Professor David Healy
Department of Psychological Medicine
Bangor
Wales LL57 2PW
United Kingdom

August 29, 2014

Tamara Brady
Colorado Public Defender's Office
1300 Broadway #400
Denver, CO 80203

Dear Ms. Brady:

Initial Report on James Eagan Holmes
DOB: 12-13-87

I have been approached by the Colorado Public Defender's Office to offer a view on the possible effects that sertraline (Zoloft) had on James Holmes, and the possible role the drug may have played in the events of July 20, 2012.

Your office has provided me with the following materials:

- Reports:
  - Dr.Raquel Gur
  - Dr. Robert Hanlon
  - Dr. Jeffrey Metzner (CMHIP) report
- Arapahoe County Jail records re medications
- Hearing: January 29-30, 2014 testimony by Dr. Metzner
- Medical & psychological records: CU Anschutz
- CMHIP medication chart
- Kaiser Permanente medical records
- Pharmacy records
- Photos of prescription medications at apartment
- Prescription medication timeline
- Mr. Holmes' Notebook
- Text Messages between James Holmes and Hillary Allen

I interviewed Mr. Holmes on the morning of April 21, 2014, in the medical wing of the Arapahoe County Jail.

I. Expertise

I am a medically qualified doctor with a further doctorate in psychopharmacology, and particular post-doctoral expertise in the adverse effects of psychotropic drugs. I qualified in 1979 from the National University of Ireland before moving to Cambridge University in England and later Cardiff University in Wales.

My professional experience with psychotropic medications dates back over thirty years. My post-doctoral thesis, conducted from 1980 to 1985, was on psychotropic drugs and their effects on serotonin reuptake mechanisms.

I have been a Professor of Psychiatry at Cardiff University and now am at Bangor University. I was a secretary of the British Association for Psychopharmacology. I have published 22 books on psychiatry, mostly linked to psychopharmacology, including the standard histories of antidepressants, antipsychotics and mood-stabilizers. One of my books on the use of psychiatric prescription drugs has been translated into several different languages and is now in its 5th edition.

I have also authored 60 chapters in books on similar issues, over 200 peer-reviewed articles and over 250 other pieces, dealing mostly with psychopharmacology. I have been invited to talk at close to 400 international meetings on all continents – again largely on issues related to psychotropic drugs.

I have been a consultant to most of the major psychiatric drug manufacturers including Eli Lilly, Pfizer, Janssen, and GlaxoSmithKline.

I have reviewed a very large proportion of both the published and unpublished studies conducted on the most popular psychotropic drugs and the risks of adverse events like suicide or homicide. 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 dealing with issues of suicide, homicide, and dependence on these drugs.

I practice clinically, treating both inpatients and outpatients who are depressed, anxious, and psychotic. I treat patients of all ages and backgrounds. I use a full range of treatment methods, including all available psychotropic drugs.

Since 1997, I have been involved in a series of cases involving suicide or homicide on Selective Serotonin Reuptake Inhibitor (SSRI) drugs. Two American SSRI civil cases have gone to trial, the Forsyth case (Prozac) and the Tobin case (Paxil). 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 (Paxil).

I have consulted on and declined to offer a view, or else offered a view that the drug was not involved in precipitating violence or suicide, in close to 100 other cases involving SSRI antidepressants. I have offered reports for inquests on over 20

individuals who have committed suicide following intake of one or other of the major SSRI drugs.

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

I have been approached to give a view about whether SSRIs might cause someone to engage in fraudulent or related criminal behaviors on a number of prior occasions. Until this year I have declined to get involved in such cases. However, I have had three cases recently in which the potential role of treatment is somewhat clearer and permitted reports to be written.

I have also been involved in a set of cases involving dependence on Paxil in both the United States and United Kingdom.

I have been involved as an expert in a series of cases involving Paxil, Zoloft, Celexa and birth defects.

I have been involved in two patent cases involving olanzapine (Zyprexa).

I have been consulted by New York State prior to a fraud action against GlaxoSmithKline in 2004.

I am an expert consultant in a Consumer Fraud case in California against Pfizer for inappropriate marketing of sertraline (Zoloft) as an antidepressant.

II. Zoloft: Efficacy and Adverse Events

Introduction

Sertraline is one of the Selective Serotonin Reuptake Inhibitor (SSRI) group of drugs, which include drugs such as Prozac and Paxil. It was brought to market by Pfizer under the trade name Zoloft. It is used primarily for the treatment of depression and anxiety.

The evidence that SSRI drugs work well is not compelling. The evidence for the effectiveness of Zoloft is sufficiently weak that a class action lawsuit has been brought against Pfizer in California, alleging consumer fraud violations. The evidence regarding clinical trial results that brought Zoloft to the market is laid out in Appendix 1.

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, clears up when treatment is discontinued, and reappears upon reintroduction of the same SSRI agent or another SSRI agent. Clinical trials have shown that the rate of suicidal acts and completed suicides in patients being treated with SSRIs compared to placebo is two times greater on the active agent than it is on the placebo.

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 (Appendix 2).

The bulk of the data on homicide while taking Zoloft has remained out of view, but there is data for Paxil. This data, laid out in Appendix 2, suggests that when patients who are being treated for depression with these drugs have an adverse response they are likely to go on to suicide, while patients who are anxious or obsessive, as Mr. Holmes was, are more likely to go on to homicide.

Trials of Zoloft and other SSRIs in healthy volunteers (Appendix 3a & 3b) also reveal agitation and suicidality and violence as adverse effects. In the same way, even in patients suffering from anxiety, where there is a very low natural rate of suicide, suicidal acts or violence, in these situations also the rate of suicides, suicidal acts and violence increase on the SSRI.

The evidence for the relative inefficacy of Zoloft and the increased rates of suicidality and homicidality with respect to this and related drugs escaped the attention of clinicians, academics and regulators for many years, as a number of pharmaceutical companies making SSRIs have handled the data on these hazards in ways that would appear to be both unscientific and unethical.

For instance, data has been miscoded so that suicides and suicidal acts while on the active agents have disappeared or have been coded under the heading of "placebo," when in fact these suicides or suicidal acts did not happen on placebo - See Let Them Eat Prozac.[1]

The vast bulk of the scientific literature in these areas has been ghostwritten and in almost all instances the data from clinical trials and clinical practice remains sequestered (See Appendix 1).

In the section below on sertraline (Zoloft) and Homicide, the mechanisms by which a drug like Zoloft can lead to homicide are laid out. These involve evidence that the drug can cause states of agitation, also called akathisia, a degree of emotional blunting and disinhibition, along with psychosis.

Attached to this report in Appendix 4, I lay out a number of accounts of the bizarre suicides or acts of violence that SSRIs can give rise to. These accounts are drawn from SSRIstories.org, a website containing a collection of over 5,000 stories that have appeared in the media (newspapers, TV, scientific journals) in which prescription drugs were mentioned and in which the drugs may be linked to a variety of adverse outcomes including violence.

Finally in Appendix 5, there is a listing of the reports to FDA's Adverse Events Reporting Database, as well as Health Canada's adverse event database and RxISK.org of events including homicidal ideation, psychosis and agitation on Zoloft. In these instances, doctors and others have been persuaded that the drug caused the problem. These data make a strong case that Zoloft can, in principle, cause problems of the kind under consideration in this case.

[1] Healy D. Let Them Eat Prozac. New York University Press, New York (2004).

Sertraline and Homicide

The first point to note here is that I have been writing a section almost word for word like this one in reports on the capacity of SSRIs like Zoloft to cause suicide or homicide for over 10 years. In other words, this section is in no way tailored to reflect one way or the other on the Holmes case.

There are three major mechanisms that can lead either to suicide or homicide on SSRIs such as Zoloft. These include an induction of agitation/akathisia, an induction of emotional blunting and/or disinhibition, and a drug-induced psychotic decompensation.

A) Agitation/Akathisia

The evidence that SSRI drugs like Zoloft can cause agitation comes directly from company clinical trial programs, such as the sertraline trials, where approximately 5% of patients on SSRIs in randomized trials dropped out of the trial because they were so agitated that they could not continue, whereas only 0.5% developed agitation while on a placebo. In the placebo cases, the agitation in some instances may have stemmed from withdrawal of prior treatments.

The best descriptions of this drug-induced agitation, otherwise known as akathisia, 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 characterized 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 sertraline and other SSRI drugs (See Appendix 3).

The fact that SSRIs cause akathisia has been conceded by company reviewers, by regulators and by the DSM-5 (*Medication-Induced Movement Disorders and Other Adverse Effects of Medication*), and a link between akathisia and suicide has been recognized by company reviewers.

The critical question is how could a drug like Zoloft cause agitation severe enough to lead to drop-outs from clinical trials at up to a 5% rate, in addition to all the less severe forms of agitation caused, without leading some individuals to suicide or violence?

The problem was hidden to some extent in the initial years after these drugs came to the market because agitation was coded in clinical trials of antidepressants under a variety of headings such as agitation, emotional lability, hyperkinesis (overactivity), and akathisia.

There have been attempts in these clinical trials to restrict the term akathisia to states of demonstrable motor restlessness, but by definition akathisia cannot be a simple motor disorder or it would be classified as a dyskinesia.[2] There is good

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

evidence that akathisia can exacerbate psychopathology in general,[3] and a consensus that it can be linked to both suicide and violence.[4] A link between akathisia and violence, including homicide, following psychotropic drug use has previously been reported.[5]

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. These effects can occur upon discontinuation of treatment, as well as in situations where the dosage is increased during the course of treatment. In addition, in the United States, these warnings explicitly apply not only to depressed patients but also to people who are not depressed – for instance, those who are 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 - Lability

SSRIs like Zoloft can cause a range of emotional changes such as reduced emotional reactivity, or "emotional blunting." This effect lays the basis for the use of these drugs to treat a wide variety of anxiety states and lays the basis for many of these drugs to 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 becomes so strong that an individual perceives it to be excessive.

This clinical trial evidence is supplemented by a growing body of case studies.[6] These and other reports 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.[7] Company monitors have

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

[4] 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.

[5] 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.

[6] Price J, Cole V, Goodwin G. Emotional side effects of selective serotonin reuptake inhibitors: a qualitative study. British J Psychiatry (2009), 195, 211-217.

[7] 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

regularly recorded the occurrence of mood change on SSRIs, and coded this to emotional lability.

Emotional blunting 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 to be uninhibited by any moral consideration of the consequences of an action. This aspect is better described as an emotional disinhibition.

The effects of drugs like Zoloft on our emotions are not confined to emotional blunting. The drug can also lead to an affective instability, so that the person experiences mood swings in greater extremes and at a much greater frequency than before. This is described as dysphoric mania.

C) Psychotic Decompensation

Since the first administration of imipramine, a serotonin reuptake inhibitor, to patients in 1955, it was noted that patients at risk of psychotic decompensation became worse on this drug.[8]

Psychotic decompensation has been a regular feature of the testing of SSRIs since. For example, in the case of Prozac, numerous early reports from hospital studies of patients with schizoaffective-type disorders indicate that they became markedly worse on this drug at a greater rate than on other drugs, as well as worse than other patients on this drug.[9]

Having reviewed trials from the clinical trial databases of Prozac, Paxil and 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.

These drug-induced states can resolve once the medication is removed, but the resolution is often delayed. The full dimensions of treatment-induced psychotic or manic reactions have yet to be mapped.[10] It has recently been estimated that these drug-induced manic or psychotic states may account for up to 8% of admissions to psychiatric facilities.[11]

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syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. J Child & Adolescent Psychopharmacology 11, 181-186.

[8] Healy D (1997). The Antidepressant Era. Harvard University Press, Cambridge, Ma.

[9] Fluoxetine Project Team Meeting Minutes August 1978. Exhibit 30 in Forsyth Vs Eli Lilly; Fluoxetine Project Team Meeting Minutes July 23, 1979.

[10] 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.

[11] 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;

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.

Sertraline and Mass Homicide

Mass homicide of the kind found in this case appears relatively unusual without psychotropic drug involvement. Almost all the mass shootings in Europe or North America in the past decade or more have involved individuals taking psychotropic medication. Such mass shootings were relatively rare before the launch of Prozac, the first of the SSRIs. Given that clinical trial data show an increased rate of hostile acts even in entirely normal people taking these drugs, it is close to impossible that at least some of these shootings will not have had a psychotropic drug component.

III. James Holmes' Medical and Psychiatric History

Mr. Holmes' background, psychiatric, and general medical histories are relatively uncomplicated.

He had counselling at the age of 8 for behavior issues at home. It is also reported that he has had trichotillomania, anxiety, and some degree of OCD for many years. He has had longstanding social anxiety that affects his ability to speak in public. This anxiety played a significant part in his difficulties at University of Colorado, and ultimately played a role in his decision to seek mental health treatment at the University.

Physically, he appears to have had infectious mononucleosis around Christmas time of 2011, which may have aggravated his difficulties in getting work done the following term at CU. When treated for this, he was given prescriptions for Ambien and Vicodin, from which he took several pills over a period of a few weeks, with no obvious adverse consequences.

Aside from this prescription for Ambien, Mr. Holmes appears to have had no other psychotropic drugs. Additionally, he has relatively little knowledge of psychotropic drugs despite his interest in neuroscience.

Referral to Dr. Fenton

Mr. Holmes first made attempts to seek assistance from the CU Student Mental Health Clinic on March 16, 2012. He initially spoke with the intake social worker, Margaret Roath, who stated that he seemed extremely anxious. She also mentioned the issue of homicidal ideation.

When Dr. Fenton first saw Mr. Holmes on March 21, 2012, she viewed him as having a schizoid personality with marked anxiety and homicidal ideation. She prescribed Klonopin, and sertraline (Zoloft).

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.

At his next appointment, Mr. Holmes complained of memory difficulties in class, which led Dr. Fenton to replace Klonopin with Propranolol 10mg BD. Dr. Fenton later reduced this dosage to 5mg BD when Mr. Holmes complained of continuing memory problems. Both Klonopin and Propranolol can be linked to memory problems. Both have also been used as antidotes to the kinds of problems Zoloft can cause.

Meanwhile Dr. Fenton increased Mr. Holmes's dosage of Zoloft from 50mg per day to 100mg per day on March 27, 2012, and from 100mg to 150mg per day on April 27, 2012.

Mr. Holmes appears to have stopped taking Zoloft somewhere around June 30, 2012, having apparently taken it faithfully according to instructions up till then. By his account, he figured that because he was dropping out of school and his associated lack of insurance would limit his medical contact with Dr. Fenton, it was better to stop treatment with Zoloft then.

Subsequent Psychotropic Drug Intake

Mr. Holmes also has a post-event psychotropic drug history. His mental state appears to have deteriorated in November 2012 with bizarre behavior, paranoid thinking and hallucinatory behavior. Mr. Holmes was hospitalized, diagnosed with psychosis, and prescribed Haldol, Ativan and benztropine. These prescriptions were later switched to risperidone, lorazepam and diphenhydramine.

Additionally, at the end of December 2012, Mr. Holmes appeared depressed and was given the SSRI Lexapro 10mg. Five days later, he was reported as having a wild look in his eyes and was placed on suicide watch. His dosage of Lexapro was not escalated after this. The problem appears to have subsided afterwards. However, Mr. Holmes reports no benefit from Lexapro. The jail medical records similarly record no benefit.

The jail staff's observations regarding Mr. Holmes's apparent agitation on Lexapro is notable, because it indicates that an SSRI has had an agitating effect on Mr. Holmes. This evidence supports an argument that the Zoloft he was taking under the care of Dr. Fenton may similarly had adverse effects on his behavior and may have played a part in the events of July 20, 2012.

IV. James Holmes on Zoloft

Based on Mr. Holmes's medical records, his notebook, what is known of his pattern of computer activity during this period, reports of his interactions with others, and the evidence from several interviews with him including my own, it appears that Mr. Holmes had a number of significant behavioral changes after being put on Zoloft. These changes include a degree of disinhibition, affective instability, altered sexual functioning, thoughts of violence, and the genesis of a delusional idea.

Disinhibition

The following notable changes in Mr. Holmes' behavior are consistent with disinhibition:

- His flirtatious approach to Hillary Allen, which was out of character for him.
- He exhibited a dramatic increase in spending habits, where previously he had been frugal.

- Significant changes in computer activity, including visiting dating sites, where he had never done so before.
- He signed up for motorcycle classes without any clear reason to do so.
- Terminating his friendship with Gargi Datta, something he would have been unlikely to do beforehand.
- He began mentioning openly the possibility of violence.

There are very few people in a position to comment on the differences between Mr. Holmes before and after going on sertraline. One of the few is Gargi Datta, his former girlfriend, who commented that:

"He began to "loosen up a bit" on medication and "became more talkative to random people."

Another source of information is the notebook that Mr. Holmes kept that he mailed to Dr. Fenton the day before the killings. In the notebook, he clearly outlines that he lost his sense of fear while taking Zoloft.

Affective Instability

Mr. Holmes' notebook and text messaging to Hillary Allen also refers to his having developed a "dysphoric mania." This is an accurate description of the affective instability that SSRIs can cause. It generally refers to a state in which the person, in very quick succession, can feel energized, reckless and invincible, and then depressed and suicidal.

When I interviewed Mr. Holmes, he confirmed that by using the term "dysphoric mania," he meant to convey feelings consistent with affective instability. At the interview, he linked this dysphoric mania to his impulses to spend excessively which were out of character for him.

Sexual Dysfunction

In line with a majority of people taking an SSRI, Mr. Holmes reported a degree of sexual dysfunction while on Zoloft. By his account, the higher the dose of treatment, the more marked these symptoms became.

Emotional Numbing

Mr. Holmes reports a degree of emotional numbing. This happened from early in treatment and became more marked as the dose of treatment with Zoloft increased. He reports that his anxiety "turned off." This overlaps to some extent with the disinhibition reported above.

Mr. Holmes also reports that his anxiety levels remained turned off even after he discontinued the sertraline. It is difficult to assess how long this lack of anxiety endured because Mr. Holmes has been taking risperidone (Risperdal) and escitalopram (Lexapro) (both of which are likely to contribute to some degree of numbing or lack of anxiety) since November 2012, and he has been in that state now for the last 18 months.

Homicidal Ideation

Mr. Holmes reports that prior to going on Zoloft he had rather non-specific global thoughts of harming others. He appears to have had a dislike of the human race, expressed for instance, in thoughts that it might be no harm to "nuke" the human race. These thoughts seem consistent with his acknowledged social phobia. Mr. Holmes expressed such thoughts to Dr. Fenton, and it is clear that she and others were concerned about these thoughts, and struggled to determine whether these thoughts indicated that Mr. Holmes was exhibiting signs of psychosis.

During the time he was taking Zoloft, Mr. Holmes describes developing new thoughts centering on the possibility of specific homicidal acts. These appear to have been new thoughts rather than thoughts continuous with his former ideas of killing people. These thoughts were focused and specific, and as he put it, "realistic." He reports these thoughts as an almost entirely different kind of homicidal ideation to anything he had had before.

In the case of people who have been regularly suicidal in the past, and who become suicidal on SSRIs, it is common to find people who are able to distinguish the suicidal thoughts they had in the past from those experienced on the medication, and for them to essentially hold both sets of thoughts in their mind at the same time.

Delusional Thinking

There was more than an emergence of a novel kind of homicidal ideation in Mr. Holmes' mental state. There was also a change in the quality of his beliefs in the domain of harms to others.

SSRI drugs like Zoloft can disrupt motivational hierarchies leading to alcoholism, violence and a range of other behaviors not usual for the person taking them. Mr. Holmes appears to have experienced a change in his motivational hierarchies in this case. After taking Zoloft, he did not just have thoughts that differ from those he had before, he had a different motivational link to his thoughts. The possibility of acting on these thoughts had emerged in a way that had not been present before.

Mr. Holmes reports clearly that communicating this new state of affairs to Dr. Fenton made the looming action even more real. In other words, the ideas were converted into something that required action.

Mr. Holmes is of the impression that he conveyed or attempted to convey this change to Dr. Fenton and others and that nothing happened in response.

Zoloft Withdrawal

When Mr. Holmes ceased taking Zoloft, he did so abruptly from a dose of 150mg. He does not recall being expressly told by Dr. Fenton about the need to taper (although the medication packaging came with some warning). He had no sense then, nor had he when I interviewed him, that Zoloft could produce dependence and a withdrawal syndrome.

He does report a confused state on withdrawal – being both more and less depressed. This is consistent with some changes to the treatment-induced emotional lability, dysphoric mania that he had been having.

He stated that after he stopped taking Zoloft, he had depressive symptoms. He in fact gives a confusing picture of how he was during the last 3 weeks before the events, describing himself as both more depressed and less depressed. When I interviewed him, he did not appear to have contemplated the possibility that such symptoms might have been linked to stopping the drug. Notably, there is evidence that some subjects who have had no akathisia or dysphoric mania while on SSRIs may suffer from symptoms like this on withdrawal.

It was clear from my interview of Mr. Holmes that the reduction in fear he experienced while on Zoloft continued after he had stopped. This is consistent with case reports of other individuals who experienced continued emotional blunting or depersonalization for months or years after stopping treatment with SSRIs, although there is no good data on the frequency with which people experience this effect.

It is possible that the loss of fear Mr. Holmes reports experiencing could have endured for 3 weeks following his cessation of Zoloft, and could have played a part in the movie theater events.

Similarly, it is possible that if Zoloft contributed to the formation of Mr. Holmes' delusional belief that he should kill people at the movie theater, this belief endured for some time after treatment has stopped.

Effort to Communicate

There is evidence that Mr. Holmes attempted to convey to others the changes he experienced following his intake of Zoloft.

On several occasions with Dr. Fenton and later Dr. Feinstein, he referred to the changes in his thinking, saying that if he told anyone what he was thinking they would then have to lock him up.

While Dr. Fenton was concerned enough to investigate further, the response given to Mr. Holmes during a clinical encounter with Dr. Fenton and Dr. Feinstein appears to have essentially conveyed to Mr. Holmes that he was responsible for his own thoughts and actions. The doctors' response may have been based on their erroneous understanding that they were still dealing with the kinds of original "misanthropic" ideas Mr. Holmes had expressed but never acted upon.

Mr. Holmes also appears to have attempted to communicate the changes he was experiencing in messages to friends, and classmates, such as Hillary Allen. In a text message to Ms. Allen he mentions he has dysphoric mania, that he is "bad news" and that while his condition was hard to handle before, it's "floodgates open" now.

There are very real difficulties in conveying the content of novel and alien thoughts like those that can be triggered by an SSRI. First, the person rarely if ever links what is happening to the drug. Few people think a drug could do something like this.

Second, the thoughts are ego-alien. They are foreign for the individual who is experiencing them, and accordingly the individual has not learnt how to handle the thoughts, or how to conduct themselves responsibly vis-à-vis these thoughts or feelings.

Third, there is difficulty linked with trying to convey material that has problematic content. People in these situations communicate obliquely. They frequently think that they have conveyed enough for others to understand what is going on, only to find that the other person has missed the message.

Fourth, there are the recognized difficulties in communicating the adverse effects of a drug to a doctor who has put you on the drug hoping to help you. When the situation deteriorates, the doctor increasingly becomes the way out of the problem and patients do not want to antagonize their doctor for this reason.

In this case, Mr. Holmes sought help with public speaking among other things. He was put on medication with a reassurance it would help. The dosage was increased even as things were spinning out of control. Mr. Holmes mentioned some problems which caused Dr. Fenton to switch his medication from Klonopin to Propranolol. However, she did not discontinue Zoloft, the medication likely to be causing or exacerbating his problems. To the contrary, she increased the dosage.

V. Summary and Conclusions

The distinctions drawn above between akathisia, emotional blunting and psychotic decompensation should not be interpreted rigidly. While there are cases that can appear to fall neatly into one or other group, many people span two or three of the groups.

In Mr. Holmes' case, there is a great deal of evidence from his accounts to others, his notebook and from my interview with him that he had akathisia. He termed the state he entered into as one of dysphoric mania. The dysphoric mania he describes appears to have consisted of a marked affective instability. This can be regarded as a phenomenon in its own right or as typical of akathisia.

In line with the descriptions of akathisia offered above, he had an emergence of thoughts of violence that were novel to him.

Additionally, Mr. Holmes strikingly describes emotional blunting. He records in his notebook and repeated to several interviewers that while taking Zoloft, his anxiety was turned off. Consistent with that, there is a degree of disinhibited behavior noted above.

Finally, Mr. Holmes appears to have become psychotic or more psychotic on treatment. He developed novel ideas involving violence to others and held these with a degree of delusional intensity.

It is unknown whether Mr. Holmes's psychosis would have taken the same path had he not been taking Zoloft during the months leading up to July 20, 2012, but it is certainly a possibility that the drug contributed to the worsening of Mr. Holmes's psychotic symptoms. It is important to note that the above-noted adverse effects of Zoloft can occur whether the person taking the drug is already psychotic, or is a healthy volunteer. The drug can produce states that can potentially account for many of the symptoms Mr. Holmes was exhibiting. However, it is also possible that Zoloft summated with Mr. Holmes's other problems to produce outcomes that his pre-existing mental illness might not have produced on its own.

Having made this point, James Holmes was not mentally healthy. He was clearly unwell enough to seek help. From his very first clinical encounter, the question was raised as to whether he was psychotic. Moreover, there have been

further episodes of Mr. Holmes exhibiting seriously disturbed, likely psychotic, behavior since the events of July 2012.

In conclusion, there appears to be no dispute that Mr. Holmes took Zoloft. His accounts and those of others are consistent with recognized adverse effects this and related drugs can have. A strong case can be made that these effects shaped his mental state and contributed to the events of July 20, 2012.

Signed this 29th day of August 2014 in Bangor, Wales, United Kingdom.

Yours sincerely,

Professor David Healy MD FRCPsych