The Lilly Suicides

by Richard DeGrandpre[1]

William Forsyth met and married his wife June in 1955. After two years of military service in West Germany, Bill left with June to Los Angeles, where Bill had grown up. Soon after arriving, Bill bought several Volkswagens and started a rental car business near the LA airport. Times were tough at first, but the business eventually caught on. Soon Bill and June had two kids, Susan and Bill Jr., and the business and other property investments continued to grow. Then in 1986 they cashed in. Four years later, after more than thirty years in California, Bill and June retired to Maui, where Bill Jr. lived. Bill Forsyth was 61 at the time. June was 54.

As is often the case with seniors who suddenly leave their home behind for the romance of a new life, the transition was difficult for Bill Forsyth. The Hawaii move did not sit well with him, although his wife was content, even thriving. Personal difficulties led to marital difficulties. But marriage counseling seemed to help, and there was a general sense in the family that Bill was working through his difficulties. Three years after the move to Maui, with Bill still feeling unsettled, a local psychiatrist prescribed Prozac. Despite being diagnosed as depressed, the psychiatrist, who had been seeing Bill since the previous year, did not believe him to be seriously depressed or suicidal. Indeed, Bill Forsyth had never spoke of or attempted suicide; nor had he any history of violence, domestic or otherwise.

After his first day on Prozac, Bill was feeling as you might expect if you've read Peter Kramer's *Listening to Prozac*. He was "better than well." The next day, however, he felt horrible, and for the first time put himself under hospital care.

After ten days Bill felt well enough to leave the hospital. He was still taking Prozac. Everyone seemed to agree that he was doing better, and the family scheduled a boat trip for the next day. When his parents failed to show that afternoon, Bill Jr. went to their home, where he found his parents lying dead in a pool of blood. After taking Prozac for 11 days, Bill Forsyth had taken a serrated knife from the kitchen and stabbed his wife fifteen times. Then he took the knife, fixed it to a chair, and impaled himself on it.

Depressed people sometimes do desperate things. Yet these were senseless acts that, at least for those who knew Bill Forsyth, were simply unimaginable. For his two grown children the only possible explanation was the drug. And so Bill Jr. and Susan decided to sue. Their lawyers would later argue that Prozac can produce a kind of psychological hijacking -- a bizarre and nightmarish syndrome, unique to the Prozac-family of drugs, marked by suicidal thoughts, extreme agitation, emotional blunting, and a craving for death. They would also argue that the company knew of these risks and, instead of warning doctors to look out for them, worked vigilantly to sweep them under the rug.

The Forsyth case was not the first wrongful death suit to be brought against Eli Lilly, nor the first to make it to trial. The first, known as the Fentress case, concerned the events of an early September morning in 1989, when Joseph Wesbecker walked into the Louisville printing plant where he had been working, armed with an AK-47 and some handguns, and began shooting. [2]

"I'm sorry, Dickie," he told a fellow worker before shooting him five times. When it was over, Wesbecker had shot twenty people, killing eight, and then shot and killed himself. One month prior to the shooting, Wesbecker had been put

Prozac. Whether Prozac made him do it we'll never know. One thing we do know, though, is it did not make him better than well.

The Fentress case, named after Joyce Fentress, now a widow, and one of the several plaintiffs who sued after the Wesbecker rampage, was the first of 160 cases pending against Prozac in the fall of 1994. By this time Prozac already represented about a third of all Lilly's income, some $2 billion. Suits were filed by families of people who had committed suicide while on Prozac, families of those who had been murdered by persons on the drug, and individuals who had themselves been harmed while taking Prozac, including a woman who worked for Eli Lilly as a sales rep. Many of these cases were dismissed. Others were settled, some for large sums. But Lilly would not settle the Fentress case. Wesbecker was a nut, they believed, and his case would send the right message: don't take Lilly and Prozac to court because you'll lose.

And they had a point. At least a year before starting on Prozac, Wesbecker began buying guns and ammunition and making threats. He also had a history of psychological problems, which had led Wesbecker to be placed on several psychiatric drugs before being put on Prozac. Other aspects of the case, however, were curious, if not compelling. After a month on Prozac, Wesbecker returned to his psychiatrist, who found him a changed man. He was agitated, his mood was erratic, and his behavior was even stranger than usual. Coleman, the psychiatrist, tried to persuade Wesbecker to go off the drug, which he saw as responsible for his agitation, and return to the hospital for further evaluation. Wesbecker went to work instead.

After the Wesbecker rampage, Eli Lilly also went to work, building a case against Wesbecker, which included approximately 400 depositions taken from people who knew him. Lilly's attorneys were determined to show that Wesbecker's

madness was the product of a poor childhood environment and abnormal psychological development. In other words, the very company that relies on marketing copy to sell the idea that depression is an internal problem of biochemistry was turning away from its biochemical theories, blaming the outer environment instead. Helped somewhat by their expert witness, anti-psychiatry hell-raiser Peter Breggin, the plaintiffs' lawyers saw the contradiction: if Lilly's drug worked by chemically altering mood and behavior, why might it not also be possible that their drug caused the disastrous mood and behavior changes noted by Wesbecker's psychiatrist just prior to the rampage?

The plaintiffs' lawyers also wanted the jury to know that Lilly had a history of concealing bad news about its drugs, a history that suggested a pattern of placing company profits ahead of public safety. In 1985, Lilly and a chief medical officer had pleaded guilty to 25 criminal counts of failing to report adverse reactions for its anti-inflammatory drug Oraflex, including four deaths, to the FDA (eventually the FDA linked the drug to several dozen deaths in the US and several hundred abroad). But the judge in the Fentress/Wesbecker case, John Potter, said no. The material was unfairly prejudicial and would not be allowed in. But then Lilly's lawyers blundered by repeatedly introducing testimony that it had always taken the reporting of adverse drug affects seriously. This opened the door to rebuttal, plaintiffs' lawyers argued, and Judge Potter finally agreed.

But the jury never heard the plaintiffs' lawyers present the evidence. During the break that followed Potter's reversal, Lilly's lawyers got together with plaintiffs' lawyers and made a secret deal. The plaintiffs would allow the case to go forward without presenting the damaging Oraflex evidence, and Lilly would in turn pay to the plaintiffs in the case what has since been described as a sum that "boggles the mind." And this is just what happened. The evidence was not presented, the jury

returned a verdict in favor or Lilly, Judge Potter dismissed the case, and Lilly and its lawyers claimed total victory. "We are pleased -- although not surprised -- by the decision," Randall L. Tobias, Lilly's then chairman and CEO, told the *New York Times*. "We have proven in a court of law, just as we have to more than 70 scientific and regulatory bodies all over the world, that Prozac is safe and effective. Our hearts go out to the victims of the terrible tragedy... But the members of the jury... came to the only logical conclusion -- that Prozac had nothing to do with Joseph Wesbecker's actions."[3]

Still, Judge Potter suspected something was amiss. While the jury was deliberating in the case, a juror had come forward to say that she had overheard settlement negotiations going on in the hallway. Then some months later, during the course of a divorce hearing involving one the plaintiffs in the case, it was revealed that he was expecting a substantial payment from Eli Lilly. Judge Potter drew his own conclusion and, in April 1995, filed a motion to amend his post-trial order, declaring that the case had not been won by Lilly but settled. Lawyers on both sides filed their objections with Kentucky's appeals court. Two months later, the appeals court ruled against Potter, arguing that he no longer had jurisdiction. The case was then appealed to the Kentucky Supreme Court. At this point the stakes had apparently become too high, as lawyers from both sides finally capitulated. They acknowledged that they had conspired to settle without settling, and on May 23, 1996, the Kentucky Supreme Court decided unanimously in favor of Judge Potter. Lilly had settled the case, not won it.

The Fentress/Wesbecker case revealed much about the back-alley tactics of Eli Lilly. "The history of Prozac litigation reads like a mystery thriller," writes Michael Grinfeld in *California Lawyer* magazine, "filled with allegations of

backroom deals, hidden agendas, and unethical behavior." What the trial did not do, however, was answer the central questions of the case: would Wesbecker have committed his rampage had he never been put on Prozac, and might the rampage been avoided altogether if the drug company had warned doctors like Wesbecker's to be on the lookout for signs of drug-induced agitation? The case against the Prozac family of antidepressants, known as the SSRIs, was not coming to an end. It was only just beginning.

II

In March, 1999, the Lilly case involving the Forsyth suicide-homicide finally made it to trial, in United States District Court in Honolulu. "I know that with all their power and money I don't have much of a chance," said the daughter, Susan Forsyth, "but I feel like I have to try."[4] There was some hope, however, as Prozac's maker was facing a different legal team than in the Fentress case, and a new expert witness: David Healy.

The recruitment of Healy into the case was important.[5] David Healy is an internationally renowned psychiatrist as well as a historian of psychiatric medicine. Author of several books, including *The Antidepressant Era* and *The Creation Of Psychopharmacology* (both published by Harvard University Press), Healy has the American equivalent of both an MD and a Ph.D. Prior to his involvement in any litigation involving the pharmaceutical industry, Healy had already raised a number of questions about the selective serotonin reuptake inhibitors, or SSRIs. He had asked whether they were best classified as antidepressants rather than as anti-anxiety drugs, and he had asked in an article whether the SSRIs might produce agitation and other problems with an unusual

frequency. Most importantly, Healy wasn't a radical; nor was he an outsider of the pharmaceutical or psychiatric establishment. Healy had a record of doing research and consulting for various drug companies, and he was not against prescribing Prozac or other psychiatric drugs. Unlike the example of the tobacco industry, drug companies do not place an importance on executives and scientists remaining in the fold, and many CEOs come from outside the industry. This means that there is a high rate of turnover, and a continual loss of institutional knowledge in the industry. It also means that, with pretrail discovery laws forcing Lilly -- and later Pfizer and SmithKline -- to allow Healy into their archives, he would be as close to an industry insider as the public was going to get. And he had plenty to say.

Pointing to Lilly's own internal documents, Healy showed that the company was well aware that its drug would, in a minority of cases, produce a psychological state like the one that overwhelmed William Forsyth, a key ingredient of which is a bizarre form of inner torture known as akathisia. Moreover, Healy argued that the company knew of this potentially catastrophic reaction prior to seeking FDA approval, and showed that they had gone to great lengths to conceal it.

In 1978, ten years before fluoxetine would be branded as Prozac and brought to market in the US, initial clinical trails began. Minutes from meetings of Lilly's Prozac project team in July and August of that year noted that "Some patients have converted from severe depression to agitation within a few days; in one case the agitation was marked and the patient had to be taken off [the] drug... There have been a fairly large number of reports of adverse reactions... Another depressed patient developed psychosis... Akathisia and restlessness were reported in some patients... In future studies the use of benzodiazepines to control the agitation will be permitted."

And it was this use of benzodiazepines -- anti-anxiety drugs like Librium, Valium, and Xanax -- that greased the rails for Prozac's eventual approval. The FDA relied only on a handful of studies submitted by Lilly, which the FDA has since described as "adequate and well-controlled trials which provided evidence of [Prozac's] efficacy,"[6] Of these studies, most permitted the simultaneous use of benzodiazepines and similar drugs, and about a quarter of the patients took them. As clinicians have since discovered, benzodiazepines are effective in reducing the Prozac-induced agitation that can lead to violence.[7] If Prozac could cause self-mutilation, suicide, or even murder in some users, these studies would never have revealed it.

But of course others would. Lilly's own internal records show a letter sent to them from the British Committee on Safety of Medicines (the British FDA equivalent) in May 1984, expressing concerns over clinical trial data they had seen: "During the treatment with the preparation [Prozac] 16 suicide attempts were made, two of these with success. As patients with a risk of suicide were excluded from the studies, it is probable that this high proportion can be attributed to an action of the preparation [Prozac]." Similar concern was expressed by the Bundes Gesundheit Amt (the German FDA equivalent) in 1985. By this time Lilly was well aware that they had a problem, summed up nicely by FDA scientist Martin Brecher, who, after noticing Lilly's effort to obscure the problem, wrote to Lilly saying... "I am skeptical whether dichotomizing on the basis of the presence or absence of poisoning with an antidepressant will provide any insight ... Most of the fluoxetine [Prozac] suicides have not been by overdose, but rather by gunshot, jumping, hanging or drowning."

By 1986, clinical-trial studies comparing Prozac with other antidepressants showed a rate of 12.5 suicides per 1,000 users of Prozac compared to only 3.8 per 1,000 on older non-SSRI antidepressants, and 2.5 per 1,000 on placebo.[8] An internal Lilly document dated March 29, 1985 also quantified the problem: "The incidence rate [of suicide] under fluoxetine [Prozac] therefore purely mathematically is 5.6 times higher than under the other active medication imipramine. ... The benefits vs. risks considerations for fluoxetine currently does not fall clearly in favor of the benefits. Therefore, it is of the greatest importance that it be determined whether there is a particular subgroup of patients who respond better to fluoxetine than to imipramine [a non-SSRI antidepressant], so that the higher incidence of suicide attempts may be tolerable."

After Prozac's entry into the market in 1988, reports quickly surfaced, confirming that the beast Lilly saw in the laboratory had now, without warning, been unleashed upon the public. In 1990, three years before Bill Forsyth killed his wife and himself, a report appeared in the *American Journal of Psychiatry* on the "Emergence of Intense Suicidal Preoccupation During Fluoxetine [Prozac] Treatment." Two Harvard psychiatrists, Martin Teicher and Jonathan Cole, and a registered nurse, Carol Gold, described cases in which patients developed serious preoccupations with suicide soon after being given Prozac.[9] They concluded:

> We were especially surprised to witness the emergence of intense, obsessive, and violent suicidal thoughts in these patients. ...No patient was actively suicidal at the time fluoxetine treatment began. Rather, all were hopeful and optimistic... Their suicidal thoughts appear to have been obsessive, as they were recurrent, persistent, and intrusive. ... It was also remarkable how violent these thoughts were. Two patients fantasized, for

the first time, about killing themselves with a gun (cases 4 and 5), and one patient (case 6) actually placed a loaded gun to her head. One patient (case 3) needed to be physically restrained to prevent self-mutilation. Patient 2, who had not prior suicidal thoughts, fantasized about killing himself in a gas explosion or a car crash.

The report by the Harvard psychiatrists prompted responses from clinicians describing similar cases. That Teicher and colleagues were on to something came as no surprise, moreover, as these were not the findings of amateurs. Jonathan Cole, the second author of the study, had a career that dates back to the 1950s, and he has been described by Pfizer, the maker of the SSRI Zoloft, as a "pioneer" in the field of psychopharmacology. Referring to the Teicher/Harvard report during the Forsyth trial, David Healy told the court that Jonathan Cole "is a man who has seen suicidal ideation and yet he and colleagues were saying that what they witnessed in this instance was something different. These are not investigators who would have easily been deceived by the ordinary kind of suicidal ideation that occurs in depression."[10]

In July, 1992, another article appeared, this time in the *Archives of General Psychiatry*. Like the Harvard report, this article had two senior researchers among its authors, William Wirshing and Theodore Van Putten, the latter of which was a leading expert on akathisia. They stressed in the report that, prior to going on Prozac, none of their patients "had a history of significant suicidal behavior; all described their distress [while on Prozac] as an intense and novel somatic-emotional state; all reported an urge to pace that paralleled the intensity of the distress; all experienced suicidal thoughts at the peak of their restless agitation;

and all experienced a remission of their agitation, restlessness, pacing urge, and suicidality after the fluoxetine [Prozac] was discontinued."

The finding that these problems emerge soon after a selective-serotonin drug is taken, and then disappear soon after the drug is withdrawn, provides compelling evidence, David Healy came to believe, that the problem is often the drug and not the so-called disease. Anthony Rothschild and Carol Locke, also of Harvard Medical School and McLean Hospital, reported three such cases in the *Journal of Clinical Psychiatry* in December, 1991. All three patients, the authors note, "were reexposed to fluoxetine [Prozac] after having previously made a serious suicide attempt during fluoxetine treatment."

The first case involved a 25-year old woman with a three-year history of depression. Two weeks after starting Prozac, and three days after having her dose increased from 20 to 40mg, she escaped from the hospital and jumped off the roof of a building. After jumping, she hit a landing, compound fracturing both her arms and legs. With the patient now in a wheelchair, the psychiatrists tried Prozac a second time. Eleven days later she noted that she was having the same adverse effects as when previously given Prozac, stating that "I tried to kill myself because of these anxiety symptoms. It was not so much the depression." All adverse reactions disappeared within three days after the drug was terminated a second time.

The second case involved a 47-year old man with an eight-year history of depression. He began experiencing severe restlessness and anxiety within two weeks after starting Prozac, from which he said death would be a welcome relief. He then jumped from a cliff, but had his fall broken by a tree. Put in psychiatric care, he was put on Prozac a second time. And when his dose was increased from 20 to 40mg, the adverse reaction returned, prompting the comment that "this is

exactly what happened the last time I was on fluoxetine [Prozac], and I feel like jumping off a cliff again." All adverse reactions disappeared twenty-four hours after being put on an additional drug.

Finally, the third patient was a 34-year old woman with a fourteen-year history of depression. About a week after the Prozac dosage was increased from 40 to 60mg, she jumped off the roof of a tall building, landing on a balcony, and suffering a fractured femur. In psychiatric care, she was put on Prozac again and, after having her dose increased, this time from 20 to 40mg, she stated that the restlessness produced by the drug was making her feel "crazy," and that she was feeling just like she did before her last suicide attempt.

Reflecting on these cases, Rothschild and Locke stressed that "Patients need to be reassured that the overwhelming symptoms being experienced are the side effects of medication and are treatable. ...Our patients had concluded their illness had taken such a dramatic turn for the worse that life was no longer worth living." Thus it seems that not only are Prozac suicides and homicides a hidden reality, the agitation and violent thoughts that precede them are likely to be misinterpreted as a sign of the very problems that the drug is said to treat. This is a horrible irony that Lilly had learned to exploit with earlier drugs, repeating the claim over and over that it's not the drug but the disease. "Prozac tends to be used by people with psychiatric problems," commented one Lilly executive. "Some people with psychiatric problems happen to be violent."

Doing what Lilly and the other manufacturers of SSRIs have failed to do all along, which is warn physicians to watch for agitation and increased suicidality soon after starting patients on an SSRI (or upping their dose), is crucial, as physicians are not otherwise likely to monitor them during the first weeks of drug use -- Joseph Wesbecker being a case in point. Of course this is partly why Lilly

has worked so stubbornly to avoid having to issue a warning, fearing that the extra burden would reduce physicians willingness to prescribe the drug. After all, a major factor in Prozac's immediate success was that it is taken only one time daily... "the safe and effective new medication, easy for both prescriber and patient." Rather than doing this, and rather than remaining quiet on the subject, Lilly has actually fought in the other direction, declaring that these side effects are in fact proof of the existence of the disease. What has been happening as a result is illustrated in a case described in the Teicher/Harvard report. A 19-year old college student had developed "disturbing and self-destructive thoughts" two weeks after starting on Prozac. When the dose was increased from 20 to 40mg, her problems became worse, and then worse again after the dose was increased from 40 to 60mg. Still convinced that "it's not the drug but the disease," the doctors increased the young woman's dose yet another time, from 60 to 80mg. At this point she begin violently banging her head and mutilating herself.

III

Growing reports suggesting that Prozac might be unsafe at any dose had Lilly running scared. One executive stated in an internal memo in 1990 that, if Prozac is taken off the market, the company could "go down the tubes."[11] Responding to concerns expressed by the FDA, Lilly agreed to conduct a study examining the question of whether Prozac induced aggression and suicidal thoughts. The result, known as the Beasley study, appeared in the September 21, 1991, issue of the *British Medical Journal*.[12]

The study, authored by Lilly employees, including psychiatrist Charles Beasley, looked and sounded like good science. On the surface it represented the

data pooled to date comparing Prozac with either older non-SSRI antidepressants or placebo. In fact the data had been hand picked to favor the company.[13] The analysis dealt with 3,065 patients, less than 12 percent of the total data in clinical-trail studies at that time. Among those who were left out was the very population most likely to become suicidal -- the five or so percent of patients who dropped out of the clinical trials because they experienced unpleasant side effects after taking Prozac. The report also made no mention of the dozen or so suicides that had already occurred in Prozac's clinical trials, a number that, given the population being studied -- primary care out-patients rather than severe depressives -- would be expected to be near zero.

The Beasley study was submitted first to the *New England Journal of Medicine,* but was rejected. Publication in the *British Medical Journal* was not as high profile but it would have to do. And it did. After seeing the report and after receiving continued assurances from Lilly that its drug does not lead to extreme acts of violence, the FDA's Psychopharmacological Drugs Advisory Committee gave the drug a new lease on life in September, 1991. To a great sigh of relief at Lilly, the committee's report stated that there was "no credible evidence of a causal link between the use of antidepressant drugs, including Prozac, and suicidality or violent behavior." From this moment on, instead of having to defend the safety of its antidepressant, Lilly could simply stand behind the "independent" conclusions of the FDA: "Our experience with Prozac does not show a cause-and-effect relationship between it and suicidal thoughts or acts. Our safety track record has been well established," notes an Eli Lilly spokesperson. Prozac was saved.

It wasn't until the Fentress and Forsyth trials that Lilly's internal documents surfaced, revealing the depth of the deception. This included the statements from

the Prozac working group in 1978, acknowledging problems with akathisia and drug-induced psychosis.[14] Also among the documents was evidence that the company had drafted wording for a package insert for Prozac stating that... "Mania and psychosis may be precipitated in susceptible patients by antidepressant therapy." This warning never made it into the final package insert, of course, but similar wording ended up being required before Lilly could sell Prozac in Germany, as Fluctin. And there was a memo dated October 2, 1990, which referenced an upcoming Prozac symposium in which the issue of suicidality was to be discussed. One Lilly employee queried another: "Then the question is what to do with the 'big' numbers on suicidality. If the report numbers are shown next to those for nausea, they seem small."

There was also a series of memos concerning two Taiwanese doctors who had completed a study entitled: "Suicidal attempts and fluoxetine (Prozac) treatment." In a memo dated April 8, 1992, a Lilly employee reports: "Mission accomplished. Professor Lu will not present or publish his fluoxetine [Prozac] vs. maprotiline suicidality data." A similar case was that of Robert Bourguignon, a Belgian doctor who, after soliciting his colleagues' experiences regarding suicidality and other side effects concerning Prozac, was sued by Lilly. A cease-and-desist order was issued, but Bourguignon eventually prevailed. The result of the survey, "Dangers of Fluoxetine," appeared in *The Lancet* in 1997. Bourguignon cites 11 reports of serious events in the paper, examples of which included severe nervousness, suicidal thoughts, and "paranoid psychosis."[15] Lilly had also canceled a clinical trial being conducted at a Hospital in Indianapolis, Lilly's hometown. While researchers doing trials for Lilly often obscured problems with akathisia by coding it as simple nervousness or anxiety, the chief researcher in the trial, Joyce

Small, was actually coding akathisia as akathisia. No doubt Lilly was displeased to find out that she was also finding the problem in nearly 1 out of 10 patients taking Prozac.[16]

Another finding, not involving case studies, also raise questions about violence with the SSRIs. Although rates of suicide were four times higher for men than women throughout the latter half of the twentieth century, women taking SSRIs suddenly and mysteriously show the same rate of suicide as men taking SSRIs. Whether Prozac and other SSRIs produce agitation and suicidal obsessions more often in women is not clear, since women are more than twice as likely to be taking SSRIs. What is clear is that, despite their high rate of antidepressant use, women taking them do not lower their risk, but rather acquire the same, higher risk of suicide as men.

In the face of all the case reports and all the epidemiological statistics, and in the face of more than 200 lawsuits claiming a link between Prozac and violence, Lilly continued throughout the 1990s to promote the view that their drug actually lowers suicide risk. "The over 10,000 patients who have been on clinical trials where people have looked at suicidality," commented a vice president of clinical investigations at Lilly on the ABC News show *20-20*, "suicidal ideation have shown without a doubt that these drugs do not increase suicidal ideation or suicide potential. In fact, they do just the opposite: They reduce it." Prior to the SSRIs, the rate of suicide in those using antidepressants on an outpatient (i.e., without hospitalization) was only about 30 suicides per 100,000 years of patient use, which is roughly the same rate of suicide as the general population.[17] However, the suicide rate for Prozac from a 1995 study published in the *British Medical Journal*, which looked at ten antidepressants used by a total of 170,000 people in

the United Kingdom, was 189 suicides per 100,000 years. In contrast to the claims of Lilly executives, this suggests a six-fold increase in suicide for Prozac relative to older, non-SSRI antidepressants, a number that is similar to Lilly's own internal assessment from 1985, which acknowledges a risk that was "5.6 times higher than under the other active medication imipramine."

There is, however, a way to test the theory once and for all, which is to give the drugs to people who have no history of depression or violence. Evidence of just this kind came unexpectedly from David Healy himself.

Back in North Wales, Healy conducted what is called a healthy volunteer study.[18] Twenty volunteers were recruited, half of which were given the SSRI Zoloft for two weeks, the other half of which were given a non-serotonin antidepressant (Edronax) for two weeks. Afterwards, following a two-week "washout" period, each was given the other drug for an additional two weeks. Healy had designed the study to compare the clinical effects of each drug, but before he knew it, he had two healthy volunteers who had became dangerously agitated and suicidal -- and both were on the SSRI Zoloft. Healy was surprised, but he would not stay surprised. Months later he would discover an unpublished study Pfizer conducted in the 1980s in which healthy female volunteers were given either Zoloft or placebo. The study was canceled four days later because all those receiving Zoloft were complaining of problems of agitation and apprehension. Healy's case was not this bad; in fact some of the healthy volunteers rated the Zoloft experience positively. One of those who didn't was a 30-year-old woman who, one week after starting Zoloft, began having nightmares about having her throat slit. Within two weeks she became suicidal. Obsessed with an idea that has struck others highjacked by SSRIs, that she should throw herself in

front of a car, she felt "it was as if there was nothing out there apart from the car, which she was going to throw herself under. She didn't think of her partner or child."

Adverse reactions like this cannot easily be blamed on psychiatric instability, given the population, and a rate of ten percent makes it clear that such results are not so rare as to be negligible. Nevertheless, these are normal volunteers, and most readers will probably see the ambiguity that still remains in cases like William Forsyth's. Did the drug cause him to do it? Did it simply precipitate the inevitable? Or did it have no bearing at all on the events of March 3, 1993? No doubt this ambiguity played a part in why, despite David Healy's testimony and the surfacing of the Lilly papers in the Forsyth trial, the jury found once again in favor of Lilly.

IV

The challenges plaintiffs' lawyers face in cases like William Forsyth's are considerable. There may be overwhelming evidence against a drug and its manufacturer, but such evidence will not be enough if it's still ambiguous when applied to the case at hand. This is especially true for the SSRIs, since suicides and homicides occur unexpectedly even when no drugs are involved. To use an analogy, a die that comes up six on every role is clearly biased, but how does one know, on any particular role, whether a six might have come up anyway?

Still, not all tragedies involving the SSRIs have been overwhelmed by ambiguity. The Australian David Hawkins was freed from prison in May, 2001, after a supreme court judge said his actions, which included the killing of his wife, were wholly out of character. Two days after going on Zoloft, the 74-year-old

Hawkins strangled his wife, then set out but failed to kill himself by carbon monoxide poisoning. "But for the Zoloft," said the judge, "which he took on the morning of August 1, 1999, it is overwhelmingly probable that Mrs. Hawkins would not have been killed on that morning."

A month after Hawkins' release, in a different case, in federal court in Cheyenne, Wyoming, a jury found against SmithKline Beecham, the maker of the drug Paxil. This was the case of Donald Schell. After complaining of anxiety, stress, and possible depression, the 60-year-old Schell was diagnosed as having mild depression and, like most SSRI users, was prescribed the drug by his family doctor. He was given promotional samples of Paxil and two days later -- the same two days of SSRI use that preceded David Hawkins' murder of his wife -- Schell committed the most violent act in recent Wyoming history. The jury in the case concluded that the SSRI can cause some individuals to commit suicide and homicide, and did just that in the case of Donald Schell, who, on February 13, 1998, shot to death his wife, his adult daughter, his infant granddaughter, and then himself.

The award of $6.4 million against SmithKline Beecham (now GlaxoSmithKline) was the first case to be lost in court by any manufacturer of an SSRI. Known as the Tobin case -- Tim Tobin was the husband of Donald Schell's deceased daughter -- the trial took two weeks to complete, after which the jury returned with a unanimous verdict in only three and a half hours. The company had faced a more experienced legal team -- the core of which was the same as in the Forsyth case, including expert witness David Healy -- and a different and apparently more effective legal strategy: in the Forsyth case, plaintiff's lawyers focused on the man, William Forsyth, but in the Tobin case they focused on the company. Also, as Healy revealed in the trial, there was much in SmithKline's

records to warrant concern about the company's behavior, and their drug. SmithKline had carefully researched Paxil and in the process had produced plenty of evidence that the drug posed the same kind of dangers as Prozac, yet did nothing about them. Among SmithKline's internal files were 34 healthy volunteer studies involving company employees. They showed that, even though these people had no noted problems of depression or anxiety, 25 percent experienced some degree of agitation after taking Paxil.[19] These studies were not conducted by psychiatrists, however, and those that had been were missing unaccountably from the company archive. Healy did find a note, though, which made reference to one. On it the investigating psychiatrist wrote that he'd never seen such a high incidence of problems in a healthy volunteer study.

Healy also discovered other problems -- problems that spoke to the myriad other adverse reactions one can experience when taking an SSRI. In addition to agitation, akathisia, suicidal thoughts, and violence, the SSRIs are also becoming known for the physical dependence they produce in many users. A class action complaint against the maker of Paxil notes:

> Currently, on one website alone there are 1,359 electronic signatures of persons complaining to GlaxoSmithKline Corporation about withdrawal reactions they have suffered from Paxil. Given that the signatures provide the full name of each person, many of whom provided their e-mail addresses and lengthy commentary, this is a reliable example of the numerosity of the persons suffering from Paxil withdrawal. Over the past two years, plaintiffs' attorneys have been individually contacted by approximately 500 Paxil withdrawal victims. The pain and suffering experienced by each of these individuals is the direct result of

> GlaxoSmithKline Corporation failure to warn users of Paxil's addictive nature, the drug's inducement of physical or psychologic dependency, and its infliction of dependency/withdrawal syndrome when the patient's Paxil dosage is reduced or terminated.[20]

This is consistent with what David Healy had found while researching the SmithKline archives. In one healthy volunteer study conducted within the company, researchers had found that, upon drug discontinuation, as many as 85 percent of the volunteers suffered agitation, bizarre dreams, insomnia, and other adverse effects. Healy noted that as much as half of the healthy volunteers taking part in the study showed symptoms that they were becoming physically dependent on the drug. The example of Lisa, a woman participating in an on-line chat session on antidepressants, illustrates the nature of the problem: "I was addicted to Effexor. Was horrified of the thought of going without it -- and for good reason!! I don't think the physical/ mental dichotomy makes sense. If you can't get by without the stuff, you're addicted. Effexor IS addictive, I'm off the stuff, but I've never been so physically sick in my life as when I was in withdrawal..."[21]

There is also a substantial problem of sexual side-effects with the SSRIs, with perhaps as many as 70 to 80 percent of users experiencing lowered sex drive and impotence. Beyond this there are a variety of more minor side-effects, including nausea, insomnia, nightmares, fatigue, drowsiness, weakness, loss of appetite, tremors, dry mouth, sweating, and even yawning. The one SSRI quality that is preferred over the older, tricyclic antidepressants is that it's difficult to overdose

on the SSRIs. Of course this hardly matters when, as illustrated in the following cases, the drug itself precipitates suicide and other forms of violence.

- Fifteen days after starting Prozac, the 56-year old singer known as Del Shannon died after he shot himself in the head with a .22 caliber rifle.

- Ten days after starting Prozac, a 41-year old woman began experiencing a longing for pain, which she satisfied by mutilating her legs, stomach, thighs, arms, and torso, along with six suicide attempts, all of which ended abruptly after she was taken off the drug.

- Three days after starting Prozac, a 58-year old man began having suicidal thoughts and tried to hang himself with a rope, prompting a discontinuation of the drug and, four days later, a complete disappearance of his suicidal ideation.

- Within a week after having her dose of Prozac gradually increased from 20 to 60mg, a 28-year old woman began to suffer akathisia and started fantasizing about jumping out of the hospital window, which prompting the discontinuation of Prozac and, in about a week, the elimination of all adverse effects.

- Twenty-four hours after accidentally increasing his dose of Prozac from 60 to 80mg, a 44 year old man began making superficial cuts to his throat, wrist, and abdomen while driving, which disappeared twenty-four hours after decreasing his dose.

- Two weeks after starting Prozac, a 32-year old woman felt better except that she began experiencing restless and out of control feelings, which led her to state that "I feel like I need to hold onto my chair or else I'll jump out the window," all of which disappeared several days after discontinuing Prozac.

- Eleven days after starting Prozac, a 63-year old Englishman suffocated his wife and then jumped off a 200 foot cliff.

- Several weeks after starting Zoloft, a 35-year old man stabbed his wife and two children while in their home, and then killed himself with a .22 caliber rifle.

- Six days after starting Prozac, a 60-year old woman stabbed and slashed herself more than 60 times as her husband ate breakfast in the kitchen; she died the next day.

- One week after his parents were told of a "terrific" new medicine called Zoloft, a 13-year old boy went into his bedroom closet and, while his family slept, killed himself by hanging.

- Almost three months after her dose of Prozac was doubled, a woman living in Randolph. Vermont took a .22 caliber pistol and shot and killed her 8-year old son, her 4-year old daughter, and then shot and killed herself.

- Several days after Brynn Hartman was given Zoloft samples by her child's psychiatrist, she shot and killed her husband, Phil Hartman, while he slept, and then, four hours later, shot and killed herself.

- Two weeks after being prescribed Prozac, a 46-year old man finished cleaning out the milking parlor on his farm, returned to the house, and shot himself in the forehead with a .22 caliber rifle.

- A few days after starting on Prozac, a 17-year old boy complained that the drug was "messing with [his] mind" and, a few days later, hung himself in his bedroom.

Tragic events like these litter the communities and countrysides of North America and Europe. Few of them ever make the headlines, however, buried instead behind the confusion and secrecy that so often marks sudden family tragedies. Before the Forsyth case made it to trial, in March, 1999, two thousand Prozac associated suicides had been reported to the FDA, recorded on the their "adverse event system." At least a quarter of these include explicit references to agitation and akathisia. Based on years of drug monitoring, the FDA has concluded that only about one percent of serious and fatal adverse drug events are ever reported on the system. This means that, as David Healy has concluded, as many as 200,000 Prozac-related suicides had taken place by 1999, 50,000 of which are likely to have been precipitated by an extreme state of agitation. And this is only for Prozac. The total number of suicides for all SSRIs, including Paxil, would of course be larger.

Still, with the cult of the SSRI many million strong, these cases are relatively rare. They are exceptional cases, people want to believe, and must therefore be weighed against the millions of others living happily in Prozac nation. There is, however, another, more chilling possibility. If most everything Lilly says is false about Prozac turns out to be true, what if most everything they say is true about Prozac turns out to be false? What if, counter to the media hype that ushered in the Prozac revolution, the SSRIs actually offer few real benefits over older, akathisia-free antidepressants, like Tofranil and Elavil? Might all this death and destruction be for not? Viewed from the outside, this seems a certain impossibility. From the inside, however, it looks like an all too likely conclusion.

V

The true story of the SSRIs begins in the 1950s, when the use of anti-depressants was confined almost exclusively to cases of clinical depression. Although there was some suggestion at the time that the new antidepressant imipramine (Tofranil) might actually make some patients feel "better than well," it was also true that, as David Healy writes in *The Antidepressant Era*, "no one was interested in imipramine in 1958." Neither was anyone interested in feeling better than well, especially if it required pumping powerful chemicals into one's brain.

Although difficult to imagine today, depression was understood to be a rare condition in the 1950s and before, and there was a commonsense distinction made between depression and unhappiness. "Depression as it is now understood both by clinicians and laypeople is an extremely recent phenomenon," continues David Healy, "and one that is largely confined to the Western world." The rate of depression in the 1950s was estimated at about 50 people per million, an estimate that would grow to 100,000 per million by the end of the century. This is a 2,000-fold increase in what is ostensibly a hereditary disease. What happened during these years is not that a disease was discovered, or its cure. What happened is that, because of ongoing changes in the drug marketplace, the pharmaceutical industry began to take an interest in depression.

Drug companies have always viewed the general public as a huge legal market for selling mind-altering drugs. And it has been one since the nineteenth century. Immediately prior to the SSRIs, the prescription drug market focused not on depression and antidepressants (the tricyclics), but on anxiety and anti-anxiety drugs (the benzodiazepines). When introduced in the 1960s, drug makers

declared the benzodiazepines, also called anxiolytics, to be powerful yet nonaddictive. The market for barbiturates (Nembutal, Seconal) was collapsing at the time, as they no longer lived up the same claim made, that they were powerful yet nonaddictive. This encouraged widespread promotion of the benzodiazepines, followed by widespread prescribing and use, with drugs like Valium becoming the most popular prescription drugs of all time. As long as millions of Americans were taking benzodiazepines, there would be no popular market for the antidepressants.

Beginning in the 1980s, however, things began to change. Fewer and fewer doctors were willing to prescribe benzodiazepines to treat every psychological whim and woe, waking up to the fact that, as it was with the barbiturates, *and now the SSRIs*, those most interested in these drugs were also likely to develop a stubborn dependence on them. A 1983 study notes, "In the past 3 years there has been a dramatic change in medical attitudes to the prescribing of benzodiazepines. Before 1980 these drugs were regarded as not only safe and effective anti-anxiety drugs and hypnotics but also free of important unwanted effects. Since then there has been rising alarm about the risks of pharmacological dependence after regular consumption of these drugs."[22] The peak year for benzodiazepine use in the United States was 1973, when over 80 million prescriptions were filled. By 1986, this number had fallen to 61 million. As the number continued to decline, a hole in the domestic drug market began to open. And the SSRIs were just the drugs to fill it.

Synthesized in the early 1970s, Prozac was in fact the fourth SSRI to come to market (not the first, as Lilly had claimed).[23] The first was a drug called zimelidine (Zelmid), developed by the European drug company Astra. Lilly

scientists David Wong, Bryan Molloy, and Ray Fuller began the search for a 5-hydroxytryptamine (serotonin) reuptake inhibitor on May 8, 1972.[24] Although the goal was to produce a drug that acted more selectively on serotonin in the brain (and could be patented accordingly), what was less clear was what the drug would be useful for. Shortly thereafter, Lilly's drug 110140 -- a.k.a. fluoxetine and Prozac -- was born. After the drug succeeded in not killing laboratory animals in initial exploratory studies (but turned cats from friendly to growling and hissing), Lilly began to inquire into what possible market might exist for their new compound. At a meeting in England around this time, psychopharmacologist Alec Coppen suggested that it might be useful as an antidepressant.[25] The response he received from Lilly was that, of all its possible uses, this was not one of them.[26] Lilly had its eye on Prozac, not as an antidepressant drug -- or a PMS, OCD, nonsmoking, shyness, or anxiety drug -- but as an antihypertensive drug.

By the 1980s, however, attitudes at Lilly had changed, although not because of any breakthrough in medicine or science. Astra's zimelidine had appeared on the market as a new (and patented) antidepressant, joined shortly thereafter by two other SSRIs (a patent is important because it ensures exclusivity for the compound, which then allows for higher pricing). With the benzodiazepine market collapsing, Lilly also began to see a larger market possibility in treating depression, which would be much the same population that had been taking the benzodiazepines. "The emergence of depression in this sense coincides with the development of the SSRIs," writes David Healy in *The Creation of Psychopharmacology*,

> which in the mid-1980s appeared capable of being developed as either anxiolytics or antidepressants. After the benzodiazepine crisis, the

> industry had a new set of compounds to sell, but its new offerings did not meet the demand from the marketplace. And indeed since their initial launch as antidepressants, various SSRIs have been licensed for the treatment of panic disorder, social phobia, post-traumatic stress disorder, OCD, and other anxiety-based conditions. Indeed, for some of the SSRIs, contrary to popular perceptions, it has simply not been possible to show that they are effective in treating classic depressive disorders.

The turning of Prozac into an antidepressant is mirrored in the case of Paxil, which was also developed in the 1970s. Paxil didn't make it to market until 1993, however, delayed by the prevailing wisdom at SmithKline that although new patented antidepressants were coming on the market (the SSRIs), they were not as effective as the existing tricyclics.[27] Trapped in a momentary spell of pharmacological honesty, SmithKline failed to grasp that when it comes to heavily promoted drugs like Prozac, being more effective needn't have anything to do with it. Of course the spell has since worn off. Paxil would go on to become a popular drug in the antidepressant market in the 1990s, and would be an effective backdoor for re-entering into the anxiety market. "From the beach-head of depression," writes David Healy, "raids can subsequently be launched on the hinterlands of anxiety." Or, as GlaxoSmithKline put it in 2001, "Millions suffer from chronic anxiety. Millions could be helped by Paxil."

With benzodiazepine sales a shadow of what they once were, the number of prescriptions filled for antidepressants in the US in 1989 more than doubled. Less than two years after its release, sales for Prozac nearly tripled, from $125 million to $350 million, which was more than the total annual US sales for all other antidepressants combined. By 1990, when the cover of *Newsweek* announced "A

Breakthrough Drug for Depression," Prozac had become the most frequently prescribed antidepressant of all time. And the antidepressant market continued to grow. Annual Prozac sales reached the $1 billion mark in 1993. By 1999, Prozac would become the number three selling drug in the entire market of prescription pharmaceuticals, with more than 76 million prescriptions filled. In fact, more than 3 billion doses of SSRIs were consumed in 1999. In 2000, annual antidepressant sales reached the $10 billion mark, with the US making up 70 percent of all world sales for the drug. Meanwhile, in Japan, the Prozac revolution never happened. Because the Japanese had experienced fewer problems with benzodiazepines, their sales remained strong, and this left little market in which to engineer a Prozac revolution.

VI

It was not at Eli Lilly but at SmithKline that the concept of selective serotonin reuptake inhibitor was minted, although all the makers of SSRIs quickly embraced it to promote their new serotonin drugs. Like the "Pentium" concept used to sell Dell, Gateway, and other computers, the SSRI concept was a brilliant marketing device. Beyond its cleverness, however, the SSRI concept never had much to support it. Paxil, Zoloft, Prozac, Celexa, Luvox are all considered SSRIs, but the term "selective" has since acquired a popular meaning that goes far beyond the one intended. The SSRIs are not selective in what they treat, or even claim to treat, since they are now hailed as cure-alls for everything from PMS to panic attacks to smoking to shyness. Nor are they selective in their biochemical actions in brain. While the older tricyclics act on two neurotransmitter chemicals in the brain, namely, serotonin and norepinephrine, the SSRIs do only the former. Hence the name "selective serotonin reuptake inhibitors." But this is not all they

do. The SSRIs may not directly impact on norepinephrine, but they do directly affect other biochemical systems, including those involving dopamine. And after acting directly on these systems, the SSRIs produce a cascade of secondary and tertiary biochemical and cellular effects, all of which remain poorly understood. While an initial dose of Prozac has been shown to increase serotonin activity in an area of the brain known as the substantia nigra, for example, long-term use has been shown to produce just the opposite effect.

What is clear about the SSRIs, or at least should be, is that people don't experience unhappiness or depression simply because they suffer a chemical imbalance of serotonin in the brain. While some SSRIs are more selective in their serotonin specificity than others (Celexa), and some are more potent in causing serotonin release than others (Luvox), these differences do not translate into one SSRI being more effective than another. Also, since drugs like Prozac raise serotonin levels almost immediately, it's hard to see how this can explain the therapeutic effects of SSRIs, which take days or weeks to be achieved.

Despite these basic pharmacological facts, Lilly and other SSRI makers succeeded in the 1990s in convincing the public that a breakthrough had taken place in the brain and pharmacological sciences, with the SSRIs designed specifically to correct a biochemical imbalance now known to be a central cause in depression. "To help bring serotonin levels closer to normal," Lilly claimed in ads in popular magazines in the 1990s, "the medicine doctors now prescribe most often is Prozac." Suddenly anyone feeling down and depressed was presented with the possibility that perhaps they too suffered from low levels of serotonin. As Peter Kramer tells it in *Listening To Prozac*, the mainstay of antidepressants before the SSRIs -- imipramine -- "is 'dirty' in its main effects and its side effects because it affects both norepinephrine and serotonin. Once imipramine's

mechanism of action was understood, pharmacologists set out to synthesize a 'clean' antidepressant."

The frequent claim that a revolution had taken place in psychiatric science also has little in the way of evidence to support it. Consider two articles from popular magazines. The first, a *Newsweek* article -- "Beyond Prozac" -- claimed in 1994 that "Research that once mapped the frontiers of disease -- identifying the brain chemistry involved in depression, paranoia and schizophrenia -- is today closing in on the chemistry of normal personality." Yet three years later, in *Time* magazine, another article states that these aspects of the brain are not at all understood:

> For depression, bulimia, obesity and the rest of the serotonin-related disorders, however, no one knows for sure what part of the brain is involved or exactly why the drugs work. ...The entire history of serotonin and of drugs that affect it has been largely a process of trial and error marked by chance discoveries, surprise connections and unanticipated therapeutic effects. ...The tools used to manipulate serotonin in the brain are more like pharmacological machetes than they are like scalpels.

The 1997 *Time* article, "The Mood Molecule," nevertheless goes on to affirm the notion that SSRI offer something positively unique:

> In the 1960s, a second class of antidepressants emerged. ... [They] had major side effects, though, including profound drowsiness and heart palpitations. The reason, scientists generally agreed, was that they affected brain chemistry too broadly. The research seemed to point to serotonin as the most important mood-enhancing chemical, though not the only one, and so neurochemists set about looking for a drug that would boost the

> influence of serotonin alone. In 1974, after a decade of work, Eli Lilly came up with Prozac, first of the so-called selective serotonin reuptake inhibitors, or SSRIs, and it was finally approved by the FDA in 1987.

The article contradicts itself, however, when it suggests that a new antidepressant has arrived on the market that acts not on serotonin but on the very neurochemical said to be irrelevant to depression, norepinephrine:

> Psychiatrists in Europe are buzzing about a new drug, reboxetine, that has just been approved for use in Britain and seems to be even more effective than Prozac for severely depressed patients. Marketed under the brand name Edronax, it totally ignores serotonin and targets another brain chemical, norepinephrine, which is also known to have a powerful effect on mood.

At this point the *Newsweek* article brings us full circle, pointing out that another recent drug, Effexor, works even more effectively than the SSRIs, which it does by acting on both norepinephrine and serotonin: "Effexor... enhances both serotonin and norepinephrine, a second chemical messenger affecting mood. With its broader effect, Effexor should help some depressed patients who don't respond to Prozac."

While selectively targeting serotonin may be key to producing akathisia, self-mutilation, suicide, and murder, it should be clear, even from this sort of journalism, that it is not key to raising people's moods. Antidepressants like Edronax show that direct actions on serotonin may not even be necessary to produce an antidepressant effect. In fact the trend at the end of the century was away from SSRIs and toward a new (or at least newly patented) set of compounds that act on both norepinephrine and serotonin.

After losing its patent on Prozac, Lilly announced late in 2001 that it was hoping to market a new and putatively more effective antidepressant than Prozac late in 2002. The drug, duloxetine, has been dubbed a "dual-action" agent because, as noted on Lilly's webpage, it "enhances levels of two important brain chemicals," serotonin and norepinephrine. A presentation on the drug by Lilly scientists at the meeting of the New Clinical Drug Evaluation Unit at the National Institute of Mental Health concluded that "The increased extracellular levels of serotonin and norepinephrine produced by duloxetine administration suggests it would enhance serotonin and norepinephrine neurotransmission and is expected to be efficacious in the treatment of major depression." So much for Prozac being a breakthrough antidepressant tailored to fit with the latest scientific knowledge. Fortunately for Lilly, the media has a poor memory. In December, 2001, the *Boston Globe* began hyping Lilly's future drug, stating that "While Prozac and drugs like it increase the amount of the chemical serotonin in the brain, duloxetine and Effexor enrich the supply of two important mood-boosting chemicals: serotonin and norepinephrine. Because these drugs have two different mechanisms of action, rather than one, doctors believe they may be more effective than Prozac-like drugs at improving patients' moods and might help more seriously depressed people."

VII

The SSRIs look be on their way out, no doubt in part because of the risks of continuing to push "selective serotonin" drugs. The cult of the SSRI is, however, still going strong. The SSRIs are magic bullets, the public has come to believe, with any suggestion to the contrary met with a rash of cries and complaints. Thus, in 1999, when science writer John Horgan wrote an op-ed piece called "Placebo

Nation" in the *New York Times*, letters poured in complaining that new antidepressants like Prozac have helped millions of people, improving countless lives. That Horgan's message provoked a response was hardly surprising, implying as it did that individuals taking Prozac and other antidepressants might be benefiting not just from the package -- that is, the pharmacological ingredients -- but from the handling -- that is, the experience of treatment. For those who have seen their mood brighten after taking Prozac, Paxil, Zoloft, or any other antidepressants for that matter, such a suggestion likely comes as a slap in the face. Prozac is not a placebo, it's a *selective serotonin reuptake inhibitor*, an SSRI!

Indeed it is. But this was not Horgan's point. Like any other psychoactive drugs, including cocaine and Ritalin, Prozac's antidepressant effects are inseparably bound up with the same psychosomatics that swamp all other moments of drug use. A placebo response might be taking place, Horgan was suggesting, with the act of taking the drug setting into motion a powerful psychological shift from hopelessness to hopefulness.[28]

Prozac has real effects, and in some users these effects may very well produce "fantastic results," "a blessed relief," "a brighter, more cheerful mood," and other "awesome results."[29]

But placebo effects are every bit as real as pharmacological ones, and their indistinguishability during drug use means that knowing what is and is not an effect of the latest mood molecules is not as easy to discern as we might like to think.

A case in point was a compound that Merck pharmaceuticals synthesized, MK-869. In the realm of psychiatric medicine, concern over placebo effects loom large, for in order to obtain FDA approval, drug companies must show that their

drugs can outperform a placebo. As recounted in a *Science* magazine article entitled "Can the Placebo Be the Cure?," early clinical trials led Merck to think its new compound had great promise as an antidepressant, and with fewer side effects than other antidepressants, Prozac included.[30]

On January 22, 1999, however, all bets were off, as Merck announced that they would not seek FDA approval for their new compound. The reason? While the latest data suggested that the drug was indeed effective in treating depression, it was no more effective than a placebo. "A novel compound -- a Merck invention known as MK-869 -- then in several clinical trials, seemed set to become a new millennium drug for millions of people who take antidepressant medication every day. The news [that MK-869 would be shelved] was a downer for Merck and Wall Street: the price of the companies stock dropped 5% on the day Merck broke the news."

Drug companies are not the only ones to face the placebo challenge. The same problem applies to any drug user who, after popping some pills, wants to know what is and is not an effect of the drug. For those reporting positive Drug experiences while on SSRIs, which may take days or weeks to occur, the question remains: can one always be so sure that the effect is really because of the drug? Might it be at least partly a placebo effect? This may appear to be the same question as is asked of juries in cases like William Forsyth's, except for one important difference: placebo effects rarely if ever include reactions like self-mutilation, suicide, and murder. A 1965 report in the *Archives of General Psychiatry* illustrates why we cannot simply assume that the psychological effects of a drug are just that and nothing more.

Lee Park and Lino Covi, two young psychiatrists at Johns Hopkins University, asked what would happen if their patients were given a placebo and told as much. To answer the question, they took fifteen newly admitted anxious and depressed patients and told them the following: "Many people with your kind of condition have been helped by what are sometimes called 'sugar pills,' and we feel that a so called sugar pill may help you, too. ... A sugar pill is a pill with no medicine it at all. ...Are you willing to try this pill?" Of the fourteen individuals who said yes to this question (all but one individual), all kept their second appointment, and all but one reported taking at least two-thirds of the prescribed pills. To their surprise, Park and Covi found that each individual taking the sugar pills experienced a reduction in psychological distress. The average "distress score" was reduced by 43 percent, meaning that a majority of them felt "quite a bit" better after a week of taking sugar pills. When asked to explain why they might be feeling better, given they were taking only sugar pills, nine of the participants pointed to the pill, five of which actually suspected or insisted that they were given an active medicine rather than a placebo. Of the remaining five, two attributed their improvements to the doctor's care rather than the pills, and three pointed to self improvement.

Among the former, one was a 45-year-old man, described as being rigid, resistant to influence, and suffering from "agitated depression." The man had experienced severe insomnia, loss of appetite, feelings of despair, death wishes, and some somatic (i.e., bodily) symptoms. During the interview he testified to a reduction in all symptoms, except for his lack of appetite. At the start of the interview he immediately declared that "It wasn't a sugar pill, it was medicine!" He also noted that upon taking the pills he was able to think more clearly, which led to a positive change in his attitude about his problems and the future. In addition

to positive psychological effects, the man also reported clear side effects of the pills, including dry mouth and butterflies in the stomach. When asked about his improvement, he implied that perhaps he was falsely told he was being given a placebo so that he would attribute the improvement to himself rather than the medication.

A second individual who had this experience was a 24-year-old woman with three children. She was clearly depressed and complained of insomnia, anorexia, irritability, and tension. After a week of taking sugar pills she also testified that "they're not sugar pills... because they worked." This woman was in fact very skeptical of a placebo being effective for anyone, and stated that the pills she received were actually more effective than other medications she had taken. She noted that she was feeling better than she had in the past 20 years, and was pleased with the idea of continuing with the same doctor and pills.

Clearly, the testimonials people offer in favor of a drug do not have to be accurate to be strong. Determining was is and is not an effect of a drug requires extracting the drug effect from a whole range of ongoing experiences, which will not necessarily be easy; it may even be theoretically impossible, as these pharmacological and nonpharmacological effects do not occur side by side in two separate realms of consciousness, but rather are experienced in combination, with the whole adding up to more than the sum of the parts.

The matter is further complicated by the fact that, according to reviewers of the antidepressant literature, most users of SSRIs are in fact active placebo responders. As the *New York Times* summarized, "A [1998] review of placebo-controlled studies of modern antidepressant drugs found that placebos and genuine drugs worked about as well." This means that much of the credit given to the SSRIs should be attributed to the placebo effect instead. The report cited by

the *Times* was one of three meta-analyses of the antidepressant literature that appeared in the 1990s, each of which independently concluded that placebo effects account for much of the effectiveness of the antidepressants.[31] Overall, about two-thirds of the effectiveness attributed to the SSRIs appears to be due to the placebo effect.

These numbers may seem confusing. People often associate a placebo effect with a placebo, and thus view drug effects and placebo effects as mutually exclusive. How can a drug effect really turn out to be partly or largely a placebo effect? In truth, placebo effects are just another way of saying that nonpharmacological factors can contribute significantly to so-called drug effects. If placebo effects are mobilized by beliefs and expectations, as they most certainly are, then what could be better than an active drug for launching the placebo effect? While some individuals will respond positively to SSRIs and not at all to placebos, a majority of individuals will experience the blessings of both pharmacological and nonpharmacological factors working in combination.

One arrives at the same conclusion when looking at the four studies Lilly submitted to the FDA for drug licensing.[32] Here it becomes clear that the dangerous adverse effects of Prozac might have been moot if the FDA had just upheld rigorous scientific standards. That is, had they relied only on data from patients receiving Prozac alone, Lilly's drug might have gone the way of Merck's MK-869. This conclusion stems from the fact that, when the results of the 135 patients taking benzodiazepines are removed from the data set that Lilly submitted, the statistical advantage of Prozac over placebo vanishes. That a benzodiazepine might make Prozac look like an effective antidepressant comes as no surprise, moreover, since anxiety has long been known to play a role in

depressive syndromes. As for the forth study Lilly submitted to the FDA, which did not allow the concurrent use of anti-anxiety drugs, it never showed an effect to begin with; that is, there was never any statistically significant difference between Prozac and placebo.

VIII

To many this conclusion will seem like a contradiction. How can the SSRIs be linked to suicides and homicides, yet for many users be effective only as a placebo? But this is also just a confusion, as there is no contradiction in suggesting that a drug is powerful, yet not very powerful in doing what it's claimed to do. In fact the very creation of the FDA, as well as the passage of the Food, Drug, and Cosmetic Act of 1938, were motivated by this very scenario, that while a variety of commercial drug products had little hope of ever working except as a placebo, their active ingredients nevertheless posed a clear hazard to the public health.

And so goes the story of the SSRIs, sadly, a century later. The spell of pharmacological magicalism was cast, Prozac was raised up as the latest panacea for masking the maliase of everyday modern life, and millions of people were exposed to a group of drugs that were more toxic, more expensive, and less effective than drugs that already existed. Given the powers of the prescription marketing machine, and given the subsequent trend back to drugs that act on neurochemicals other than serotonin, it should be clear that Prozac was not even necessary for the "Prozac revolution" to occur. Any number of non-SSRI antidepressants might have been fashioned for the revolution, just as they are being fashioned now for the next one. Shrink-wrapped with the same promise of

becoming "better than well," these new wonder drugs could have given the people just what they wanted, and without all the wreckage.

* * *

"The Lilly Suicides" is excerpted from the forthcoming book, The Cult of Pharmacology*, to be published by Duke University Press. A shorter version of this essay was published in the May/June, 2002 issue of* Adbusters *(www.adbusters.org)*

[1] Richard DeGrandpre is the author of *Ritalin Nation* (1999, Norton) and *Digitopia* (2001, Random House). He can be reached via email at rdegrandpre@hotmail.com.

[2] Read John Cornwell's *The Power to Harm.* New York: Viking (1996).

[3] Read "Protecting Prozac" by Michael Jonathan Grinfeld, *California Lawyer* (December, 1998).

[4] Read "They Said it was Safe" by Sarah Boseley, *The Guardian* (Saturday October 30, 1999).

[5] Read "Healy General Causation Report" and "Zoloft Suicide: Causal Mechanisms: The Healy Report" at www.justiceseekers.com.

[6] Read "The Antidepressant Web" by Charles Medawar in *The International Journal of Risk & Safety in Medicine, 10,* 75-126 (1997; find at www.socialaudit.org.uk); see also, P. R. Breggin's *Talking Back to Prozac,* New York: St. Martin's Press (1994).

[7] Read, e.g., William C. Wirshing et al.'s "Fluoxetine, Akathisia, and Suicidality: Is There a Causal Connection?" in the *Archives of General Psychiatry, 49* (1992).

[8] Read "Zoloft Suicide: Causal Mechanisms: The Healy Report" at www.justiceseekers.com.

[9] Read "Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment" by Martin H. Teicher et al. in the *American Journal of Psychiatry,* Vol. 147, No. 2 (February 1990). A total of six cases were reported: Case 1 was a 62-year-old woman who began experiencing suicidal thoughts and other adverse side effects eleven days after starting Prozac, but then experienced a complete reversal of these effects three days after stopping the drug. She described the experience as "uniquely bad," stating that "death would be a welcomed result." Case 2 was a 39-year-old man who developed a serious preoccupation with suicide and fantasies of self-destruction one month after starting Prozac. The sudden change in his manner led his elderly mother and former wife both to make "emergency calls" to his medical-care providers. Several weeks after the drug was discontinued there were no signs of any Prozac-related problems. Case 3 was a 19-year-old female college student who developed "disturbing and self-destructive thoughts" two weeks after starting Prozac. When the dose was increased from 20-40mg, the problems became worse, and then worse again after the dose was increased from 40-60mg. Inexplicably, she then had her dose increased from 60-80mg, which led her to banging her head and mutilating herself. She did not show marked improvement until three months after the drug was discontinued. Case 4 was a 39-year-old woman who experienced a worsening of depression and the emergence of suicidal thoughts two weeks after starting Prozac. For the first time she began to have thoughts of buying a gun and killing herself. She improved markedly after Prozac was discontinued. Case 5 was a 39-year-old woman who, after going on Prozac, experienced the return of suicidal thoughts for the first time in years. However, "in contrast to her past experience with suicidal feelings, she now embraced these impulses and hid them from the clinicians." Suicidal thoughts diminished about 11 days after Prozac was discontinued. Case 6 was very similar to Case 4.

[10] From David Healy's testimony to the court in United States District Court, Susan Forsyth vs. Eli Lilly and Company, Civil No. 95-00185.

[11] Read "They Said it was Safe" by Sarah Boseley, *The Guardian* (Saturday October 30, 1999). Excellent follow-up articles by Boseley can be found at www.guardian.co.uk.

[12] See "Fluoxetine and Suicide: A Meta-analysis of Controlled Trails of Treatment for Depression" by C. M. Beasley, B E. Dornseif, and J. C. Bosomworth in the *British Medical Journal, 303* (1991).

[13] Read "From the Psychopharmacology File" by David Healy in his collection of interviews, *The Psychopharmacologist*s. London: Altman (1996). The 1995 report by S. Jick, A. D. Dean, and H. Jick, "Antidepressants and Suicide" offers a more credible comparison of suicide rates for Prozac. Looking at ten antidepressants used by a total of 170,000 patients in primary care settings in the United Kingdom, these researchers found that Prozac, the only SSRI included in the study, was associated with at least twice a higher rate of suicide as other antidepressants. The reported rate of suicide for Prozac in the Jicks' study was about 189 suicides per 100,000 years of patient use of the drug (patient years are calculated because individuals taking older drugs will have often taken them for longer periods). Lilly claims that this rate is lower than the overall rates of suicide with depressed patients, which is about 600 suicides per 100,000 years. But this higher rate derives from data for severely depressed patients only, whereas the vast majority of people taking Prozac experience only mild to moderate depression. As Lilly's own packaging stated in 1996, Prozac's efficacy "was established in 5- and 6-week trials with depressed outpatients... the antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied."

[14] See also, Meltzer et al.'s "Extrapyramidal Side Effects and Increased Serum Prolactin Following Fluoxetine, a New Antidepressant" in the *Journal of Neural Transmission, 45* (1979).

[15] Read "Dangers of Fluoxetine" in *The Lancet* (January 18, 1997).

[16] From David Healy's testimony to the court in United States District Court, Susan Forsyth vs. Eli Lilly and Company, Civil No. 95-00185; another study puts rate as high as 25 percent. Read "Fluoxetine Induced Akathisia: Clinical and Theoretical Implications" by J. F. Lipinski, G. Mally, P. Zimmerman, and H. G. Pope in *Journal of Clinical Psychiatry, 50* (1989).

[17] The statistic "years of patient use" is used because it controls for the fact that older antidepressants have been used for longer periods than others; see "From the Psychopharmacology File" by David Healy in his collection of interviews, *The Psychopharmacologist*s. London: Altman (1996).

[18] Read "Antidepressant Induced Suicidality" by David Healy in *Primary Care Psychiatry, 6* (2000).

[19] Read "Murder, Suicide" by Sarah Boseley in *The Guardian* (Monday June 11, 2001).

[20] Go to http://www.quitpaxil.org/.

[21] Emphasis in original; quoted in Medawar (1997); find at www.socialaudit.org.uk.

[22] Read "Gradual Withdrawal of Diazepam after Long-Term Therapy" by P. Tyrer and R. Owen in *The Lancet* (June, 1983).

[23] See David Healy's *The Antidepressant Era*.

[24] See "Prozac (Fluoxetine, Lilly 110140), the First Selective Serotonin Reuptake Inhibitor and an Antidepressant Drug: Twenty Years Since its First Publication" by D. T. Wong et al. in *Life Sciences*, *57* (1995).

[25] See David Healy's *The Antidepressant Era*.

[26] ibid.

[27] ibid.

[28] As a review of antidepressant effectiveness in the *Journal of the American Medical Association* concluded in 1964, "depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self-limited and the spontaneous or placebo-induced improvement rate is often high. For example, in a series of nine controlled studies on hospitalized patients, 57% of the patients given placebo therapy showed improvement in two to six weeks." J. O. Cole, "Therapeutic Efficacy of Antidepressant Drugs, a Review," *JAMA, 190,* (1964).

[29] Praise for SSRIs from an on-line chat session; quoted in Medawar (1997).

[30] April 9, 1999.

[31]Read " Listening to Prozac and Hearing Placebo" by I. Kirsch & G. Sapirstein in *Prevention and Treatment*, an on-line journal of the American Psychological Association (June, 1998; find to: www.apa.org); Kirsch and Sapirstein reported that nearly all the variation in the efficacy of antidepressants across studies could be accounted for by variation in the magnitude of the placebo effect; they also found that active placebos -- drugs that should have no pharmacological or clinical efficacy in the treatment of depression -- were just as effective as were the antidepressants. See also, S. Fisher & R. P. Greenberg, *The Limits of Biological Treatments for Psychological Distress*. Hillsdale, NJ: Erlbaum (1998); for an excellent overview of these ideas, see S. Fisher & R. Greenberg's "Prescriptions for Happiness" in *Psychology Today* (September/October, 1995).

[32] Read Breggin (1994).