and lunacy, in reference to criminal offences and punishments. page 30

As regards a possible delirium, there is the fact that his attack on xxxxx xxxxxx and subsequent self-destruction appears to have been quite frenzied.

As regards an automatism, there is a clear external factor here. Second, Mr Clancy did not voluntarily have this drug in the way one might have taken alcohol for instance. Third the akathisia that can be inferred in Mr Clancy's case can appropriately be regarded as giving rise to an automatism that led to either a partial or perhaps a total alienation of reason.

Against the notion of an automatism however is the fact that such behaviours typically bear little or no relationship to the likely motives of the subject. When someone kills someone else while sleep walking, there is usually no reason why they might have done this. In Mr Clancy's case the situation is different – and this difference applies to both the killing and also his self-destruction.

Having made this point, the behaviours evinced under SSRIs while commonly ego-alien are also often consistent with the subject's prior mental state. In these cases the drug can aggravate a pre-existing agitation and disinhibit, in the way that LSD for instance can. In such a case there is a partial rather than outright alienation of reason. Current thinking has not resolved the medico-legal complexities involved in such cases.

As regards the role of Shane Clancy's doctors, in many countries the citalopram prescribed for him at the time of his death comes with written warnings about the potential for suicide and violence. I am not clear what written warnings if any actually accompanied the form of the drug Shane Clancy was given, or what verbal warnings his doctors may have given him.

However these warnings have only recently been instituted and come against a background of almost 20 years of strenuous efforts by pharmaceutical companies to deny that their drugs come with these risks. The warnings that now exist do more in these circumstances to defend companies against legal actions against them than they do to safeguard patients or alert doctors. The issuing of warnings against a background of so many years of medical practice in using the drugs in a particular way has done little to change standard medical practice and there is no evidence from the records available to me that Shane Clancy's doctors behaved in a manner that was substantially different to the manner in which a significant number of other doctors would have approached this problem.

Having made this point, an inquest like this with the attention attendant to it has the potential to educate doctors to the risks inherent in treatment with drugs like citalopram bringing home to doctors the force of the warnings and the need to alert patients and others involved in their care as to these risks.

Summary

Taking both the likelihood of alternate explanations into account and their consistency with the medical records, and considering the details I have of the events surrounding Mr Clancy's death, a case can be made that citalopram induced at least a partial alienation of reason in him such that he neither destroyed himself nor killed xxxxx xxxxxxxx in a manner that would warrant verdicts of suicide or of murder.

Mr Clancy was not without his problems prior to the events that led to his death but he is just the kind of person who was recruited to clinical trials of the SSRI group of drugs, in which despite whatever suicidal ideation they had before treatment and despite the difficulty of their social circumstances, there was a 2 ½ times greater rate of suicides, suicidal acts and acts of violence on active treatment than there was on placebo.

Given the materials available to me, I would support an open verdict in this case.

Yours sincerely

Professor David Healy MD FRCPsych