

18 Pushing children into suicide with happy pills

GLAXO STUDY 329

In 2001, GlaxoSmithKline published a trial in children and adolescents, study 329.¹ This study reported that Paxil (Seroxat) was effective with minimal side effects, and it was widely believed and cited, no less than 184 times by 2010, which is remarkable. However, the trial was fraudulent. We know this because the Attorney General of New York State sued the company in 2004 for repeated and persistent consumer fraud in relation to concealing harms of Paxil,² which opened the company's archives as part of a settlement.

Glaxo lied to its sales force, telling them that trial 329 showed 'REMARKABLE Efficacy and Safety',³ while the company admitted in internal documents that the study didn't show Paxil was effective. The study was negative for efficacy on all eight protocol-specified outcomes and positive for harm. These indisputable facts were washed away with extensive data manipulations, so that the published paper, which – although it was ghostwritten – had 22 'authors', ended up reporting positive effects.^{3,4} The data massage produced four statistically significant effects after splitting the data in various ways, and it was clear that many variations were tried before the data confessed. The paper didn't leave any trace of the torture; in fact, it falsely stated that the new outcomes were declared a priori.

For harms, the manipulations were even worse. The internal unpublished study report that became available through litigation showed that at least eight children became suicidal on Paxil versus one on placebo. This was a serious and statistically significant harm of Paxil ($P = 0.035$). There were 11 serious adverse effects in total among 93 children treated with Paxil and two among 87 children treated with placebo, which was also significant ($P = 0.01$, my calculation; the paper didn't say that this difference was statistically significant). This means that for every 10 children treated with Paxil instead of placebo, there was one more serious adverse event (the inverse of the risk difference, $11/93 - 2/87$, is 10). However, the abstract of the paper ended thus:

'Conclusions: Paroxetine is generally well tolerated and effective for major depression in adolescents.'

An early draft of the paper prepared for *JAMA* didn't discuss serious adverse effects at all! *JAMA* rejected the paper, and later drafts mentioned that worsening depression, emotional lability, headache and hostility were considered related or possibly related to treatment. The published paper did mention the serious

adverse effects, but only headache in one patient was considered by the treating investigator to be related to paroxetine treatment. I have my doubts about whether the treating investigators really made these decisions. As the adverse events were reported to the company and appeared in earlier drafts, it's more likely that it was people employed by Glaxo that interpreted the drug's harms so generously. In the published paper, five cases of suicidal thoughts and behaviour were listed as 'emotional lability' and three additional cases of suicidal ideation or self-harm were called 'hospitalisation'.

At least three adolescents threatened or attempted suicide, but this wasn't described in the paper. Its first author, Martin Keller, wrote that they were terminated from the study because of non-compliance.² There were other issues the published paper said nothing about. For one of the suicidal teenagers, the treating psychiatrist asked a researcher involved with the study to break the blind, which he refused although the protocol provided for this. Another 'non-compliant' teenager ingested 82 tablets of paracetamol, which is a deadly dose. Most curiously, another teenager was enrolled with the same trial number as the suicidal one, although this should be impossible, but perhaps the new patient took what remained of the study drug? This raises the uncomfortable question whether some patients who had fared badly were excluded from the trial. When the FDA demanded the company to review the data again, there were four additional cases of intentional self-injury, suicidal ideation or suicide attempt, all on paroxetine.

Keller is some character. He double-billed his travel expenses, which were reimbursed both by his university and the drug sponsor. Further, the Massachusetts Department of Mental Health had paid Brown's psychiatry department, which Keller chaired, hundreds of thousands of dollars to fund research that wasn't being conducted. Keller himself received hundreds of thousands of dollars from drug companies every year that he didn't disclose. A social worker found a computer disc in the hallway and opened it to see to whom she should return it. She realised that adolescents were listed as if they had been enrolled in a study, which wasn't true. It seemed they were made up, which would have been tempting given that \$25 000 was offered by the drug company for each vulnerable teenager. The president of a chapter of the National Alliance for the Mentally Ill, supposed to be a patient advocacy group but heavily supported by big pharma, lectured for patients and their relatives on drug company money, which he didn't reveal, and the honoraria were whitewashed.²

Keller never admitted there was anything wrong with the way he reported study 329. And his misdeeds didn't harm his career. His department has received \$50 million in research funding and a spokesperson from Brown said that 'Brown takes seriously the integrity of its scientific research. Dr Keller's research regarding Paxil complied with Brown's research standards.' Well, thanks for letting us know that, with such ethical standards, we should never apply for a job at Brown's.

The role of the journal, *Journal of the American Academy of Child and Adolescent Psychiatry*, was similarly depressing. Although the journal's editors were shown evidence that the article misrepresented the science, they refused to convey this information to the medical community and to retract the article, thereby jeopardising their scientific standing and moral responsibility to

prescribers and patients.⁴ An explanation for this passivity can likely be found by following the money that goes to the journal's owner.

What caused the greatest public uproar was that Glaxo pushed its drug for use in children, although it not only didn't work in children, it was also very harmful, and it wasn't even approved for use in children. The illegal marketing involved withholding trials showing Paxil was ineffective.⁵ An internal company document showed that the company knew what it was doing: 'It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.'⁴

The ruthless marketing worked. From 1998 to 2001, five million prescriptions a year were being written for Paxil and Zoloft for children and adolescents.⁶ We should remember that there are real tragedies behind the numbers and real people who have paid with their lives for the companies' unscrupulous lies, frauds and crimes:⁷

Matt Miller was unhappy. Having moved to a new neighborhood and a new school, Matt was thrust into unknown territory without his support system of old friends with whom he had grown up. That summer, Matt was prescribed Zoloft ... and was told to call his doctor in a week. On a Sunday night, after taking his seventh pill, Matt went to his bedroom closet, where there was a hook just a little higher than he was tall. Matt hung himself, having to lift his legs off the floor and hold himself there until he passed out. He was only thirteen years old.

Jeremy Lown, a teenager, suffered from Tourette's syndrome. To treat his uncontrollable tics and verbal outbursts, his neurologist prescribed Prozac. Three weeks after starting the medication, Jeremy hanged himself in the woods behind his house.⁸

Candace, a 12-year-old girl, was prescribed Zoloft because she suffered from anxiety. She was a happy child that had never been depressed or had suicidal ideation. She hanged herself after 4 days.⁹

Vicky Hartman was given a sample pack of Zoloft by her child's doctor. She didn't suffer from any mental disorder but mentioned she needed a 'pick-me-up' to help with stress. Soon after starting the medication, she shot her husband and herself.⁸

A man hanged himself after taking Prozac, which his cardiologist had prescribed for chest pain, and a woman shot herself after taking the Prozac her family doctor had prescribed for migraine.

Twenty-year-old student Justin Cheslek had trouble sleeping and was prescribed sleeping pills by his doctor.¹⁰ A few days later, he complained to the doctor that the pills made him feel groggy and 'depressed'. The doctor gave him Paxil, and Justin told his mother that Paxil made him feel awful, wound up, jumpy and unable to sit still or concentrate. Two weeks later, the doctor gave him another SSRI, Effexor (venlafaxine), which caused a seizure after the first tablet. Justin still felt 'really, really bad' and 3 weeks after he took his first Paxil tablet, he hanged himself. Justin had no history of depression and if he hadn't used the term 'depressed', he might not have been prescribed SSRIs. He just had trouble

sleeping. In the days before his death, Justin described a feeling of wanting to jump out of his skin, a symptom typical of akathisia, which may lead to suicide.

In November 2010, Nancy and Shaun McCartney's 18-year-old son, Brennan, went to their family doctor with a chest cold.¹¹ The extroverted high school student mentioned feeling sad over breaking up with a girl he'd been seeing for 3 months. He left with a script for an antibiotic and a sample pack of CipraleX. Nancy expressed concern, as Brennan had no history of depression, but he assured her the doctor had said it would help. On the fourth day, Brennan seemed agitated when he left the house and he failed to come home. The next day his body was found. He had hung himself in a local park. Nancy wanted to warn other Canadians about CipraleX and submitted an adverse reaction report, and when she noticed a typo on her entry, she called the Vigilance Branch requesting a correction. She also asked for an updated copy but was told she'd have to file an access to information request. Seven months later, anyone searching CipraleX on MedEffect would find 317 reports, including five suicides, 12 suicide attempts and many references to suicidal ideation, but not Nancy's submission. When the journalist writing about the tragedy asked Health Canada why, its spokesperson responded weeks later saying the entry was in the database and provided a screen grab. However, subsequent searches using the same terms failed to find it. It's unbelievable. Not even suicides reported to the authorities may be traceable in their records.

Here is an example that the advertising of prescription drugs to the public, which is legal in the United States, can kill healthy people who don't need them:¹²

Ten years ago my irrepressible teenage daughter Caitlin returned from holiday with relatives in the US, where prescription drugs are widely advertised; she saw an ad for an antidepressant drug called Prozac and wanted to try it. She went to our local GP and it took her 8 minutes to get the prescription. Sixty-three days later, during which time she descended into unprecedented chaos, including neural twitches, violent nightmares and self-harm, she hanged herself.

CONCEALING SUICIDES AND SUICIDE ATTEMPTS IN CLINICAL TRIALS

I shall explore here what the true risks of suicide and suicidality with SSRIs are. They are certainly much larger than what the drug companies have told us. David Healy performed a study in 20 healthy volunteers – all with no history of depression or other mental illness – and to his big surprise two of them became suicidal when they received sertraline.¹³ One of them was on her way out the door to kill herself in front of a train or a car when a phone call saved her. Both volunteers remained disturbed several months later and seriously questioned the stability of their personalities. Pfizer's own studies in healthy volunteers had shown similar deleterious effects, but most of these data are hidden in company files.¹³

FDA reviewers and independent researchers found that the big companies had concealed cases of suicidal thoughts and acts by labelling them 'emotional lability'.¹³⁻¹⁵ However, the FDA bosses suppressed this information. When safety officer Andrew Mosholder concluded that SSRIs cause increased suicidality

among teenagers, the FDA prevented him from presenting his findings at an advisory meeting and suppressed his report. When the report was leaked, the FDA's reaction was to do a criminal investigation into the leak.^{16,17}

There were other problems. In data submitted by GlaxoSmithKline to the FDA in the late 1980s and early 1990s, the company had included suicide attempts from the washout period before the patients were randomised in the results for the placebo arms of trials, but not from the paroxetine arms. A Harvard psychiatrist, Joseph Glenmullen, who studied the released papers for the lawyers, said that it's virtually impossible that Glaxo simply misunderstood the data. Martin Brecher, the FDA scientist who reviewed paroxetine's safety, said that this use of the washout data was scientifically illegitimate.¹⁸ Indeed, I believe it's fraud.

David Healy wrote in 2002¹⁹ that, based on data he had obtained from the FDA, three of five suicide attempts on placebo in a sertraline trial²⁰ had occurred during washout rather than while on placebo and that two suicides and three of six attempts on placebo in a paroxetine trial²⁰ had also occurred in the washout period. Healy's observations weren't denied by Pfizer and Glaxo,^{21,22} but Glaxo again provided a glaring example that their lies are not of this world:²²

The 'drug' v. 'true placebo' analysis Dr Healy describes is not only scientifically invalid, but also misleading. Major depressive disorder is a potentially very serious illness associated with substantial morbidity, mortality, suicidal ideation, suicide attempts and completed suicide. Unwarranted conclusions about the use and risk of antidepressants, including paroxetine, do a disservice to patients and physicians.

So, should we trust people who deliberately hide suicidal harms of their drug and hide trials that showed no effect and make billions out of their frauds, who are only responsible to their shareholders, and who nonetheless wants us to believe that patient welfare is their primary concern? Or should we trust an academic like Healy whose job it is to take care of the patients?

At least three companies, Glaxo, Lilly and Pfizer, added cases of suicide and suicide attempts in patients to the placebo arm of their trials, although they didn't occur while the patients were randomised to placebo.^{13,19,23-25} These omissions can be important for the companies in court cases. For example, a man on paroxetine had murdered his wife, daughter and granddaughter and committed suicide, but in its defence, Glaxo said that its trials didn't show an increased risk of suicide on paroxetine.²⁶

The pervasive scientific misconduct has distorted seriously our perception of the benefits and harms of SSRIs. As an example, a 2004 systematic review showed that, when unpublished trials were included, a favourable risk-benefit profile changed to an unfavourable one for several of the SSRIs.²⁷ Also in 2004, a researcher used the full reports of Glaxo's trials that were made available on the internet as a result of litigation, and he found in his meta-analysis that paroxetine increased significantly suicidal tendencies, odds ratio 2.77 (95% confidence interval 1.03 to 7.41).¹⁴ He included three trials, among them the unpublished study 377, which didn't show that paroxetine was better than placebo (Glaxo had stated in an internal document that 'There are no plans to publish data

from Study 377.’)²⁸ He also included the infamous study 329. He described that an 11-year-old boy who threatened to harm himself and was hospitalised was coded as a case of exacerbated depression, and that a 14-year-old boy who had harmed himself and expressed hopelessness and possible suicide thoughts and was hospitalised was coded as a case of aggression.

It is widely believed that SSRIs only increase suicidal behaviour in people below 25 years of age, but this is not correct. A 2006 FDA analysis of 372 placebo-controlled trials of SSRIs and similar drugs involving 100 000 patients found that up to about 40 years of age, the drugs increased suicidal behaviour, and in older patients, they decreased it (*see* Figure 18.1).²⁹ However, as explained below, it is much worse than this. A major weakness of the FDA study is that the agency asked the companies to adjudicate possibly suicide-related adverse events and send them to the FDA, which didn’t verify whether they were correct or whether some had been left out. We already know that the companies have cheated shamelessly when publishing suicidal events. Why should they not continue cheating when they know that the FDA doesn’t check what they are doing? Furthermore, collection of adverse events was limited to within one day of stopping randomised treatment, although stopping an SSRI increases the risk of suicidality for several days or weeks. This rule therefore also seriously underestimated the harms of SSRIs.

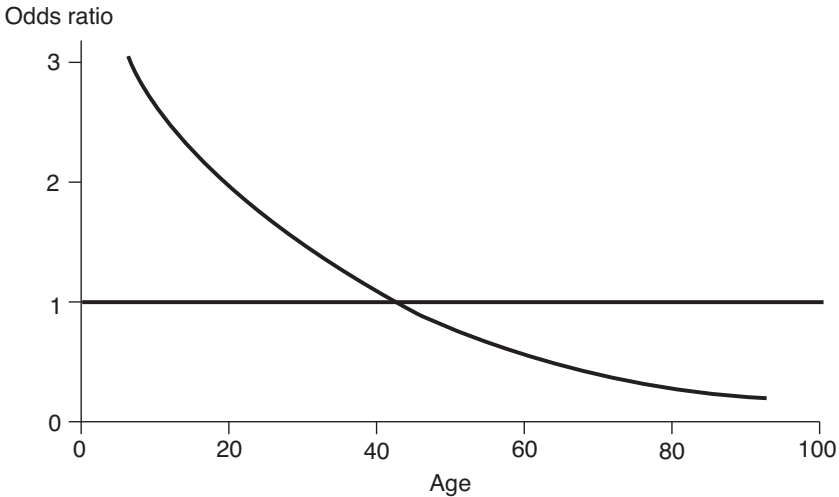


Figure 18.1 FDA meta-analysis of 372 placebo-controlled trials of SSRIs and similar drugs involving nearly 100 000 patients. Odds ratios for suicidal behaviour for active drug relative to placebo by age

Other data show that the huge FDA analysis *cannot* be reliable. An internal Lilly memo from 1984 reported that the German drug agency described two suicides and 16 suicide attempts among only 1427 patients on fluoxetine in clinical trials even though patients at risk of suicide were excluded from the trials.³⁰ A memo from Lilly Germany listed nine suicides in 6993 patients on fluoxetine in the

trials.³¹ In contrast, there were only five suicides in total in FDA's analysis of 52 960 patients on SSRI drugs, or one per 10 000 patients, although one would have expected 74 and 68, respectively, based on the two Lilly reports, or 13 per 10 000 patients.

Many suicides are missing in the FDA analysis. In a 1995 meta-analysis, there were five suicides on paroxetine in 2963 patients,³² which is 17 per 10 000 patients. This meta-analysis wrongly reported two suicides on placebo, which had occurred in the washout period. The UK drug regulator was much more careful than the FDA and did not only search for suicide terms in the documents but also read text in case report forms and narratives.³³ *They showed that paroxetine was harmful in adults with major depressive disorder.* There were 11 suicide attempts on paroxetine (3455 patients) and only one on placebo (1978 patients), $P = 0.058$ for the difference. I wonder why no suicides were reported, as we would have expected six on paroxetine.

A 2005 meta-analysis that built on data in a report the UK drug regulator had made found nine suicides in 23 804 patients,³⁴ or four per 10 000. This was an unusually low rate, and it has been shown that the companies underreported the suicide risk.³⁵ There were other oddities; the researchers found that non-fatal self-harm and suicidality were seriously underreported compared to the reported suicides.

A 2005 meta-analysis of published trials including 87 650 patients conducted by independent researchers included all ages and found double as many suicide attempts on drug than on placebo.³⁶ Even so, they found that many suicide attempts must have been missing, e.g. by asking the investigators, some of whom responded that there were suicide attempts they had not reported, while others replied that they didn't even look for them in their trials. There were other issues related to trial design that likely led to underestimation of suicide attempts, e.g. events occurring shortly after active treatment is stopped might very well be caused by the drug but were not counted.

It is abundantly clear that suicides, suicidality and violence caused by SSRIs are grossly underestimated,³⁷ and we also know the reasons. First, there is outright fraud. Second, many suicidal events have been coded as something else. Third, the drug industry has taken great care to bias its trials by only recruiting people at very low risk of committing suicide. Fourth, the companies have urged the investigators to use benzodiazepines in addition to the trial drugs, which blunt some of the violent reactions that would otherwise have occurred. Fifth, some trials have run-in periods on active drug, and patients who don't tolerate it aren't randomised, which comes close to scientific misconduct, as it artificially minimises the occurrence of suicidality. Sixth, and perhaps the worst of all the biases, events occurring shortly after active treatment is stopped, e.g. because the patients feel very badly, might very well be suicidal events caused by the drug but are often not registered. Seventh, many trials are buried in company archives and these are not the most positive ones.

Given what I have just described above, and earlier, e.g. that middle-aged women who use duloxetine for urinary incontinence have a suicide attempt rate that is more than double the rate among other women of a similar age, my take on all this is:

SSRIs likely increase the risk of suicide at all ages. These drugs are immensely harmful.

LUNDBECK'S EVERGREENING OF CITALOPRAM

Lundbeck launched citalopram (Cipramil or Celexa) in 1989. It became one of the most widely used SSRIs and provided the company with most of its income. That was a risky situation to be in but Lundbeck was lucky. Citalopram is a stereoisomer and consists of two halves, which are mirror images of each other, but only one of them is active.

Lundbeck patented the active half before the old patent ran out and called the rejuvenated me-again drug escitalopram (Cipralext or Lexapro), which it launched in 2002. When the patent for citalopram expired, generics of Cipramil entered the market at much lower prices, but the price of Cipralext continued to be very high. When I checked the Danish prices in 2009, Cipralext cost 19 times as much for a daily dose as Cipramil. This enormous price difference should have deterred the doctors from using Cipralext, but it didn't. The sales of Cipralext were six times higher in monetary terms than the sales of citalopram both at hospitals and in primary care. I calculated that if all patients had received the cheapest citalopram instead of Cipralext or other SSRIs, Danish taxpayers could have saved around €30 million a year, or 87% of the total amount spent on SSRIs.

How is it possible for doctors to have such a blatant disregard for the public purse to which we all contribute and why can it continue year after year? The old recipe with a blend of money and hyped research seems infallible. A psychiatrist described vividly that when Lundbeck launched Cipralext in 2002, most of the Danish psychiatrists (she did say most, although there are more than a thousand psychiatrists in Denmark) were invited to a meeting in Paris. That meeting seems to have been enjoyable, 'with expensive lecturers – of course from Lundbeck's own "stable" – luxurious hotel and gourmet food. A so-called whore trip. Under influence? No, of course not, a doctor doesn't get influenced, right?'³⁸

When the patent of Cipramil was expiring, Jack M Gorman published an article in a special supplement of *CNS Spectrums*, a neuropsychiatric journal he edits.³⁹ The article concluded that escitalopram may have a faster onset of action and greater overall effect than citalopram⁴⁰ Gorman was a paid consultant to Forest that marketed both drugs in North America, and Forest paid Medworks Media, the publisher of *CNS Spectrums*, to print the article. At the same time, *Medical Letter*, an independent drug bulletin with no advertising, also reviewed the two drugs and found no difference between them.⁴¹

On one of the occasions where I was invited to give a lecture for Danish psychiatrists, I expressed my doubts that a drug could be better than itself to a person sitting close to me at the lunch table. She was a chemist working at Lundbeck and didn't agree. She sent me a copy of Gorman's paper, which on page 2 says: 'Brought to you by an unrestricted educational grant from Forest Pharmaceuticals, Inc.' Oh no, I thought I would never accept 'an unrestricted educational grant' from a drug company, not even in the form of a reprint, but here it was. All three authors worked for Forest, Gorman as a consultant and

the others in the company. The paper was a meta-analysis of three trials that compared the two drugs with placebo.

What am I supposed to make out of a paper published in a bought supplement to a journal edited by a person who is also bought by the company? Nothing, I would say. We cannot trust the drug industry, and a paper published this way is nothing but an advertisement. There are so many ways a trial can be manipulated, and in SSRI trials it's particularly crucial how the statistician deals with dropped out patients and other missing values.⁴² On top of this, Lundbeck was in a pretty desperate situation. I therefore wouldn't believe anything unless I got access to the raw data and analysed them myself.

But it isn't necessary to go to such lengths. What Forest published was small differences between the two drugs and between active drugs and placebo (*see* Figure 18.2). After 8 weeks, the difference between the two drugs was 1, on a scale that goes from 0 to 60, and the difference between active drugs and placebo was 3. Obviously, a difference of 1 on a 60-point scale has no importance for the patients. Furthermore, as explained in Chapter 4, it doesn't take much unblinding before we find a difference of 3 between active drugs and placebo, even if the drugs have no effect on depression. There is therefore no good reason to use a drug that is 19 times more expensive than itself.

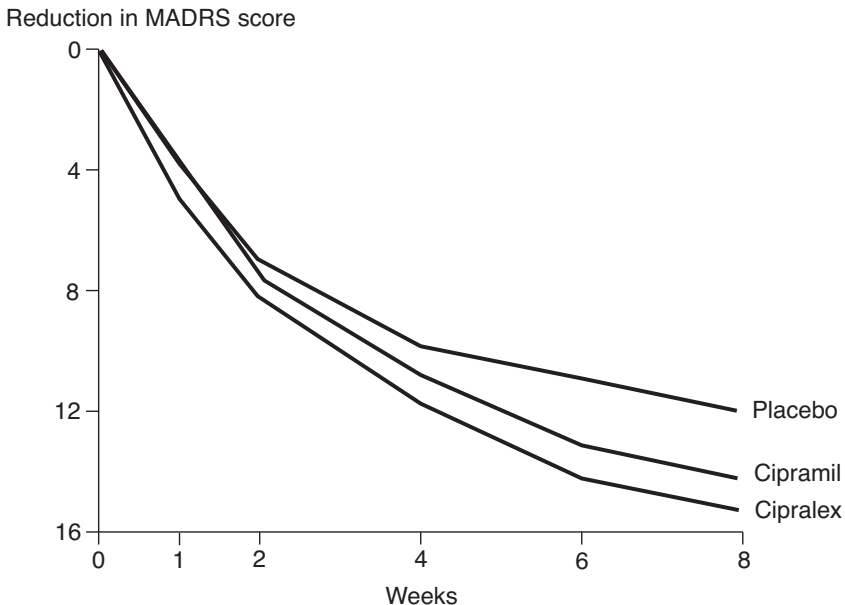


Figure 18.2 Change from baseline in MADRS score throughout 8 weeks; the scale goes from 0 to 60. Redrawn

The official task of the government-funded Danish Institute for Rational Drug Therapy is to inform Danish doctors about drugs in an evidence-based fashion. In 2002, the institute reviewed the clinical documentation for Lundbeck's me-gain drug, escitalopram, and informed Danish doctors that it didn't have clear

advantages over the old drug, which contained the same active substance.⁴³ Lundbeck complained loudly about this in the press and said it was beyond the institute's competence to give statements that could affect the international competition and damage Danish drug exports.⁴⁴

Although it *wasn't* beyond the institute's competence to give recommendations about new drugs, whatever the consequences for drug exports, the institute was reprimanded by the minister of health and it declined to comment when asked by a journalist, for pretty obvious reasons. The Danish drug industry has tried for years to get political backing for closing down the institute, which is a thorn in its flesh, as it reduces sales of expensive drugs, but it hasn't succeeded.

It seems that our highly praised governmental institute is only allowed to tell the truth about imported drugs, not about drugs we export. An untenable position that shows that *principles are only valid as long as they don't cost too much*.

Two years after these events, the institute announced that escitalopram was better than citalopram and might be tried if the effect of citalopram hadn't been satisfactory.⁴⁵ The institute must have stepped on its toes to find a politically correct way to express themselves.⁴⁶ Its information to doctors now stated that they should usually choose the cheapest SSRI, as there are no major differences between the drugs. About escitalopram it said that 'Two studies have shown that the effect of escitalopram comes somewhat faster than that of venlafaxine and citalopram, but with about the same maximum effect', and 'In a single study it was made likely in a subgroup analysis that escitalopram is a little better in severe depression than venlafaxine and citalopram.'

I had a big laugh when I saw the four references in support of these statements. Paper is grateful, as we say; it doesn't protest, no matter what you write on it. One of the academic authors was Stuart Montgomery, who concealed that he worked for Pfizer helping the company to get sertraline approved at the same time as he worked for the UK drug regulator that approved the drug (*see* Chapter 10). I laughed again when an employee from the institute was interviewed in the TV news. She was pressured by the journalist who asked her if she couldn't imagine any situation where it *might* be an advantage that the drug worked faster. Yes, she said, if a patient was about to throw herself out the window! She learned the hard way how to deal with journalists. Jokes won't do on the news, particularly not if they are about patients. It was doubly ironic, as it has never been demonstrated that SSRIs decrease the risk of suicide; they seem to increase the risk (*see* above).

Four independent reviews of the evidence – by the FDA, the American advisory group Micromedex, the Stockholm Medical Council and the Danish institute – concluded that escitalopram offers no significant benefit over its predecessor.⁴⁷ The Cochrane review on escitalopram says that it's better than citalopram but warns against this finding because of potential sponsorship bias.⁴⁸ The trials were performed by Lundbeck and many negative antidepressant trials never get published. Furthermore, the reporting of the outcomes in the included studies was often unclear or incomplete. Analyses made by disinterested parties who have access to the data, such as scientists working at drug agencies, have repeatedly found that there are no important differences in benefits and harms of the various

SSRIs, whereas what gets published is seriously misleading.^{29,42,49} Comprehensive reviews by other researchers have also failed to find important differences.⁵⁰

In 2003, Lundbeck breached the UK industry code of practice in its advertising.⁵¹ The company breached the code on five counts, notably by claiming that ‘Cipraxel is significantly more effective than Cipramil in treating depression’. The company also attributed adverse effects to citalopram in its literature on escitalopram that weren’t mentioned in promotional material for citalopram. This confirms the adage that it’s surprising how quickly a good drug becomes a bad drug when a more expensive drug comes around. The UK advertising campaign was intensive and highly successful, as escitalopram rapidly gained market share.

Lundbeck’s CEO, Erik Sprunk-Jansen, retired in 2003 and started a company selling herbal medicine. One of the products is Masculine, which ‘Spices up your love life’, and is said to give extra energy that strengthens the lust and blood circulation,⁵² typical mumbo-jumbo pep talk for alternative medicine. It doesn’t seem to matter much what drug pushers sell, as long as they sell *something*.

In 2011, we asked Lundbeck for unpublished trials of its antidepressant drugs, which we needed for our research on suicidality, but we were told that the company, as a matter of principle, doesn’t hand out the clinical documentation that forms the basis for marketing authorisation. The same year, Lundbeck’s new CEO, Ulf Wiinberg, denied in an interview that the increase in suicidal events with happy pills in children and adolescents means that the drugs increase the risk of suicide.⁵³ He even stated that treatment of depression in children and adolescents *decreases* the suicide risk, in violation of the labelling that warns that the drugs may increase the risk of suicide. Why does any doctor trust what the companies tell them?

Events in America were also interesting. In 2001, Lundbeck’s American partner Forest had performed a trial of citalopram (Celexa) for compulsive shopping disorder (I’m not joking), and Good Morning America told the viewers that this new disorder could affect as many as 20 million Americans of which 90% were women.⁵⁴ Gorman appeared as an expert in the programme and said that 80% of the compulsive shoppers had slowed their purchases on Celexa. The ensuing flurry of publicity forced the APA to say it had no intention of adding such a disorder to the DSM.

In 2010, the US Justice Department announced that Forest had pleaded guilty to charges relating to obstruction of justice and the illegal promotion of citalopram (Celexa) and escitalopram (Lexapro) for use in treating children and adolescents with depression.⁵⁵ Forest agreed to pay more than \$313 million to resolve criminal and civil liability arising from these matters and also faced numerous court cases from parents to children who had either committed suicide or had tried.⁵⁶ There were also charges that the company launched seeding studies, which were marketing efforts to promote the drugs’ use. Two whistle-blowers would receive approximately \$14 million, and Forest signed a Corporate Integrity Agreement.^{55,57} Six years earlier, a Forest executive had testified before Congress that Forest followed the law and had not promoted Celexa and Lexapro to children, although Forest had illegally done exactly that.⁵⁸

The government mentioned that Forest publicised and circulated the positive

results of a double-blind, placebo-controlled Forest study in 2004 on the use of Celexa in adolescents while, at the same time, failed to discuss the negative results of a contemporaneous double-blind, placebo-controlled Lundbeck study on the use of Celexa in adolescents, finished in 2002 in Europe but only mentioned in a textbook in Danish in 2003 in a single line of a chart.⁵⁹ For 3 years, Forest executives didn't disclose those results within the company or to outside researchers who published results on Celexa, and the existence of the Lundbeck study first came to public light when the *New York Times* published an article about it. Only then did Forest acknowledge the study as well as another, earlier trial that also failed to show any benefits of Lexapro as a depression treatment for children.^{55,57}

Forest's official excuse for not mentioning the negative trials was that 'there was no citable public reference for the authors to examine'.⁵⁹ But drug makers often announce trials with positive results without waiting for the results to be published, e.g. Forest issued a news release that highlighted the outcome of the positive Celexa trial already in 2001, shortly after the trial's completion.

Forest had 19000 advisory board members⁵⁸ and used illegal kickbacks to induce physicians and others to prescribe Celexa and Lexapro, which allegedly included cash payments disguised as grants or consulting fees, expensive meals and lavish entertainment. On one occasion, Forest paid physicians five hundred dollars to dine at one of the most expensive restaurants in Manhattan and called them consultants – for the evening it seemed, and they didn't do any consulting.⁵⁴ Vermont officials found that Forest's payments to doctors in 2008 were surpassed only by those of Eli Lilly, Pfizer, Novartis and Merck – companies with annual sales that were five to 10 times larger than Forest's.⁶⁰

What was Lundbeck's reaction to the crimes? 'We know Forest is a decent and ethically responsible firm and we are therefore certain that this is an isolated error.'⁵⁶ Perhaps this confidence in Forest's business ethics was related to the fact that Lexapro sold for \$2.3 billion in 2008.⁵⁷ At any rate, we do know something about what it means to be 'a decent and ethically responsible firm'. In 2009, the US Senate released documents it had requested from Forest.⁶¹ They start out by saying that Forest will communicate that Lexapro offers superior efficacy and tolerability over all SSRIs, which is pure fantasy.

We are also told that the antidepressant market is the most heavily detailed category in the drug industry and that the sales mirror the promotional effort. Forest will develop ghostwritten articles for 'thought leaders', which will 'allow us to fold Lexapro messages', and will also use thought leaders at sponsored symposia, which will be published in supplements to medical journals to 'help disseminate relevant Lexapro data and messages to key target audiences'.

The thought leaders, advisors and Lexapro investigators will be kept informed by monthly mailings, and Forest will use the consultant services of thought leaders and advisors to obtain critical feedback and recommendations on 'educational and promotional strategies and tactics'. Forest recruited about 2000 psychiatrists and primary care physicians whom the company trained to 'serve as faculty for the Lexapro Speakers' Bureau Program'. It was obligatory that speakers used the slide kit prepared by Forest.

The documents include details of a huge programme of phase IV studies (seedling trials it seems) and describe that investigator grants would cover the costs of ‘Thought Leader Initiated Phase IV studies with Lexapro’. The outcome of all these studies seemed to have been determined beforehand, even before the studies started, as key messages were listed for each study:

- Escitalopram has the lowest potential for drug interactions
- Escitalopram has an excellent dosing profile
- Escitalopram represents a new more selective and/or potent generation of SSRIs
- Escitalopram is an effective first-line treatment for depression
- Escitalopram has a favourable side-effect profile
- Escitalopram has improved side-effect, drug interaction and safety profiles resulting from the removal of the inactive moiety, the R-enantiomer
- Escitalopram is a refinement of citalopram in terms of antidepressant effect and tolerability.

Forest provided ‘unrestricted grants’ to professional societies, e.g. the American Psychiatric Association, so that they could develop ‘reasonable practice’ guidelines. What was meant by this was ‘to improve the percent of patients who adhere to the full duration of therapy’. Forest became a corporate sponsor of the American College of Physicians ‘which provides additional marketing opportunities’, and this organisation was also involved with developing the ‘reasonable practice’ guidelines.

I could throw up. Total corruption of academic medicine resulting in immense harms to patients who cannot get off the drug once they have adhered to ‘the full duration of therapy’. So this is a ‘decent and ethically responsible firm’,⁵⁶ right?

ANTIPSYCHOTIC DRUGS

Antipsychotics are dangerous drugs that should only be used if there is a compelling reason, and preferably as short-term therapy at a low dose because the drugs produce severe and permanent brain damage. As explained above, even most patients with schizophrenia can avoid the drugs and it results in much better long-term outcomes than if they are treated and substantial financial savings as well.²¹

Antipsychotics increase the risk of dying substantially through a variety of mechanisms, which include suicide, cardiac arrhythmias, diabetes and major weight gains.⁹

The drug companies have caused tremendous harm by their widespread illegal and aggressive promotion of the drugs for off-label use (*see* Chapter 3). The legal use is also increasing, e.g. in children, the use of antipsychotics went up eight-fold between 1993–1998 and 2005–2009, and it doubled in adults.⁶²

The story of antipsychotics has many similarities to that of the SSRIs. The clinical research wasn’t aimed at clarifying the role of the new drugs for clinicians and patients but was driven by marketing strategy, and new drugs were much hyped although large, independent government-funded trials found they weren’t better than old drugs^{63–65} (*see also* Chapter 9). A trial of 498 patients

with a first-episode schizophrenia found no difference in discontinuation rates between four newer drugs and haloperidol.⁶⁵ Discontinuation rate is a sound outcome, as it combines perceptions of benefits and harms of the drugs. The study was funded by three drug companies but they were kept at arm's length.

Antipsychotics are standard treatment for bipolar disorder, which is mainly iatrogenic, caused by SSRIs and ADHD drugs, and they are also used for depression when treatment with an antidepressant is not enough. We now see advertisements, e.g. for AstraZeneca, about combination therapy for depression, and there are even preparations that combine the drugs in the same pill, e.g. Symbyax from Lilly, which contains Prozac (fluoxetine) and Zyprexa (olanzapine),⁴⁸ two of the worst psychotropic drugs ever invented.

Like for the SSRIs, there are many perverse trials supporting antipsychotics for virtually everything. In 2011, an AstraZeneca trial studying whether quetiapine could prevent the development of psychosis in people as young as 15 years 'at risk' of psychosis was stopped after protests that it was unethical.⁶⁶ There is no good reason to believe that these drugs can prevent psychosis, in fact, they *cause* psychosis in the long run (see above);²¹ and most people 'at risk' would never have developed psychosis.

A 2009 meta-analysis of 150 trials with 21 533 patients showed that psychiatrists had been duped for 20 years.^{63,67} The drug industry invented catchy but entirely misleading terms such as 'second generation antipsychotics' and 'atypical antipsychotics', but there is nothing special about the new drugs, and as they are widely heterogeneous, it's wrong to divide them into two classes.

It's remarkable that it was possible to show in a meta-analysis of published trials that new drugs aren't better than old ones, as the research literature is so flawed. Haloperidol is the comparator in most of the trials, and their design is often flawed, using too high doses or too quick dose increases for haloperidol and other old drugs, resulting in a false claim that a new drug is similarly effective but better tolerated.⁶⁸ An analysis of 2000 trials in schizophrenia revealed a disaster area of poor-quality research that didn't even improve over time, and with 640 different instruments to measure the outcome; 369 of these mostly homemade scales were only used once!⁶⁹

Unsurprisingly, an internal Pfizer memorandum shows that the flaws are introduced deliberately:⁷⁰

If we were going to have to increase dothiepin dosage from 75 mg to 100 mg, we should do so at 1 week rather than at 2 weeks, which would result in a high drop-out rate on dothiepin due to side effects. By 2 weeks, patients have learnt to live with side effects.

ZYPREXA, ANOTHER TERRIBLE ELI LILLY DRUG TURNED INTO A BLOCKBUSTER

The deceptions worked, as always. Everybody wants a 'modern' drug, whatever that means, and this bad habit is extremely costly, even when the 'modern' drug is only an old drug in disguise. Olanzapine was an old substance and the patent was running out, but Lilly got a new patent by showing that it produced less

elevation of cholesterol in dogs than a never-marketed drug!⁹ This was totally ludicrous, and in fact, olanzapine raises cholesterol more than most other drugs. It could therefore have been marketed as a cholesterol-raising drug, but that wouldn't have made Zyprexa a blockbuster with sales of around \$5 billion per year for more than a decade.⁹

A Cochrane review from 2005 reported that the largest trial with olanzapine had been published 142 times in papers and conference abstracts.⁷¹ I am not kidding, it was the same trial in 142 publications. The carpet bombing also included criminal activities (*see* Chapter 3), and the aggressive marketing made Zyprexa the most widely used antipsychotic drug in the world, although it isn't any better than far cheaper alternatives. In 2005, Zyprexa was Lilly's top-selling drug at \$4.2 billion.⁷²

Money, marketing and lies ensured that doctors didn't use the old cheap drugs. In 2002, the sales of Zyprexa were 54 times larger than the sales for haloperidol in Denmark, amounting to a staggering €30 million a year, although our country is very small. There was no excuse for this. Two years earlier, a meta-analysis was published in the *BMJ* that concluded that 'the new drugs have no unequivocal advantages for first line use'.⁷³

The last time I checked the price for Zyprexa, it cost seven times as much as haloperidol. It's irresponsible to waste so much money, and patient organisations contribute to this. They only know what the drug firms have told them, or what the psychiatrists have told them, which is about the same, as the psychiatrists also generally only know what the drug firms have told them. It was therefore not surprising when the chairman of an organisation for psychiatric patients in 2001 called it unethical that Danish psychiatrists in her view were too slow to use the newer antipsychotics such as Zyprexa and Risperdal (risperidone).⁷⁴ A researcher explained that many patients on Zyprexa increased their body weight by 15–25 kg during a few months, that there was a risk of diabetes, and that increased cholesterol was commonly seen. He also commented on the adverse effects of Risperdal and said that the likely reason that the chairman wanted these drugs to be used much more was that the adverse effects were little known. Wise words indeed.

In Chapter 3, I described that Lilly agreed to pay more than \$1.4 billion for illegal marketing for numerous off-label uses including Alzheimer's, depression and dementia, and Zyprexa was pushed particularly hard in children and the elderly, although the harms of the drug are substantial, inducing heart failure, pneumonia, considerable weight gain and diabetes.⁷⁵ In 2006, internal Lilly documents were leaked to the *New York Times*, which demonstrate the extent to which the company downplayed the risks of its drug.^{72,76} Lilly's chief scientist, Alan Breier, told employees in 1999 that 'weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule', but the company didn't discuss with outsiders that a 1999 study, disclosed in the documents, found that blood sugar levels in the patients increased steadily for 3 years.⁷⁶ Lilly instigated legal action against a number of doctors, lawyers, journalists and activists to stop them from publishing the incriminating leaked documents on the internet, and after the injunction, they disappeared.

In 2007, Lilly still maintained that 'numerous studies ... have not found that

Zyprexa causes diabetes', even though Zyprexa and similar drugs since 2003 on their label had carried an FDA warning that hyperglycaemia had been reported. Lilly's own studies showed that 30% of the patients gained at least 10 kg in weight after a year on the drug, and both psychiatrists and endocrinologists said that Zyprexa caused many more patients to become diabetic than other drugs.⁷⁶

Zyprexa is likely more harmful than many other antipsychotics.⁷⁷ In 2001, Lilly's best-selling antidepressant Prozac was running out of patent and the company was desperate to somehow fool people into using Zyprexa also for mood disorders and called it a mood-stabiliser rather than an antipsychotic. It doesn't stabilise the mood, and it was also a challenge that general practitioners were worried about the harms of antipsychotics, but Lilly was determined to 'change their paradigm'. The internal documents say it all. In psychiatry, it doesn't really matter which drugs you have, as most drugs can be used more or less for everything, and psychiatrists are easily amenable for manipulation, even in the way they define and name their diseases.

Let's estimate how many people Lilly has killed with Zyprexa. In 2007, it was reported that more than 20 million people had taken Zyprexa.⁷⁸ A meta-analysis of the randomised trials of olanzapine and similar drugs given to patients with Alzheimer's disease or dementia showed that 3.5% died on drug and 2.3% on placebo ($P = 0.02$).⁷⁹ Thus, for every 100 patients treated, there was one additional death on the drug. Elderly patients are often treated with several drugs and are more vulnerable to their harms, which means that the death rate is likely higher than in younger patients. However, the reviewed trials generally ran for only 10–12 weeks, and most patients in real life are treated for years. Further, drugs like Zyprexa are most used in the elderly, and as deaths are often underreported in trials, the true death rate is likely higher than shown in the meta-analysis. One death in a hundred therefore seems a reasonable estimate to use. I therefore estimate that 200 000 of the 20 million patients treated with Zyprexa have been killed because of the drug's harms. What is particularly sadening is that many of these patients shouldn't have been treated with Zyprexa.

As Zyprexa is not the only drug, the death toll must be much higher than this. AstraZeneca silenced a trial that showed that quetiapine (Seroquel) led to high rates of treatment discontinuations and significant weight increases while the company at the same time presented data at European and US meetings that indicated that the drug *helped* psychotic patients *lose* weight.⁸⁰ Speakers Slide Kit and at least one journal article stated that quetiapine didn't increase body weight while internal data showed that 18% of the patients had a weight gain of at least 7%.⁷⁷ AstraZeneca propagated other lies.⁷⁷ It presented a meta-analysis of four trials showing that quetiapine had better effect than haloperidol, but internal documents released through litigation showed it was exactly the opposite: quetiapine was *less* effective than haloperidol.

THE BOTTOM LINE OF PSYCHOTROPIC DRUGS

How come we have allowed drug companies to lie so much, commit habitual crime and kill hundreds of thousands of patients, and yet we do nothing? Why

don't we put those responsible in jail? Why are many people still against allowing citizens to get access to all the raw data from all clinical trials and why are they against scrapping the whole system and only allow publicly employed academics to test drugs in patients, independently of the drug industry?

I know some excellent psychiatrists who help their patients a lot, e.g. David Healy uses watchful waiting before giving drugs to first-episode patients.²¹ I also know that some drugs can be helpful sometimes for some patients. And I am not 'antipsychiatry' in any way. But my studies in this area lead me to a very uncomfortable conclusion:

Our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good.

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