7. Experiment at the End of the Millennium

From the Deposition of John Heiligenstein (1994):

Q. Can you conceive as a clinical research physician and scientist, anything that would change your opinion on whether or not Prozac has a causal relationship between it and suicidality?
A. I doubt if there is any study that could be done that could possibly demonstrate a relationship between fluoxetine and suicidality.[1]

Before I became an expert witness, in the course of lectures for Pharmacia & Upjohn following the launch of reboxetine, I had wondered why the quality-of-life scale they used (the SASS) showed better results for reboxetine than for Prozac (see chapter 4).[2] One possibility was that the emotional indifference caused by Prozac and other SSRIs might be associated with some people improving but not returning to normal; a pervasive indifference might lead people to rate down their quality-of-life. Reboxetine had no actions on the serotonin system. As early as 1997, I suggested that a study in which healthy volunteers took reboxetine or an SSRI might lead to a lowering of quality of life as represented by SASS scores.

Rudolph Hoehn-Saric and colleagues from Johns Hopkins University had examined emotional difference as early as 1990.[3] Hoehn-Saric described four people on either Luvox or Prozac who had become indifferent or disinhibited. One woman changed personality completely, presenting herself almost naked at parties. Hoehn-Saric speculated on serotonin connections to the frontal lobes and wondered whether in some patients the effects of an SSRI might not amount to a "mild" lobotomy. Other articles making similar arguments have followed.[4]

Clinicians occasionally see extreme disinhibition in patients taking SSRIs, but milder forms were in my experience relatively common. One man on Zoloft I treated memorably described a loss of concern for others. Normally he would help older women having trouble crossing the road but on Zoloft he found himself much more likely to walk past them. Since I was prescribing Zoloft frequently, similar cases often came my way. In one, a sophisticated professional described a split within himself, part of him consciously watching the more instinctive side. He found he was having to intervene much more deliberately than usual to stop himself doing socially unacceptable things—such as bludgeoning to death kids he caught trying to break into his car. This seemed to lie midway between disinhibition and blunting.

There might be a good side to this. One wonderful woman found that where normally she was too conscientious at work and wouldn't relax until every last 't' was crossed and 'i' dotted, on Prozac she could leave work at 5 p.m. without anxiety, and handle bosses' comments on her work without taking them to heart. Prozac had produced a certain beneficial nonchalance or mellowness in her case. Was this woman being chemically "lobotomized" to fit into a stressful work situation? Should she instead have protested bad working conditions or sexism from her boss? The medical students who saw her argued she should have protested and perhaps resigned. I suggested they were being young and romantic, and that life would teach them otherwise. Was it our decision whether she should protest or take pills? Who gave medical people that authority? This is the country that Lauren Slater explores in *Prozac Diary.*[5]

The possibility of emotional blunting occurred to me when the April 1999 killings in Littleton, Colorado hit the news. One of the students, Eric Harris, was reported to have been on Luvox. Within hours of this news, the APA website posted a message saying that, "Despite a decade of research, there is little valid evidence to prove a causal relationship between the use of antidepressant medications and destructive behavior. On the other hand, there is ample evidence that undiagnosed and untreated mental illness exacts a heavy toll on those who suffer from these disorders as well as those around them."[6] Here came the "blame-the-disease-not-the drug" message again.

Against this background, I suggested to my contacts in Pharmacia that it would be valuable to see what happened to SASS scores in a group of healthy volunteers taking an SSRI or reboxetine in a design that had them taking one drug for two weeks, halting for two weeks, and then crossing over to the other drug. Would SASS scores end up on average lower in people taking the SSRI than in people taking reboxetine? If the figures panned out, they might allow P&U to make some statements about the levels of wellbeing that depressed people who remained on treatment were likely to experience on reboxetine, compared, for instance, to an SSRI.

Submitting such ideas to pharmaceutical companies is a hit-and-miss affair. They chunter through bureaucratic scrutiny at local, national, and finally international levels. Companies tend to be very risk averse. Even when a company is broadly speaking in favor of the idea, should someone spot a potential snag—however minor and improbable—it will likely stall the project. You wouldn't want to base a scientific program on support from the industry. Pharmacia didn't bite.

Most university departments have "slush funds" built up in endowment accounts from work done on clinical trials or legal work, or where companies or others have offered general support to a department. We luckily had a small fund, to which SmithKline Beecham had been the biggest contributors.

Getting Organized

There were a few key things to be sorted out. First, with which SSRI should reboxetine be compared? Prozac was a non-starter because of its long half-life. Even after two weeks' washout, most subjects would still retain it in their bodies and feel its effects. Luvox was too likely to cause nausea. Paxil had become too associated with withdrawal problems. I had treated withdrawal problems of a number of nursing colleagues put on Paxil, some still suffering three months later despite short durations of treatment. No one would have volunteered.

That left either Zoloft or Celexa. Zoloft was the natural choice for two reasons. Even though I had first noticed the phenomenon of emotional blunting in patients taking Zoloft, I was nevertheless well disposed to this pill, so that when it came out I was among its main prescribers in North Wales. As the psychiatric representative on our hospital's Formulary Committee two years before, I had argued for the removal of Prozac from the formulary and its replacement with Zoloft and Celexa. There were good reasons for this quite apart from any suicidal ideation that Prozac might trigger. Prozac's long half-life and risk of interacting with other pills made it unsuitable for use in a general hospital setting where, by definition, people would be on other pills.

My second reason for picking Zoloft was that it came in 50mg and 100mg forms. There was consensus that 100mg of Zoloft was the equivalent of 20mg of Prozac. The 50mg tablet was generally perceived as being a weaker dose. This made it possible for us to draw up a protocol which involved a step up from either 4mg of reboxetine, which our volunteers would take for the first five days, or 50mg of Zoloft, to 8mg of reboxetine or 100mg of Zoloft for the subsequent 10 days of that arm of the study. Nobody was going to accuse us of exceeding the normal clinical doses and bringing about the results by poisoning our volunteers.

We considered the demands of the study on its subjects, who would take pills for four weeks, ingesting chemicals that affected their brain-function, and fill out rating scales for eight weeks. How much should we pay the volunteers? Institutional Review Boards (European ethical committees) have struggled with this policy question for some time. IRBs came into being in response to public perceptions that medical students, patients, or other subjects such as company personnel—because in a position in some way dependent on the good will of the person running the experiment—might feel coerced into participating. Deciding whether subjects are being unfairly influenced by the prospect of financial gain is an easier issue to resolve than whether other more subtle forms of pressure are involved. An ideal arrangement is where subjects are so persuaded by the merits of the study that they volunteer without payment of any sort. However, this ideal is neither expected nor demanded. Instead, some inconvenience money is usually paid.

After taking this through our IRB, we fixed on a figure of £400 to be paid to our subjects at the end of the study, £50 for each week.[7] By the end, everyone thought the amount of money compensated for the inconvenience research subjects were put through.

Our group was 11 women and 9 men, aged between 27 and 52.[8] Some were consultant or trainee psychiatrists. There were senior and junior nursing staff but no nursing trainees. Some were Senior Administrative Staff. Most knew the others. One woman dropped out as coincidental developments in her personal life made it difficult to know whether any assessments of her mood, emotional state, and sense of well-being would reflect the actions of the drugs rather than her circumstances. This left us with 19 subjects.

Why were they doing this? The primary motivation appeared to be simple curiosity. Some wanted to know what these pills they regularly handed out to their patients were like. For others it was curiosity about themselves. We told them we would be assessing their personalities and would feed them back the results of assessments. We also told them the study was of the “better than well” phenomenon described for Prozac. For others it may simply have been something novel to do. These various motivations can skew a sample: for instance, risk takers might be more inclined to participate in this study than others who were more conservative.

I was influenced by a study done by Peter Joyce and Roger Mulder in New Zealand with depressed patients.[9] They had shown that certain personality profiles were more likely to respond to drugs active on the serotonin system, while others responded to drugs active on the norepinephrine system. The world had paid no heed to this study;

the findings were not good for business. They suggested that SSRIs should be used for certain people who were depressed and not others; a drug like reboxetine for example, rather than being a general antidepressant, would have its own smaller niche. In order to test whether the personalities of our volunteers might influence their response to Zoloft and reboxetine, we asked them to complete a number of personality scales, including the ones Joyce and Mulder used.

First baseline assessments of personality and completion of other rating scales were done a week before the trial proper began. We organized all drugs to look identical. Everyone involved in the study was blind as to who was getting what. All drugs were handed out the same day to all subjects.

Conventional wisdom holds that antidepressants do not work for the better part of two or three weeks. Keeping our volunteers on each of these drugs for four weeks would have been optimal, but two blocks of four weeks' exposure to each of the two drugs seemed far too long for healthy volunteers. So we compromised on two weeks' exposure to each drug. This left me worried that we might expose these colleagues to risks without learning anything, but it was the best we could manage.

First Impressions—"Better than Well"

From the very first day it was obvious something was happening. One of my closest colleagues, Tony Roberts, was so changed by whichever drug he had first that even his patients noticed. Everyone agreed he was more mellow than usual. Tony himself was aware of this and provided a number of examples of situations that would previously have bothered or irritated him. This was emotional blunting in its good form.

One woman in the group, Joanna, experienced a similar effect from the first day. She was much more relaxed and commented that this "Chill Pill" she'd just been put on was something that she might be able to get used to.

Pretty soon, however, we realized that things weren't going to fit easily into our original ideas about trying to map emotional indifference onto the SASS. For a start, it was surprisingly difficult to decide who was on which drug. We had assumed the known side effects of the two drugs would enable us to guess. But both drugs seemed to be causing nausea, although only Zoloft had been supposed to do so. Both were causing sleeplessness, where reboxetine was supposedly much more likely to do so. Both interfered with sexual functioning, especially in men–something we had expected only on Zoloft.

We encountered strange results not on the side effects list for either drug. Subjects complained of feeling cold, with chilblains and patches of cold perspiration. This strange side effect seemed more likely to be caused by reboxetine, but nothing on the company's data sheet prepared me for this. Some volunteers complained from the second day of stiffness or pain in their jaws, pain in their throats, or forced yawning. This was not something they could have picked up by suggestion or read in the datasheets of either drug. But I knew what it was: several years before we had written about six cases of patients with precisely these problems on SSRIs—then the largest

series of cases reported of this potentially ominous problem.[10] It later turned out that half our volunteers suffered from this side effect in some form. I would never have expected this to appear at all in the course of a two-week study on this kind of dose. To have it happening in half the group was extraordinary.[11]

I had expected reboxetine to make people more aware of their emotions and feelings, maybe making them *too* emotional. Zoloft, in contrast, should blunt them somewhat, for good or bad. Things were more complicated. Was reboxetine having a paradoxical calming effect, just as Ritalin did? The crucial question was whether subjects could tell the drugs apart when they went onto the second drug. If they couldn't, the study would be pointless. Within a day or two of starting the second drug, it was clear that they could distinguish between the two and knew almost immediately which they preferred.

But a significant number of people were doing very well on Zoloft. Tony Roberts had assumed he was taking Zoloft the first time round because he had diarrhea and changes in sexual functioning that pointed strongly towards Zoloft. Now on what he was convinced was reboxetine, he was having trouble passing water, constipation, and a range of other problems. If so, he had clearly had a much better two weeks on Zoloft, and surely his SASS scores would reflect that.

The plan was to finish the study with a focus group before the blind was broken. Participants had been asked to keep a diary throughout. They had been encouraged to check for any effects of the drugs with their partners, parents, or others living with them. The question now was: could our volunteers put into words the differences between the two drugs? This was the heart of the experiment. Did the SSRIs produce some kind of emotional blunting compared with reboxetine? If so, how did this affect daily life? What everyday words expressed what was going on?

Breaking the Blind

Our focus group met two weeks after the study ended. We already knew that almost everyone had preferred one of the two drugs. But two-thirds rated themselves as having done "better than well" on one or other of the drugs. Although this was a study of well-being, antidepressants weren't supposed to make people who were normal feel "better than well." Not even Peter Kramer had said this. The argument of his famous *Listening to Prozac* was that people who were mildly depressed on Prozac became better than well. Here were people who had never been depressed claiming to be in some way better than normal.

Just as strikingly, two-thirds of the group felt significantly worse on one of the two drugs—not simply by virtue of inconvenient side effects such as difficulties in passing water, but worse in terms of either being depressed or disturbed or in some other way realizing this was not a drug for them. The implication was that there was a very high chance, perhaps approaching 50/50, that primary care physicians could put their patients on a pill unsuitable for them.

This explained at a stroke why people generally don't take antidepressants for long. It is rare for any survey to find more than 40% of people continuing to take their antidepressant after 4 weeks. The SSRIs had been sold on the basis that they didn't

affect transmitters such as norepinephrine or acetylcholine. They were therefore supposedly cleaner and should have fewer side effects. This should translate into better compliance, but it never has.[12]

It turned out that Joyce and Mulder's findings of personality differences between people responding to drugs like reboxetine or Zoloft mapped exactly onto the findings in our group.[13] There was a right drug and wrong drug for people. Simply making a drug cleaner was not going to help if in the cleaned-up molecule kept the wrong bit for a large number of patients. Indeed, a cleaned-up and stronger "wrong bit" might be far more dangerous than a messy older drug.

This had great implications. Pharmaceutical industry trials showed each of the SSRIs appeared marginally if any better than placebo. This left companies open to critics' charges that the drugs didn't work. But had industry selected populations along personality profile lines, it now seemed they would have produced results showing much bigger differences between SSRIs and placebo. However, they would then only have been able to market the drugs to a smaller group of people. Our results for Zoloft were in fact much more convincing in the group of healthy volunteers who preferred it than the clinical trials Pfizer had submitted to the FDA in pursuit of a license.

When we broke the blind, Tony Roberts found out he had done well on Zoloft and poorly on reboxetine. This led him to expect that everyone else who had done really well had had Zoloft, but this was not the way it went. The proportions of people doing well on one drug and poorly on the other were split almost evenly between the two drugs. Where one person had done well on Zoloft and poorly on reboxetine, the next person at the table had experienced just the reverse.[14]

Despite many people doing well on Zoloft, when we analyzed the overall results, the original hypothesis was upheld—volunteers' quality of life or social functioning scores as a group fell on Zoloft but remained unaltered by reboxetine. This seemed to explain why no one had published the quality-of-life results on SSRIs.

Chasing the question of whether Zoloft caused emotional blunting, half the group said it had given them "a nothing bothers me" feeling. Reactions were split about this: some liked the effect; others found it made them emotionally dead. Reboxetine, in contrast, didn't seem to make anyone feel indifferent—calm, perhaps, but not indifferent. Its effects were better described as energizing—again, good for some but not for others.

One small event in the focus group went unnoticed except by two people there. When I asked whether anyone had noticed any other side effects, one volunteer mentioned vivid and disturbing dreams of killing herself. I skated over this, helped by two other volunteers claiming they had lots more dreams than usual. I broadened out the question to whether anyone had become depressed on either of the two drugs. Yes, two had—on reboxetine. Both were women, and described the experience as like the Baby Blues. Neither, however, was remotely suicidal.

Becoming Suicidal[15]

I now knew two people in our study had become suicidal. The roots of what had

happened lay at the start of the study. When Tony Roberts had done obviously well from the outset, Joanna had done equally well. When we switched drugs Tony became visibly uncomfortable with urinary retention and genito-urinary pain. It seemed highly likely that this was caused by reboxetine. He was the one person we thought knew what he was taking. But where Tony had physical problems, Joanna had a far more dramatic and worrying change. Within days of going on the second drug, it was evident that for her this was no Chill Pill. The bloom was gone from her normally extraverted, and confident self. She now looked almost shrunken, worried, and nervous. She withdrew from interactions with others. She began demanding support from Dinah Cattell, one of the study monitors. Dinah alerted me that Joanna was doing things she would later regret, such as impulsively spending more money than she would normally do. Worse, she was doing other things she was reluctant to tell.

This had worrying implications for healthy volunteer studies. I had not envisaged anything this s problematic when I had presented the study to the IRB. I had told them that the scale of any problems should be no worse than what might happen to someone taking an antihistamine. By the end of the first week of her second drug, the effects on Joanna could not be described as minor. She was in turmoil. I was convinced she was on reboxetine; Dinah thought she was on Zoloft.

In the second week, things got even worse. Over the weekend Joanna had dreams of slitting her throat open and bleeding to death in the bed beside her partner. These dreams woke her at 3 a.m. and left her frightened and unable to get back to sleep. The same dream recurred on three successive nights.

Toward the middle of that week, we decided Joanna couldn't be let continue whatever she was taking. She was told to stop on more than one occasion. We weren't to know she wasn't registering anything we told her. This may not be unusual. When Joseph Wesbecker was advised by his physician Dr Coleman to stop his Prozac, he had argued that he still felt it was doing something for him.[16]

By this time the change in Joanna was startling. She might begin to cry for no obvious reason. If anyone asked how she was she brushed it off, telling him or her that any moment now she would be better again. Her mood was swinging from gloom to doom in a matter of minutes, so much so that a number of people described her as almost manic. She was bothered by how irritable and snappy with others she had become. She described an increasing sense of disinhibition. Her diary entries record a feeling that she had become two selves, an adult and a child, and it seemed her adult could only watch while the child responded to things impulsively and emotionally.

She took a pill that night. When this was discovered the following day, the pills were removed from her. That night alone in her house was one of the worst of her life. She felt things were watching her. She checked behind doors in case there was anything there. She began to write her diary but couldn't concentrate on it; her diary entry records a hope that she would make it through the night. She suddenly decided she should go out and throw herself in front of a car or a train. It was as if there was nothing out there apart from the vehicle she was going to throw herself under. She didn't think of her partner or her child. This lack of feeling for them ate away at her later. When our biology changes, we change, but even in the midst of a high fever,

when everything was unreal, she still knew she loved her daughter. Now she felt nothing.

All her anxiety vanished once the thought of death crystallized in her mind. Putting an end to herself, even in this violent way, seemed a way to solve her anguish and pain. She was in fact on her way out the door to kill herself when the phone rang. It was as though a hypnotic trance was broken. Joanna had the wit to seek out the company of others, tell them she was having a bad night and ask them to keep an eye on her. They laughed, wondering what had gotten into her. She looked normal. No one guessed her state, and although having company helped, no one looked after her. The following morning, deeply distressed, she called Dinah, who spent most of the day with her. Joanna had become a fragile, vulnerable woman, still at serious risk of suicide. On my instructions, she said nothing about all this in the focus group.

Then Max spoke. I had known nothing about Max's problems. She also had done well on whatever the first drug was, felling both more energetic and more calm. But from the start of the second drug, she found herself irritable and snappy. A lot of her colleagues remarked on the change—more assertive, some said. But Max didn't see it that way. She saw herself become impulsive and disinhibited. Where others saw her speaking out assertively, she saw herself doing things without regard for consequences. Her mood, like Joanna's, veered from high to low. Both could swing from tears to mania within an hour.

Max became disinhibited in a more serious sense. Driving home one day from shopping with her mother, she came to a point where the road narrowed and traffic had to slow. A group of 18-year old boys began making obscene gestures and shouting derogatory remarks. Max stopped her car in the middle of the traffic and climbed out. She went over to the youths and manhandled one, warning him that if he continued she would "deck him."

She should have been alarmed at taking on a group of young men this way. How did she know they wouldn't take down her car registration and follow her home? What then—slash her tires, steal her car, or throw a brick through the window of her house? Her mother, who knew that in the ordinary course of events her daughter would have realized this, was frightened at what was happening. Where others had seen her as merely assertive at work, Max knew she had gone past mere assertiveness. But it was not her new aggression but her ideas about suicide that led her to the brink of quitting the study. She is a woman prone to lucid dreaming—someone who can rise and talk in her sleep and appear wide-awake while doing so. This makes it difficult to be fully sure of what happened. But in the middle of the second week, she had episodes on two successive nights during which she found herself thinking of the beam in the ceiling of her bedroom, planning to hang herself from it. She was drawn to it, controlled by it, and knew she didn't care that finding her body the next day would disturb the rest of the family.

She later thought things might have been different had she not been a volunteer. Had she been on this drug for weeks and felt trapped because her doctor had told her she needed it, she might well have gone on to suicide. Things were eased because after the first night she lowered her dose from two pills to one, knowing she only had three more days of the study to get through. But she would never knowingly go on these

pills again.

After-effects

No one had warned these women they might ever feel the way they had done on either of these pills. Our study had been about how well people could be and whether anyone could be made "better than well." We never thought to warn anyone about suicidal ideation. Even with my background, I saw the possibility of making totally normal people suicidal in this way as a merely theoretical risk. Had we set out to design a study to do this, I would have figured on recruiting a hundred volunteers. Nothing in the published figures suggested we would be likely to pick up an effect like this in so small a group.

Unprepared for what was going on, Max committed nothing to paper. Worried about being diagnosed as crazy, she told no one what was going on until she learned someone else had been through something similar.

Neither woman drew the conclusion that it was "just" the pill. Finding each other reduced the isolation but didn't solve the problem. One of the consequences of this study was to bring home as nothing else had done the potential long-term injury we can do to people by making them suicidal. Even someone like me, watching from the outside, and firmly committed to the idea that when this happened on drugs it was caused *by* the drugs, found myself pulled by a strange attractor. Surely someone in whom this had happened must have had something wrong with her to begin with, some disorder in her personality. It was worse for the two women, who were difficult to reassure on this point.

Nothing on the personality tests we had done beforehand, nothing on the variety of tests of wellbeing or social functioning that were conducted, indicated any abnormality in either of these two subjects. Nothing on the tests would have enabled anyone from Eli Lilly or Pfizer to predict that these two out of the twenty subjects would suffer this problem. If anything, Joanna and Max showed less than average traces of any kind of depressive thinking. Furthermore, in line with the early reports from Prozac, the effect had been manifest in women rather than men. Maybe this explained why the FDA database on Prozac-associated suicides contained an equal ratio of females to males rather than the expected four men for every one woman.

While we may have accidentally demonstrated conclusively that the drugs could cause the problem, even looking at the beast straight in the face we didn't know what we were dealing with. Two volunteers on reboxetine became "depressed," but neither became suicidal. Neither Max nor Joanna became depressed on Zoloft. It didn't seem to be akathisia either: two other subjects on Zoloft became akathisic but not suicidal. There did seem to be some link with disinhibition. Zoloft had caused disinhibition, and perhaps in these two more markedly than in others. This was not something we were geared up to explore. Clinical trials suggest this may be happening with considerable frequency, but as of yet it has been left unscrutinized by the entire psychiatric field.

Max's case highlighted the theme of hanging, so common to SSRI suicides. At close hand our impressions were that someone who did finally hang herself would do so in

an almost calm frame of mind. This fit with what I've heard from people about children or partners who had hanged themselves in bedrooms next door to their children or to their siblings. If they had wanted to commit suicide, why didn't they go elsewhere? People who kill themselves by hanging ordinarily don't do it in the middle of the night in a bedroom next door to the rest of their family. Nor do they throw themselves out fourth-floor windows to land on concrete where their children would find them. The common theme seemed to be of lack of concern for those left behind.

This was the experiment in which Richard Smith said he could see no value. Doubtless an arch skeptic would have required us to re-expose Max and Joanna double blind to see if the problem recurred. Obviously we could not re-expose these two women in circumstances where we could not guarantee their safety. Quite apart from the impossibility of ethical committee approval for such an experiment, someone who didn't believe the original study would find a means of dismissing the results of a subsequent re-exposure. We might have been told "Second time around, they could have told the drugs apart by their side effects and this time around both women would have had so much invested they would have 'put on' suicidality."

The injury we had done both of these women was greater than these near escapes suggested. Both remained disturbed several months later; both seriously questioned the stability of their personalities. At first this struck me as ludicrous. But we had great difficult persuading them that it had been the drug—and only the drug. Their view of themselves had been shaken. We had had at least a medium-term impact on both women's self-esteem.

This connected a number of facts. A case in point was John Marshall, whom I had seen a few weeks before (chapter 6). His medical notes indicated that those seeing him interpreted his drug-induced nerves and later suicide attempt as evidence of a personality disorder. Another woman was referred to my clinic after an overdose. She had received news her father was dying; her partner had left her in financial straits just as she returned to university as a mature student; her eldest son, who was ill, had suddenly decided to return home to live. Stressed, she consulted her primary care physician who had put her on Prozac. She carried out a number of concealed suicide attempts over the following few weeks until one brought her to the local accident department. Clinical impressions were of a possible personality disorder. There were no more suicide attempts once the Prozac was stopped. But how long would the label "personality disorder" remain in her medical notes? Then there was a 61-year-old woman assessed after a suicide attempt. She had been on a benzodiazepine, which her primary care physician had been reducing for months. At the last step, when she was on ½ mg of benzodiazepine per day, he switched her to Prozac. Within a week she became suicidal for the first time in her life.

These were typical cases. How many similar stress reactions were being labeled as personality problems? This connected all the way back to Tony L, the first person I'd seen have problems on Prozac, for whom the long-term effects were disastrous.

To the outside world the suicide attempts caused by Prozac and other SSRIs were near misses, lucky escapes. But everything known from research into suicide indicated that one of the factors that made successful suicide most likely was a previous attempt. If Prozac and Zoloft induced suicide attempts or marked suicidal ideation, might this in

some way lower the threshold for a future suicide attempt?

Perhaps the best analogy is with pre-cancerous cells of the cervix. If, in the course of a trial of an experimental drug, a subject developed pre-cancerous cells in the cervix, which cleared up when the drug was halted, the manufacturers would almost certainly claim that their drug had caused nothing. But it seems a distinct possibility that such an event would make future development of cancer of the cervix more likely.

Even forearmed by theoretical knowledge, it was difficult not to feel the power of the idea sucking Max and Joanna in— "Something must have been wrong with me to begin with for me to end up this way."—"Why didn't it happen to anyone else, then?"

Critics of the pharmaceutical industry sometimes have real problems when they meet the people behind drugs like Prozac or Zoloft: they seem to expect to meet the Devil incarnate rather than some very decent and likeable human beings.[17] It's easy to demonize people after the event, but in real life it's rare for the good guys and the bad guys to be clearly distinguishable. In this case, however, we had just met a much more medieval devil, something mindless and alien and capable of sucking any good there was out of someone.[18]

A Twist to the Tale

Our obvious next step was to check whether anyone who gave drugs to healthy volunteers as part of their research, or in phase 1 studies for pharmaceutical companies, had encountered anything like this. They had. In fact our high incidence of serious problems could be topped by other studies.

Prior to reboxetine's European launch, I took part in a March 1998 consultancy panel meeting for Pharmacia with a number of panelists including Ian Hindmarch, a professor of psychopharmacology at the University of Surrey and an expert on healthy volunteer studies. He was an enthusiastic supporter of the SSRIs, which looked much better than some of the older tricyclic antidepressants on driving simulation tests and other cognitive function tests.

I mentioned an article by Andrew Solomon just published in the *New Yorker*[19], in which he compared the effects of Zoloft to taking 55 cups of black coffee and Paxil to taking 11 cups. To my surprise all the others present demanded copies of this piece. No one was keener than Ian. As he explained to me afterwards, he'd had a similar experience years before. As part of a set of studies carried out for many companies, he'd run one study, which as he remembered it involved 10 to 12 subjects, where all those randomized to Zoloft dropped out because of marked agitation or anxiety. He'd never seen anything like it. At the time, possible suicidality on SSRIs had not been an issue and no one had inquired about this in particular. But the reactions, if anything, seemed even more marked than in our study.

"Of course we've always known that these drugs could do funny things to healthy volunteers," Mervyn Whitford, a colleague who had worked extensively in the pharmaceutical industry, told me. Had we? It turns out we had. So much so, that workers in this area in the 1980s, such as Saletu in Vienna[20] and Warrington in England,[21] specifically documented the adverse effects of SSRIs (including Zoloft) on

healthy volunteers, and remarked on the discrepancy between how bad these drugs could make healthy volunteers and how they seemed to have quite the opposite effects in depression. They rationalized this by arguing that the brains of depressives were obviously very different to those of healthy people.

This made sense in the 1960s and 1970s, when people diagnosed with depression were older and their condition didn't respond to Valium but did to ECT. The trouble with the SSRIs was that nobody had envisaged a situation where the majority of people most likely to get these drugs would be much closer to healthy volunteers than to endogenous depressives—13-year-olds stressed out at school, like Matthew Miller, for instance, or Caitlin Hurcombe, or Craig Clark. No one realized cases of Valium were about to become cases of Prozac. Against this background, the fact that companies not only knew about SSRIs' deleterious effects on healthy volunteers but also had commissioned and conducted studies demonstrating exactly this was nothing short of stunning.

This healthy volunteer study also gave us an opportunity to put figures on the extent to which drugs like Zoloft might increase the risk of suicide for someone like Matthew Miller, using the United Kingdom as the backdrop to our study. First, the combined population of England and Wales is slightly over 50 million. Second, there are just over 5,000 suicides on average per annum in England and Wales. Extrapolating from the second point, we get approximately 200 suicides per fortnight in England and Wales.

Certain assumptions can then be made. The first concerns how many of these 200 suicides per fortnight will be in entirely normal individuals with no mental illness and without significant interpersonal legal or financial problems—the biggest predictors of suicide. None of our healthy volunteers had either factor. Many experts would insist there are probably no suicides in totally normal individuals lacking any of those factors. Nevertheless, let us assume that ten of the 200 suicides involve totally normal, unstressed individuals.

It is generally accepted that for every successful suicide there are ten suicide attempts. This would give 100 suicide attempts in totally normal unstressed individuals in England and Wales in the course of a fortnight. One more assumption has to be made. How many people become actively suicidal for every suicide attempt? If we assume there are ten people actively suicidal for every suicide attempt, this would lead to 1,000 instances of actively suicidality in totally normal individuals with no current interpersonal legal or financial problems over any fortnight period in England and Wales.

How many people are at risk for active suicidality? In a population of slightly over 50 million, we could exclude 30 million as juveniles or individuals with mental illness or significant interpersonal legal or financial problems. This leaves 20 million people at risk.[22]

Calculating the probability for two healthy volunteers without mental illness and no current interpersonal legal or financial problems becoming suicidal during a two-week period on Zoloft gives a probability of $p = 0.0000005$.[23] Put another way, if 1,000 out of 20 million totally normal individuals are likely to be actively suicidal compared

with 1 out of 10 taking Zoloft, it follows that Zoloft makes you 2,000 times more likely to be suicidal than normal.

Critics might argue this involves piling assumption on assumption, but there is considerable scope to modify these assumptions unrealistically in favor of Lilly and Pfizer without changing the significance of the findings. In fact, the more reasonable question would be: How could our finding of suicidality be explained in any way other than being caused by Zoloft?

Far from rising to this challenge, the response of senior figures in the field was to contact the editors of *Primary Care Psychiatry*, in which the first reports appeared, to castigate them for publishing these anecdotes in an era of evidence-based medicine.

A New Problem

In the late ’80s, as companies outsourced drug and market development, university medicine departments might witness severe patient agitation on an SSRI and not know what to do. No one had warned them this could happen. In the mid- to late-1980s, the suicide story had not yet begun to roll. There was no overwhelming reason for reporting the findings in a journal or other public forum. Reporting ran the risk of alienating the sponsoring company. Even reporting it to the company might lose business. Why report it if they were all but certain to know it anyway? University people were not to know that it was quite possible that no hands-on work with the drug actually took place anywhere within these vast corporations.

The only group of people who might know something were the regulators. I wrote to the MCA in Britain and the FDA, giving details of our study. Did they have other data on file remotely like ours? My contacts suggested they *must* have—in which case it seemed the regulators were in a bind if they had the data on file, and just as big a bind if they didn’t.

We had now blundered into a situation where, once the chairman of an IRB committee knew about the results of our study and others, they would find it very difficult to permit any study with healthy volunteers to go ahead, even one involving only medical and nursing staff, without clear warnings and close monitoring. Even with these in place, university studies in healthy volunteers must be insured. Would any insurance agency underwrite such a study? And yet these drugs were available without warnings, or monitoring, being prescribed in ever-increasing amounts to people for stress reactions rather than depression and—still more worryingly—prescribed ever more frequently for children and teenagers. On the face of it, this was an extraordinary situation.

Let us return to the deposition of Leigh Thompson in the Wesbecker trial:

A: Now in terms of whether we specifically designed a study to address the issue of suicidality separate from all of the other issues of efficacy and safety, the answer is no.
Q: You didn’t then, did you, haven’t now either, have you?
A: We’ve worked extremely hard on trying to figure out how to address that issue; yes indeed we’ve spent an awfully lot of time and money on trying to

figure out how to do.
Q: How much time?
A: Of my time or total people at Lilly?
Q: Whatever the time we're speaking of when you say we spent an awfully lot of time and money.
A: Well I can say that I personally have spent hundreds of hours on this specific issue, talking to experts, reading the literature and trying to decide how we could possibly do these kind of studies. I can only speak for myself, but I know that many other people spent far more time than I did at Lilly working on this.
Q: Has anybody figured it out yet?
A: Not to my knowledge.
Q: How much money has been spent?
A: I don't know what the total amount of spending would be…
There followed a series of thrusts and parries until:
Q: You said it's been very expensive.
A: Yes, sir.
Q: I would assume that you had some facts; you're not just pulling that out of the top of your head, are you, Doctor Thompson?
A: No, sir.
Q: All right, how expensive has it been?
A: Millions of dollars.[24]

What a healthy volunteer study does is to take depression out of the equation. If suicidality happens on Prozac or Zoloft or Paxil in these circumstances, it is difficult to see how it cannot have been caused at least in part by the drug. Our study cost only $15,000 to run. Similar studies with even more clearcut results were sitting in company archives, apparently inaccessible to national regulators such as the MCA in Britain— who, almost a year after I began to correspond with them apparently ended up with a *four-page summary* of Ian Hindmarch's study.[25]

Few of the many healthy volunteer studies done by SSRI companies as part of their development work on these drugs have been published. In the case of Prozac, 12 out of 53 have been reported on. In the case of Paxil, approximately 14 out of 35 healthy volunteer pre-launch studies have appeared. In the case of Zoloft, as few as seven of approximately 35 pre-launch studies are available. It is difficult to have much confidence in the published work when the data reported commonly excludes material concerning behavioral toxicity, even failing to mention suicide when it has occurred.

This material had been lying around for years before the first public concerns were raised about Prozac. Why had it played no part in the debate hitherto? Why did regulators not know what these studies had found? Why were no academic voices raised demanding access to this material? The combination of our healthy volunteer study and my involvement in ongoing legal actions led me to access the healthy volunteer archives of Pfizer and of SmithKline. Was it merely coincidence that pretty well as I walked in through the door of Pfizer's archives to look for these data, I got the sack?

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1. Deposition of John Heiligenstein in *Fentress vs Eli Lilly* 27th April (1994).
2. Healy D. The case for an individual approach to the treatment of depression. *Journal of Clinical Psychiatry* 61 (supplement 6), 24–28 (1999); Healy D. Reboxetine, fluoxetine and social functioning as

an outcome measure in antidepressant trials: implications. *Primary Care Psychiatry* 4, 81–9 (1998).
3. Hoehn-Saric R, Lipsey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. *Journal of Clinical Psychopharmacology* 10, 343–5 (1990).
4. Garland EJ, Baerg EA (2001). Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J Child & Adolescent Psychopharmacology* 11, 181–6.
5. Slater L (1998). *Prozac Diary*. Random House, New York
6. APA Online release no 99–19, April 28th 1999, statement by APA President, Rodrigo Munoz.
7. £400 at that point was approximately $600, $75.00 per week of the study.
8. Further details of this study can be found in Healy D. Emergence of antidepressant induced suicidality. *Primary Care Psychiatry* 6, 23–8 (2000). Details were also presented at the Annual Royal College of Psychiatrists meeting in Edinburgh in July 2000, the BAP meeting in Cambridge in July 2000, and the ECNP meeting in Munich in September 2000.
9. Joyce PR, Mulder RT, Cloninger CR. Temperament predicts clomipramine and desipramine response in major depression. *Journal of Affective Disorders* 30, 35–46 (1994).
10. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. *Human Psychopharmacology* 10, 215–20 (1995).
11. It was only clear at the end of the study that up to 50% were affected.
12. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared to tricyclic antidepressants: a meta-analysis. *British Medical Journal* 310, 1433–38 (1995).
13. Results presented at the Royal College of Psychiatrists annual meeting in Edinburgh, July 2000, the BAP annual meeting in Cambridge, July 2000 and the ECNP meeting in Munich, September 2000.
14. Tranter R, Healy H, Cattell D, Healy D (2002). Functional effects of agents differentially selective to serotonergic or noradrenergic systems. *Psychological Medicine* 31, 517–24.
15. A peer-reviewed version of this section can be found in Healy D. Emergence of antidepressant induced suicidality. *Primary Care Psychiatry* 6, 23–8 (2000). The full study is in: Tranter R, Healy H, Cattell D, Healy D. Functional variations in agents differentially selective to monoaminergic systems. *Psychological Medicine* 32, 517–24 (2002).
16. See Glenmullen J. *Prozac Backlash*. Simon & Shuster (2000) for more details on this issue.
17. For the best description of encounters between critics and the industry see Braithwaite J. *Corporate Crime in the Pharmaceutical Industry*. Routledge & Kegan Paul, London (1986)
18. Medieval is being used here to refer to Scholastic views of the Devil. Prior theologies had seen good and evil as opposite powers in the Universe (good guys and bad guys) but Thomas of Aquinas introduced the idea of evil as an absence of good—a void.
19. Solomon A. Anatomy of Melancholy. *The New Yorker*, January 12th 47–61 (1998).
20. Saletu B Grunberger J, Linzmayer L (1986). On the central effects of serotonin reuptake inhibitors: quantitative EEG and psychometric studies with sertraline and imipramine. *J Neural Transmission* 67, 241–66; Grunberger J, Saletu B (1980). Determination of pharmacodynamics of psychotropic drugs by psychometric analysis. *Prog Neuropsychopharmacol* 4, 417–34.
21. Warrington SJ, Dana-Haeri J, Sinclair AJ (1989). Cardiovascular and psychomotor effects of repeated doses of paroxetine: a comparison with amitriptyline and placebo in healthy men.APS 80, supplement 350, 42–4.
22 These figures have all been calculated conservatively and are favorable for Lilly and Pfizer.
23 These calculations and the details behind them were presented at the Royal College of Psychiatrists Meeting in Edinburgh in July 2000 and the BAP Meeting in Cambridge in July 2000.
24. Deposition of W Leigh Thompson in *Fentress vs Eli Lilly*, July 20th 1994.
25. The full correspondence with the MCA, stretching over almost two years, is on *socialaudit.org*., and on healyprozac.com.