The SSRI Issues

In the course of the 1990s, the antidepressant group of drugs known as the SSRIs – Selective Serotonin Reuptake Inhibitors – Prozac, Zoloft and Paxil became household names. These drugs came from obscurity to being among the best-known drugs on the planet.

But where antibiotics removed certain diseases completely, in the 1990s we have become more depressed. With the SSRIs, we entered an Age of Depression despite the existence of these "happiness" pills.

There is no account of what has been happening to us during this period, even though the SSRIs have given rise to a new language in which we understand ourselves – a biobabble to replace the psychobabble of Freudian terms that so coloured our identities during the 20th Century.

These drugs have given rise to hundreds of legal actions following suicides and homicides, one of which the Tobin versus SmithKline case resulted in a first ever finding against a pharmaceutical company for a psychiatric side-effect of a psychotropic drug. In addition, the spectre of dependence hangs over these drugs, with a recently filed class action for physical dependence on Paxil/Seroxat.

These drugs have also appeared to play a central part in a growing set of issues in the world of academic medicine, surrounding academic freedom and the changing face of the scientific literature. There are increasing concerns that a considerable proportion of the therapeutics literature may be ghost written and in general that the data from clinical trials, which is voluntarily contributed by the patients seeking healthcare, has become the property of pharmaceutical companies. The fact that much of our data never sees the light of day may in fact put those of us who seek help in a state of legal jeopardy. The definitive history of this group of drugs remains to be written. The following history aims at starting the

The History of the SSRIs

The scientific literature does not carry many full-page corrections, but in 1997 a full page "Correction" appeared in the journal Life Sciences[i]. The correction referred to an article published in 1995 by David Wong, Frank Bymaster, and Eric Engleman from Eli Lilly entitled "Prozac, The First Selective Serotonin Reuptake Inhibitor And An Antidepressant Drug 20 Years Since Its First Publication"[ii]. The authors of the correction, Arvid Carlsson and David Wong agreed that the 1995 article might have given the misleading impression that Prozac was the first of the SSRIs.

Prozac was neither the first made SSRI, nor the first patented, nor the first put into clinical trials, nor the first launched. It was one of a set of siblings, including Paxil, Zoloft, Luvox and Celexa, most of which have since become household names and two others, Zelmid and Indalpine. Each of these siblings was to have a distinctive personality; from the start, Paxil raised questions about dependence, Luvox was brilliantly niche-marketed for OCD, Zelmid was a casualty of side effects while Indalpine was attacked by antipsychiatry fringe groups. The career of each of the siblings prefigured some aspect of what was later to happen to Prozac.

The origin of the SSRIs lies in 1967. Following early studies with imipramine, Paul Kielholz became the Professor of Psychiatry in Basel. Given the presence in Basel of the major Swiss chemical companies, Kielholz was well placed to become a leading figure in the world of psychopharmacology. Depression was his area of interest. He believed that it was under recognized and poorly treated. As part of his philosophy, Kielholz believed that more had to be done than to simply teach physicians to detect depression and put patients on treatment. Different antidepressants did quite different things, he argued, and it was important to select the right antidepressant for the right patient[iii].

In Kielholz's schema, some drugs such as the MAOIs and desipramine acted by being drive enhancing. Other drugs such as trimipramine got patients well by their sedative effects. But antidepressants also had some other action on mood or emotions that appeared to be important, and clomipramine appeared to have more of this other mysterious action than other antidepressants did.

This was a striking observation. By the mid-1960s, the MAOIs were rapidly disappearing from clinical practice because of worries about a dangerous interaction between them and cheese[iv]. Their demise left the TCAs on the market as the gold standard antidepressants. The structure of the classic tricyclic molecules suggested a set of keys to the same lock. Schildkraut's Catecholamine theory outlined in 1965 claimed that the one thing all these agents did in common was to inhibit norepinephrine reuptake. Kielholz's key insight in contrast was that despite these appearances, these drugs were in fact doing quite different things.

Stimulated by the new drugs, a new generation of neuroscientists was emerging. One of these was Arvid Carlsson from Sweden. Carlsson had a string of early research successes to his credit, including participation in a key project that demonstrated the existence of neurotransmitter pathways in the brain. He had discovered dopamine in the brain and was among the first to suggest that it might be abnormal in Parkinson's Disease, speculations that led to a Nobel Prize[v]. In addition, by this time he had put forward the first evidence in what later became the dopamine hypothesis of schizophrenia[vi].

Faced with Kielholz's schema in the late 1960s, Carlsson immediately saw a connection between the different effects of antidepressants proposed by Kielholz and the effects of these same drugs on various neurotransmitter systems. The tricyclics that Kielholz claimed were drive enhancing had effects on the norepinephrine system, whereas clomipramine in particular had effects on the serotonin system[vii]. This led Carlsson to suggest that it would be worth developing drugs that only inhibited the reuptake of serotonin. A drug like this might help clarify the nature of what this other mysterious action that antidepressants had might be, and it might also produce a useful agent for the treatment of depression.

But being able to detect an effect when a drug is acting on a brain system logically assumes there is no abnormality in that system. If the SSRIs corrected an abnormality in the serotonin system all that would show up was normalization of the person being treated. Kielholz's claim, in contrast, was that drugs active on the serotonin system were detectably doing something different to other drugs. If there were an abnormality of the serotonin system, which SSRIs corrected, these should be among the most potent drugs to treat depression, whereas in fact they are among the weakest, with little evidence that they work in cases of severe depression. If Kielholz and

Carlsson are right and SSRIs do something different to other antidepressants, if for instance they produce some kind of anxiolysis, one might expect them to be useful across a range of mixed anxiety and depressive states rather than just for depression. This is exactly what is found.

Zelmid – the First SSRI

In the late 1960s, following Kielholz's lead, Carlsson, working with Hanns Corrodi and Peder Berndtsson at Astra's plant in Hässle in Sweden, took the anti-histamine chlorpheniramine and manipulating the molecule, came up with compound H102-09, later called zimeldine and finally given the brand name Zelmid[viii]. Carlsson applied for a patent on Zelmid in Sweden, Belgium and Great Britain as a selective serotonin uptake inhibitor on April 28th 1971. The first patent was published in March of 1972. Prozac was patented in 1974.

Zelmid went into clinical trials, where it was compared with the norepinephrine reuptake inhibitor desipramine. The trials were short, and they were not conducted in severe depression. The first results were presented in 1980 and Zelmid was launched in Europe at a meeting in 1982. The first trials of Prozac in depression were not published until 1985 and it was launched in 1988.

Due to vigorous promotion, Zelmid began to be prescribed widely. Clinicians were interested to know what effects this genuinely novel drug had. It caused more nausea and insomnia than previous antidepressants but it also appeared to help some people who hadn't responded to other drugs and it looked set to have a place in the market.

Astra had signed a co-marketing agreement with Merck to market Zelmid in the United States. Had this happened, there would probably never have been a Prozac phenomenon. Merck at the time were the largest pharmaceutical company in the world and recognized as marketers par excellence. In 1982, six years before the launch of Prozac in the United States, the data on Zelmid was delivered to the FDA. Just at this time, however, it became clear that Zelmid could in rare cases cause a serious neurological disorder called Guillain-Barré Syndrome. This potentially fatal disorder led to the immediate removal of the drug from the market[ix].

Astra had already begun the development of a derivative of Zelmid, called alaproclate, when Zelmid ran into trouble. Alaproclate was being investigated for both depression and Alzheimer's disease. But it caused liver problems in one strain of laboratory mice and this was enough to lead Astra to drop it[x]. Shortly after this, Astra introduced an innovative antipsychotic, remoxipride, which looked like it would have significantly fewer side effects than older agents. Several months after its launch, however, remoxipride was reported to cause aplastic anemia in a small number of people and it too was withdrawn.

In the face of this series of setbacks, Astra contemplated withdrawing from the research-based pharmaceutical market, in favor of a focus on over-the-counter medicines. Around 1990, it was estimated that new FDA regulations and other hurdles to drug development meant that the cost of bringing a drug to market had rocketed to $300 million[xi]. With these costs, no company can easily survive the loss of its flagship compounds. Astra only kept going because they also had a breakthrough anti-ulcer drug, the first of the proton-pump inhibitors, omeprazole[xii], which in 1990 was on its way to becoming one of the best-selling drugs on the market. Despite the revenues from omeprazole, Astra were forced into a merger later in the decade. This story indicates how big the stakes can be. A troublesome side effect emerging early in the life of a new compound can lead to the demise of a company.

If the side effect that emerges is one that can be portrayed as part of the disease being treated, for example, suicidality on an antidepressant, what would a company do if the alternative is to have the company go down the tubes? This is the ethical dilemma that has faced all of the SSRI companies. It is a dilemma that has been set up in part by the current patent system.

The history of Zelmid contains two points of special note given the story to come about Prozac and suicide. During the clinical trials and post-launch studies for Zelmid, a greater number of suicide attempts were noted among patients on Zelmid than had been expected. No one knew what to make of this at the time, especially as the same trials indicated that some of the people who did best on Zelmid had been those who were more suicidal to begin with[xiii]. Lilly was later to run into serious difficulties getting a license for Prozac in Germany. For many outsiders later, it was to be something of a mystery as to why German regulators presented with similar data on Prozac came to a different answer about its suicide risk than regulators in America.

The Germans, however, had prior exposure to zimeldine and fluvoxamine, whereas Prozac was the first SSRI the FDA was faced with.

The second point is this. While Carlsson spent two years in correspondence with senior executives in Lilly before the paper correcting the misleading impression as to who had discovered the SSRIs was published, in fact, there had been relatively selective serotonin reuptake inhibitors on the market long before Carlsson's work. In order to produce zimeldine, Carlsson and colleagues manipulated the structure of an existing antihistamine, chlorpheniramine. This was a potent serotonin reuptake inhibitor that in subsequent clinical studies has been shown to have many of the properties of the SSRIs[xiv]. It is effective in treating anxiety disorders and panic attacks, for example. If companies or scientists had simply wanted SSRIs to see what effects these new compounds might have, they didn't need to go to the trouble that many of them did to create new drugs. The primary difference between chlorpheniramine and zimeldine was that zimeldine was a new molecule. This allowed Astra to take out a patent on the new compound. The patent system offers the possibility of huge returns but it also brings responsibilities, which Astra had to acknowledge.

Indalpine & Psychiatry under Siege

Another manipulation of the antihistamines, stimulated by Carlsson and Kielholz's observations, produced Indalpine[xv]. Gerard le Fur, first developed Indalpine in one of the oldest French pharmaceutical companies, Fournier Frères, a division within Pharmuka. Pharmuka and Indalpine were then taken over by Rhône Poulenc, who fast-tracked Indalpine's development. It went into clinical trials in France and, under the trade name Upstene hit the market in France and a number of other European countries just after Zelmid. Indalpine was greeted enthusiastically by French psychiatrists. It produced responses in patients who hadn't responded to other drugs[xvi].

But then Indalpine ran into trouble. Clinical trials in other European countries suggested that it might lead to neutropenia – a lowering of the white blood cell count[xvii]. For the most part this is not a serious problem and it happens regularly but transiently with many psychotropic drugs. In rare cases, if undetected, it can be fatal. The discovery that Indalpine produced this side effect however came at the wrong time. Out of the blue, to the astonishment of most French psychiatrists, Indalpine was removed from the market.

French clinicians were extremely upset and lobbied the company and the government to maintain Indalpine on the market. The experience of Pierre Lambert from Lyon in the south of France was fairly typical. He and his colleagues had investigated more psychotropic drugs before launch than any other group in either Europe or America[xviii]. They had had dramatic results with Indalpine. It was both effective and was doing something quite different from other drugs – as might be expected, given the rationale for developing SSRIs. This was symbolized for them in the suicide of one of their patients. Chronically depressed, she had been transformed by Indalpine. When the drug was withdrawn from the market, she relapsed. Nothing else appeared to make any difference. She kept going in the hope that the drug might be restored to the market, but when it wasn't, she committed suicide. Her suicide note asked that instead of flowers, a headstone, or anything else at her funeral, a collection should be made for medical research. Her family later donated the suicide letter and the proceeds of the collection to research.

Indalpine had been borne at the wrong time. This was a time when the development sequence for compounds had not been set in stone. Animal studies aimed at detecting problems could continue in parallel with studies in people. The toxicology studies in animals that were still ongoing when the drug was launched clinically eventually raised the possibility of potential liver problems as some of the animals went on to develop liver cancer. There is no guarantee that the same would have happened in humans. But Indalpine may have been a victim of its own success. By this stage it was being prescribed far more widely than Rhône Poulenc had expected and it was therefore a statistical certainty that some of those getting Indalpine would also develop liver cancers. In light of the toxicology data, if even a few liver cancers occurred in people taking the drug, who was to know whether these were simply coincidental or whether they had been triggered by the drug? These are difficult calculations for a company to make. Rhône Poulenc opted to withdraw Indalpine from the French market in 1985.

But there was a subtext to the Indalpine events. While it was removed for one reason, there had also been a campaign against Indalpine and Rhône-Poulenc on account of the neutropenia it could cause. A new group to psychiatry, the 'ecology' movement had taken up this issue in Germany. A range of ecologist or Green groups had emerged in Germany in the 1970s, some of which were descendants of the antipsychiatry protests in 1968 that had contributed to the student revolutions of the 1960s. The ecologists were

against physical therapies in psychiatry. This was a time when campaigning had led to electroconvulsive therapy being effectively banned in a number of countries. Psychiatry was under siege[xix].

In addition to indalpine, the "ecologists" set their sights on another antidepressant – nomifensine. This was the only antidepressant to act on the dopamine system. In a small number of cases it triggered a hemolytic anemia. The drug's manufacturer, Hoechst, knew of fourteen patients who had died while taking the drug; one was the daughter of a politician. Nomifensine was withdrawn. Senior European psychiatrists were reeling at these developments. In the face of this onslaught from "fringe groups", they dug in. This was not a matter of protecting the pharmaceutical industry. This was a case of losing useful drugs. At the time they were removed, there were no other drugs like indalpine or nomifensine on the market.

The ecologists then targeted the best selling antidepressant in Europe, mianserin[xx]. Like indalpine, mianserin could also lower white cell counts. The drug's manufacturer, Organon, received letters pointing out that the drug could trigger this potentially fatal problem. Far from buckling, Roger Pinder, a senior scientist within the CNS division of Organon, supported by many opinion leaders from psychiatry, some of whom would later defend Prozac, responded. The company and its supporters pointed out that all currently available antidepressants except mianserin could be lethal in overdose, so that even if some people did die from white cell problems with mianserin, overall fewer would die using it than would die on any other antidepressant. The Germans were not impressed – death from overdose was not something they were prepared to factor into their equations. Suicide after all was illegal.

Organon's defense worked across Europe, except in Britain, where the Committee on Safety in Medicines wanted it withdrawn. This led to a series of legal cases; Organon made it clear they were prepared to take the matter all the way to the European Court. The situation was unprecedented. In the ordinary course of events, a company faced with regulatory disapproval would comply with what the regulators requested. Eventually Organon won but even though mianserin remained on the market, the disputes led to a collapse of mianserin sales in most countries[xxi].

The Organon defense involved a risk-benefit calculation, in which death from suicide was put in the equation. Once this is done, newer

antidepressants, including both mianserin and the SSRIs, which are safe in overdose, although much more expensive than and no more effective than the older antidepressants, may appear safer overall. This argument was new for regulators, who were being asked to contemplate a scenario equivalent to the Pope being urged to allow condoms on the basis that they minimize the spread of AIDS. The problems arguably were even greater for regulators than for the Pope, in that the regulators were faced with the dilemma that letting a drug with a known hazard onto the market opened them up to legal actions. This was uncharted territory.

With the demise of mianserin, the newly emerging SSRIs benefited from the Organon defense. At meetings in the early 1990s, SSRI company people or friendly clinicians would "scare" anyone supporting the older drugs by asking how they would defend a lawsuit initiated by the relatives of someone who had died from a tricyclic overdose. Safety in overdose became a key card that was played by Lilly in their arguments with the regulators over the safety of Prozac.

Eerily, therefore, the events surrounding indalpine and mianserin put in place a set of jigsaw pieces that gave glimpses of what was later to be the Prozac story. Indalpine had seen the emergence a struggle between the pharmaceutical industry and "fringe groups", between pharmacovigilance divisions within companies and a set of pharmacovigilantes - in Germany, the ecologists; in America, the Church of Scientology. Suicide had become an issue in these debates with a presumption that newer drugs would be better than older drugs. In what now seems an uncanny echo of Pierre Lambert's indalpine patient, Lilly were later to produce a media strategy which emphasized the fact that the people who were going to die as a result of the controversies over Prozac were the depressed people, who because of the controversy were not going to receive it. No one at this point, however, had contemplated the possibility that the newer drugs might trigger suicidality.

The defense of mianserin demonstrated the need for companies to mobilize a coalition of scientists to argue the company's case, a network of "friends"[xxii]. Some of the key players Roger Pinder had brought into the argument were Stuart Montgomery from St. Mary's Hospital in London, John Henry from the Poisons Center in Britain, and Brian Leonard, a pharmacologist from Ireland, later president of the British Association for Psychopharmacology. These were among the people who later played a part in managing the

controversy around Prozac in Europe. A similar network was put in place by Lilly in the United States.

And finally, lawsuits had become a weapon. Companies, from the mid-1980s, would need sophisticated legal advice on how to swim in these new waters.

The Marketing of Luvox.

The first serotonin reuptake inhibitor to arrive and survive on the world market was fluvoxamine. Hendrik Welle from Utrecht and Volkert Classens from the Duphar Laboratories in Weesp, who applied for a patent on it in 1975, developed fluvoxamine in 1973 from the antihistamine tripelennamine[xxiii]. Duphar launched fluvoxamine in 1983 in Switzerland and subsequently in other European countries between 1984 and 1986.

But in Germany fluvoxamine was held up because in clinical trials there had been a higher number of suicides and suicide attempts on fluvoxamine than on the drugs with which it was being compared. Duphar were asked to account for this before the drug would be licensed. Jenny Wakelin working with the company consulted with experts around Europe before coming up with the apparently clinching data. When the trials were re-analyzed focussing specifically on those who were most suicidal to begin with, it appeared that fluvoxamine was more likely to reduce suicidality than the comparator drugs imipramine and amitriptyline. The lesson genuinely drawn by many from this was that the apparently higher rate of suicide attempts on fluvoxamine was a chance development and that in fact SSRIs might be even more anti-suicidal than older drugs[xxiv]. The "experts" were learning how to handle the regulators on this issue.

As with Zelmid before it, there was a natural interest on the part of clinicians to try fluvoxamine. In the 1980s, this meant that the first patients to get a new antidepressant would be patients who were hospitalized with depression, who seemed unresponsive to other therapies. This is not a promising patient group on whom to try out a new drug. It has since become clear that SSRIs do not do very well for in-patient depressions. This lack of response along with a severe nausea in a significant number of patients led to the clinical impression that fluvoxamine was unlikely to make significant inroads into the antidepressant market. It never did.

Another route to salvation, however, opened up for fluvoxamine. By general consent, clomipramine is now viewed as the most powerful antidepressant ever made[xxv]. This tricyclic antidepressant, with actions on both the norepinephrine and serotonin system, was the last of the major tricyclic antidepressants to come to market. Initially, many viewed it as just another me-too drug. The FDA regarded it as the kind of copycat drug they were keen to discourage and accordingly they did not license it.

One man changed that. George Beaumont, a physician with Geigy, became aware of reports that clomipramine might help treat obsessive-compulsive disorder (OCD) based on earlier work by Jean Guyotat in Lyon[xxvi] and Juan Lopez-Ibor in Madrid[xxvii]. He set out to establish a niche for clomipramine in the treatment of OCD, even though OCD at that stage was thought to be a rare disorder and as such not a promising market. Beaumont organized a series of studies and based on the results of these wrote treatment for OCD into clomipramine's licence application in Great Britain. It was licensed for the treatment of both depression and OCD[xxviii].

A further series of studies came from Judith Rapoport at the NIMH, who gave children with OCD either desipramine, which has no effect on the serotonin system, or clomipramine, which at that stage was the most potent serotonin reuptake inhibitor. The study demonstrated conclusively that OCD responded to clomipramine but not to desipramine. The conventional wisdom up till then had been that the early results showing a benefit for clomipramine in OCD were because an "antidepressant" like clomipramine cleared up the mood disorder that went with OCD, and this led to the improvement. But desipramine was also an antidepressant, and Rapoport's study had just demonstrated that it had no effects for OCD[xxix]. There was something distinctive about drugs that were active on the serotonin system.

Following the publication of Rapoport's results and in particular following her book The Boy Who Couldn't Stop Washing, which became a runaway bestseller, the scene quickly changed[xxx]. Rapoport appeared on chat shows like Donahue and Oprah, and OCD, which had formerly been thought to be a rare disorder, came out of the shadows. Many patients who had suffered silently, concealing their rituals and intrusive thoughts from others for fear of being ridiculed or, worse still, being thought to be insane and committed to a hospital, came forward for further studies and for treatment.

Where before OCD had been regarded by companies as even less interesting than they had regarded depression in the 1950s, by the late 1980s under the influence of Rapoport and the success of clomipramine, it had become clear to companies that there was a market worth pursuing. Clomipramine was eventually licensed in the United States for the treatment of OCD rather than the treatment of depression. Meanwhile, Duphar set up a marketing agreement with Upjohn to develop fluvoxamine for OCD and it made its way on to the US market under the brand name Luvox. Luvox was the low profile SSRI, until the shootings at Columbine High School in Colorado, when it became clear that one of the shooters, Eric Harris, was on Luvox. Being used for OCD.

Celexa – The New Kid on the Block

Hans Lundbeck founded Lundbeck in 1915. Based in Copenhagen, the company is now owned by the Lundbeck Foundation. It is not listed on the stock exchange. Its pharmaceutical division was built up after the war by a charismatic chemist PV Pedersen, who had joined the Danish army at the end of the war and was sent into the laboratories of German chemical companies to plunder promising compounds. Pedersen came back with ketobemidon, a painkiller that was to form the basis of Lundbeck's subsequent development[xxxi].

In 1971, the company hired Klaus Bøgesø as a medicinal chemist. Over the years Bøgesø turned out to have a Midas touch at the game of drug hunting, creating more molecules that made it to the market than almost any other medicinal chemist in the field. The challenge facing him in 1971 following his recruitment was to produce a selective norepinephrine reuptake inhibitor. Like other companies at the time, Lundbeck had little interest in an SSRI.

Bøgesø began from an accident in the laboratory. Trying to create a derivative of their norepinephrine reuptake inhibiting antidepressant melitracen, Lundbeck chemists accidentally produced a new chemical – a phenylphthalene. Against all the odds, just like melitracen, this was also a selective norepinephrine reuptake inhibitor. Two potential antidepressants came out of this – talopram and tasulopram, which were pressed into clinical trials. Both however turned out to be energizing, and in a number of cases there were suicide attempts. The fact that there were suicide attempts appeared to confirm another proposal of Paul Kielholz, that activating antidepressants might lead to suicide. Lundbeck's experience suggested that norepinephrine reuptake inhibitors were likely to lead to just this problem.

Lundbeck retreated, scared. If norepinephrine reuptake inhibitors were likely to trigger suicide, the greatest hazard of an antidepressant, then Kielholz's view suggested that an SSRI would be less likely to lead to suicide. Bøgesø's job was to see whether the new series of drugs could be converted into a series of SSRIs. Following a lead from Carlsson on how to do this, he converted talopram into citalopram, the most selective serotonin reuptake inhibitor to come to the market.

The detour through talopram left Lundbeck behind its competitors. In Sweden and a number of other European countries after its launch, nevertheless, citalopram became the best selling antidepressant. Many French psychiatrists felt it was the closest of the remaining SSRIs to Indalpine. When it arrived on the British market, in 1996, it was the 5th of the SSRIs, an aging series of compounds. Few of the professional pundits gave it much of a chance. To the surprise of everyone, however, Lundbeck's strategy was extremely effective. They undercut the cost of the other SSRIs. They promoted themselves as the most selective SSRI and therefore the one least likely to cause side effects. The marketing worked.

In the United States, the story was even more extraordinary. In January of 1998, the New Yorker, carried an article by Andrew Solomon titled "Anatomy of Melancholy"[xxxii]. This gave an account of the author's own depression. Within a month of the article appearing, Solomon received 2000 letters from other depression sufferers. His article was subsequently anthologized in more than thirty books and he was propelled forward as a spokesman for sufferers from depression, in forums such as the American Psychiatric Association[xxxiii]. Clearly he had struck a nerve. One of the striking points in the piece was his description of the effects of Zoloft on him as being like drinking 55 cups of black coffee, with the effects of Paxil being marginally better at the equivalent of 11 cups of black coffee. Users seemed to know about this stimulating effect at a time when both manufacturers and clinicians were denying it[xxxiv].

Even though clinical trial results suggest that, on the black coffee scale, citalopram rates lower than other SSRIs, after trying to negotiate a marketing agreement with Pfizer and then with Warner-Lambert, Lundbeck gave up on the U.S. market. Finally, however, they were seduced into a licensing arrangement with Forrest Laboratories, a small pharmaceutical company, run by a chief executive who appeared confident this drug could

run, even though it would have to come from the back of the field. The chief executive was Howard Solomon, Andrew Solomon's father[xxxv]. Launched in September of 1998, Celexa took off dramatically, confounding expectations. A package of undercutting the price of others and aggressive marketing led Celexa to capture so large a market share that it became front-page news[xxxvi].

Zoloft & The Interface between Research and Marketing.

Pfizer's SSRI sertraline (Zoloft) began life in 1977. Playing around with the nuclei of some of the original antipsychotic molecules, chemists in the company produced a new series of norepinephrine reuptake inhibitors, of which tametraline looked the most promising. Pfizer took tametraline into clinical trials but side effects stopped its development[xxxvii]. One of their chemists Willard Welch then transformed tametraline into a new series of serotonin reuptake inhibitors. By this time, Zelmid had been reported to have antidepressant effects and so this series was taken further, leading in 1979 to sertraline.

Pfizer were some years behind the competition. When Zoloft hit the market in North America in 1992 and in Britain and other European countries from 1990 through to 1993, Pfizer emphasized the pharmacokinetic differences between Zoloft and the other SSRIs – that is the length of its half-life, the routes of its breakdown, and its liability to interact with other compounds in the body. The Pfizer claim was that Zoloft was much less likely to interact with other compounds and as such was much safer than Prozac, for example, which interfered with the breakdown of a range of other compounds and lasted for several weeks in the blood stream.

This was a marketing strategy, which produced lots of data. It produced the appearance of science. But very little of these data were clinically relevant. The approach was geared at making Zoloft appear "clean" compared with Prozac and Paxil. This was a War between Sisters. At repeated seminars, clinicians would be faced again and again with data on the pharmacokinetic properties or receptor profiles of each of these drugs that appeared to sustain claims for minimal advantages of one drug over the other. It was immensely tedious but it worked and Zoloft during the course of the 1990s came to rival Prozac in terms of volume of its sales[xxxviii].

Pfizer had a program called CRAM – Central Research Assists Marketing. All new drugs from early in their development go through this program,

which is headed up by marketers. The significance of this is that the interface between science and marketing gets blurred. For example, after Zoloft's release, Pfizer established a PRIME-MD research program. This aimed at collecting data about primary care depression. It involved educating primary care physicians about the cases collected. This of course made it likely that many of these doctors would go on to treat patients who had been identified as depressed and that Zoloft would be the first drug tried. Another research program, RHYTHMS, was aimed at studying patient education and compliance. Good on paper, the immediate downside to this is that just such a program may lead to patients continuing treatment despite suffering from adverse reactions, in a way that may put them at risk for suicide. The downside to the larger picture is that this is technology being used to boost corporate profits, masquerading as science, rather than a scientific effort to answer clinical questions.

Paxil & The Specter of Dependence

Paroxetine (Paxil) was first developed in 1978 by Jorgen Buus-Lassen and colleagues working in a small Danish company called Ferrosan. Paroxetine, however, was only the second SSRI produced by Buus-Lassen. In 1975, this group had produced femoxetine, which was in clinical trials by the time paroxetine came along. Femoxetine had a disadvantage compared to paroxetine -- it needed high doses, between 300 and 600 mg. It was not going to be a simple once-a-day pill. But its clinical trial portfolio looked better than paroxetine's[xxxix].

Ferrosan sold paroxetine to Beecham pharmaceuticals in 1980. Beecham later merged with SmithKline & French to become SmithKline Beecham (SB) and later at the turn of the millennium with Glaxo to become Glaxo-SmithKline (GSK), at that point the world's largest pharmaceutical corporation. Ferrosan had meanwhile been acquired by Novo-Nordisk, which had little interest in psychiatry, and femoxetine died from neglect.

In the early 1980s, I was based in the Department of Pharmacology in University College Galway, working on serotonin uptake in depressed patients. Rates of serotonin uptake appeared to be low in depression, one of the few things that could be shown to be abnormal in these patients[xl]. This brought me into contact with Beecham and paroxetine. Given my research, it was natural to ask what a serotonin reuptake inhibitor looked like to industry. To my amazement, I discovered that Beecham was considering shelving paroxetine because it didn't appear to be as effective as older

antidepressants in clinical trials. A large Danish study run by the Danish University Antidepressant Group later confirmed this[xli]. This was at a time when the size of the non-hospital depression market still appeared relatively small. It was, therefore, not obvious how a less effective antidepressant, even if it were safer, could be expected to take a significant share in this market.

The clinical development of paroxetine accordingly lagged way behind that of Zelmid and Indalpine and considerably behind that of Luvox and Prozac. Paroxetine ended up being licensed as Paxil in 1993 in the United States and Seroxat in 1992 in the United Kingdom. As part of the effort to make up ground on the others, marketers within what was now SmithKline Beecham coined the acronym SSRI. Compared to the other serotonin reuptake inhibitors, paroxetine was supposedly the selective serotonin reuptake inhibitor – the SSRI[xlii]. The name worked -- too well. It was adopted for the entire group of compounds. In this way, Paxil made Prozac and Zoloft into SSRIs.

The idea of an SSRI conveys the impression of a clean and specific drug that would be freer of side effects than the non-selective TCAs. However, selectivity for pharmacologists and selectivity for clinicians meant different things. For pharmacologists, an SSRI might act on every brain system other than the norepinephrine system and therefore might be in this sense an even dirtier drug than any of the TCAs. Clinicians were misled if they thought that selective meant that these drugs only acted on one brain site, but this was exactly what the marketing of these drugs suggested to clinicians.

Where Upjohn had targeted OCD in an effort to carve out a distinctive identity for Luvox, SmithKline targeted panic disorder, anxious depressions, generalized anxiety disorder and social phobia. When the company got a license to market Paxil for social phobia, its stock rose; an anti-shyness pill was potentially a huge market.

Social phobia had until the 1990s been a condition that was almost unknown in the Western world[xliii]. First described in the 1960s at the Institute of Psychiatry in London by Isaac Marks, social phobia presented rarely to clinics. It would be a mistake to think that SmithKline somehow invented social phobia because in the Far East it appears that social phobias are the most common nervous condition. But there is clearly an overlap between social phobia and shyness. As a consequence, there is a real risk that

legitimate efforts to market a treatment that is of benefit for a disabling medical condition will at the same time capture a significant number of people who are simply shy and may be at more risk from the treatment than from their shyness. Furthermore, the name social phobia apparently did not suit the brave new world, and in the late 1990s the term was jettisoned and replaced by social anxiety disorder. This jettisoning does raise real questions about the culture of psychiatry in the 1990s[xliv].

The targeting of Paxil for anxiety disorders contained a hidden snag, however. Soon after its launch, primary care physicians and others through adverse event reporting systems began to describe patient dependence on SSRIs[xlv]. This began happening first in Great Britain[xlvi]. There was a much greater volume of reports for Paxil than for other SSRIs. This may stem from the short half-life of the drug. The emergence of the specter of dependence with Paxil however may also owe something to the fact that it more than other SSRIs was being used to treat patients who were anxious. Among these were a group of individuals who were particularly likely to develop phobias. If so, why not a withdrawal phobia?

There may be something to each of these explanations, but these are not the whole story. The ability of Paxil to produce dependence even in healthy volunteers who had only been on it for brief periods of time had been noted by SmithKline years before the drug came on the market[xlvii].

With reports of withdrawal symptoms circulating in the mid-1990s, Lilly saw a market opportunity and convened a panel of 'opinion leaders' to discuss the phenomenon of what were termed antidepressant discontinuation syndromes rather than dependence problems. Prozac with its very long half-life seemed less likely to cause this problem than the other SSRIs[xlviii] - or less likely to cause a problem that would be linked to withdrawal. Lilly saw a market opportunity vis-a-vis Paxil and Zoloft, their closest competitors, and began to run advertisements about discontinuation syndromes[xlix].

In so doing however, Lilly pointed to a general problem with the SSRIs, blowing a hole in the process in many of the theories about addiction and dependence. A key reason for the development of SSRIs as antidepressants lay in the fact that clinicians suspected that all anxiolytics or tranquilizers would in due course produce dependence, just as the benzodiazepines and barbiturates had done. In the late 1980s and early 1990s, the antidepressants in contrast were a group of drugs that were not associated with dependence.

Clinicians felt comfortable denying the capacity of these drugs to produce addiction or dependence. When the Royal College of Psychiatrists launched its Defeat Depression campaign in the 1992, it surveyed the population using professional polling organizations and found that most people thought the antidepressants were likely to be addictive. On the basis of this the Royal College felt it was important to emphasize that antidepressants were not addictive. The backs of Prozac packets contain an explicit statement: Don't worry about taking Prozac over a long period of time – Prozac is not addictive.

And indeed the SSRIs are not addictive in the sense that they will transform someone into a junkie, who is likely to mortgage their livelihood and their future for an ongoing supply of drugs. They do not lead to a life of crime or dissolution. But this does not mean that the antidepressants – at least the SSRIs - don't produce significant dependence. SSRI dependence may in fact be more common and serious than benzodiazepine dependence. It may not be possible for many people to get off treatment without great difficulties. In lay terms, you can just as easily become hooked to SSRIs as to benzodiazepines.

Far from the problem with SSRIs being simply one of dependence that emerges on withdrawal from the drugs, these drugs produce what are more appropriately termed stress syndromes. The SSRIs are alien chemicals rather than replacement chemicals, like insulin or thyroid hormone. As such, they are a brain stressor. The consequences of this stress can be apparent in some individuals when the stress is withdrawn and the system attempts to get back into equilibrium. But in others the stresses can be visible during the course of treatment. With the SSRIs, a problem called poop-out had been noted from early on[l]. Poop-out refers to a phenomenon where after time the drugs appear to lose potency and individuals have to increase the doses with successive increases re-instituting response in some cases[li].

As with many of the other problems with the SSRIs, this phenomenon first came to light in Internet chat rooms rather than through physicians being informed by companies of the existence of a problem[lii]. Because companies denied the existence of the problem, they could not advise on the best means of managing it. Clinicians were left to their own devices. This is hardly the kind of partnership that is supposed to characterize prescription-only arrangements.

The Paxil dependence story in fact opened up one of the great mysteries in psychopharmacology, a mystery that is yet to be resolved. In the early 1960s discontinuation problems with antidepressants and antipsychotics had been widely reported. The issue of dependence on these drugs was debated in international psychopharmacology meetings, and agreement was reached that these drugs produced dependence of a different type to that produced by cocaine and the amphetamines on one hand or the opiates, alcohol and barbiturates on the other. Recognition of these dependence syndromes vanished shortly after, however[liii]. Why?

To appreciate this needs some understanding of the history of addiction. Up until the 1950s, addiction was seen largely as a personality disorder. It was only in the 1940s that the work of Abe Wikler and Harris Isbell put the role of withdrawal syndromes to alcohol, opiates, and barbiturates firmly on the map as a cause of dependence. In the 1960s, it was discovered that cocaine and the amphetamines were drugs that animals could be taught to self-administer. The animals apparently developed cravings for these drugs. These drugs had an abuse liability that they in fact shared with alcohol, the barbiturates and the opiates. These discoveries gave rise to the notion of drug dependence and they underpinned some of the definitions of addiction and dependence that were adopted in the 1970s. But according to these criteria, the benzodiazepines were not drugs of dependence as their abuse liability was low in animal models. This was part of the reason the psychiatric establishment reacted with disbelief in the face of criticisms from patient groups and others of therapeutic drug dependence.

However in the 1960s, there had also been a clear recognition that antidepressants and antipsychotics, which did not cause cravings or tolerance, could cause dependence. The recognition of this therapeutic drug dependence vanished by 1970[liv]. The eclipse of therapeutic drug dependence owes a great deal to the growing use of LSD and the hallucinogens as well as opiates and amphetamine in the 1960s by middle-class and student populations. This new use of psychotropic substances contributed significantly to the student revolutions of the late 1960s and the development of anti-psychiatry, which put a range of physical therapies, including ECT and the antipsychotics in the firing line.

Psychiatry somehow had to work out a system to accommodate the fact that all psychotropic drugs ran the risk of producing dependence but yet some

drugs were going to be used therapeutically. Few would argue that there is a God-given order to the universe so that only "bad" drugs cause problems to people. But this is exactly what mainstream clinical practice now argues in practice. Neither DSM-III nor DSM-IV recognizes the possibility of therapeutic drug dependence. Similarly we have difficulties embracing the possibility that "Good" drugs might trigger suicide, but no difficulties in accepting that LSD might do this -- even though there is an overlap between the actions of both LSD and cocaine on the serotonin system on the one side and the SSRIs on the other.

A key feature of the Paxil story is that ultimately dependence on SSRIs is more likely to bring this group of drugs into public disrepute rather than the issue of SSRIs and suicide. Suicide is something that anyone contemplating using an SSRI finds hard to envisage a drug causing, but we can readily envisage getting hooked to a drug and we dread the possibility.

PROZAC[lv]

In the 1960s Eli Lilly's best-selling antidepressant was nortriptyline, a norepinephrine reuptake inhibitor. Lilly was having great problems coming up with another antidepressant to succeed it. In late 1971, biochemists and pharmacists working in their laboratories in Indianapolis in what was then, in terms of central nervous system drugs, a small pharmaceutical company compared to some of the other players in the field, synthesized a range of new compounds, a group of phenoxyphenyl-propylamines from existing antihistamines. Where Carlsson had used chlorpheniramine, Bryan Molloy in Lilly used diphenhydramine.

Molecular synthesis in drug companies in the 1970s was carried out by medicinal chemists putting molecules through a series of reactions to see whether new structures emerged. Biochemists then tested out the impact of the new structures on body systems, in this case the biochemistry of brain neurotransmitter systems. Pharmacologists then submitted the new agents to a range of animal tests in an effort to get some feel for the likely functional or behavioral impact of the new drug in humans.

As the chemist who synthesized the new series of compounds, Molloy was in this literal sense Prozac's creator. One of the 57 phenoxyphenyl-propylamines he produced was given the code LY-94939, another LY-82816. LY-94939, later called nisoxetine, was a selective norepinephrine reuptake inhibitor. Nisoxetine's early laboratory profiling left many happy

that the company finally had the antidepressant it needed. It was moved forward into clinical trials.

Lilly had little interest in a serotonin reuptake inhibitor. But in line with standard practice at the time, the other compounds in the series were investigated. David Wong, a biochemist with little or no experience in psychopharmacology, as something of a sideline tested the series on a serotonin reuptake inhibitor assay. Several of them came out as serotonin inhibitors. LY-82816 stood out from the others as the compound with the least effects on the norepinephrine system. The compound was difficult to work with, as it couldn't easily be dissolved, so it was reformulated as a chloride salt, becoming LY-110140. At this point, work on LY-110140 was an academic exercise, meriting publication in a journal, the first specifically about a serotonin reuptake-inhibiting drug[lvi]. On the basis of this Wong is sometimes described as the discoverer of Prozac.

As reports of Zelmid's progress came through, Frank Bymaster and Ray Fuller looked at LY-110140's effects on behavior. They screened it for antidepressant activity. The best-known screening test involved trying to block the sedative effects of reserpine on animals. All of the antidepressants then on the market did this. LY-110140 didn't[lvii].

Another of the tests employed was a rat aggression model. If a drug made rats more aggressive so that when placed in a cage with other rats they were more likely to attack these other rats, conventional wisdom at the time had it that such drugs were likely to have stimulant properties of a type that might be useful in the treatment of depression. LY-110140 had these properties.

Around 1975, therefore, Lilly had a compound that for its time had a relatively unusual biochemical effect, and some poorly characterized behavioral effects, but was otherwise a mystery. Carlsson's work suggested such a compound might be useful for treating nerves or depression, but most companies at the time were cautious about these claims. They were adopting a wait and see attitude. When it came to putting their eggs in an antidepressant basket, Lilly plumped for nisoxetine.

What was the future for LY-110410, which on September 11th 1975 was first called fluoxetine? There were a number of possibilities. While it had been developed first within the CNS group, drugs active on the serotonin system looked in animal models of the time as if they might have antihypertensive

properties. The market for pills to lower blood pressure was a much greater market than the market for antidepressants. If fluoxetine had shown any clear antihypertensive action in humans, there is little doubt that it would have been developed as an antihypertensive. The "behavioral effects" would have been written out of the script in the course of a market development program, which would have emphasized the rational engineering of a selective anti-hypertensive.

Reserpine, after all, was first of all shown to be an antihypertensive and only subsequently shown to be antipsychotic and antidepressant. Chlorpromazine is also antihypertensive. Most of the antihypertensives currently on the market in fact reduce blood pressure by acting on the brain rather than on blood vessels or the heart. Do some of them have effects on behavior, in contrast to the message of selectivity that company advertising delivers to both prescribers and patients? Almost certainly yes!

There were other lucrative possibilities for fluoxetine. Early screening suggested that the drug might produce weight loss. An anti-obesity agent was certain to make vastly more money than any antidepressant would. The hint that Prozac had weight-reducing properties almost certainly drove some of the early mania, which later helped its marketing to hit the road running. This idea was still a big part of the fluoxetine development program as late as 1990, when the company hoped to licence fluoxetine in a 60mg pill under the trade name Loban for eating disorders. The vast amounts of money to be made in this market made Redux headline news a few years later. Released in 1996, Redux (dexfenfluramine) acted on the serotonergic system in a related manner to the SSRIs. It enjoyed massive sales for Wyeth as an anti-obesity agent. Eighteen months after launch, however, it was found to cause heart valve defects and pulmonary disease with startling frequency[lviii]. It was withdrawn, leaving a huge series of legal actions in its wake[lix].

Perhaps apocryphally, a number of clinical investigators were invited to a consultancy panel meeting in Britain in the late 1970s, one of whom was Alec Coppen, a leading psychopharmacologist and one of the first advocates of the serotonin hypothesis of depression. These investigators were presented with data on a range of Lilly compounds and their possible biochemical and behavioral effects. Coppen recalls suggesting at the meeting that LY-110140 might be an antidepressant only to be met with a reply that if fluoxetine was ever developed, there was little chance it would be for depression[lx].

There were good reasons why Lilly might think this way. In the late 1970s, Bob Shulman coordinated early clinical studies of the drug. These were aimed at testing whether the drug was tolerable and at getting some feel for what its behavioral effects might be in humans. One of the first surprises was that many patients became agitated and akathisic on it. The first clinical triallist was Herbert Meltzer, then a Professor of Psychiatry in Chicago. Meltzer had a long-standing interest in the extra-pyramidal side effects of the antipsychotics. On first testing LY-110410, he thought there had been a mistake when one of his patients developed a dystonic reaction. He was certain that the patient had accidentally been given the antipsychotic haloperidol[lxi]. Other patients in his center subsequently developed akathisia and other extra-pyramidal problems.

Meltzer found little or no effect on depression. Other senior clinicians that had been approached found something similar. Adolph Pfefferbaum had 6 out of 15 patients improved. Joyce Small found 3 out of 11 much improved. James Claghorn found 2 out of 7 improved and 2 out of 7 much worse[lxii].

Following on Meltzer's study, other patients in other centers were noted to become agitated. This led to recommendations from Lilly monitors that it would be necessary to put at least some patients on benzodiazepines at the same time they were taking fluoxetine[lxiii]. One of the far-reaching implications of this is that there is probably no clinical trial in which fluoxetine on its own compared to placebo has been shown to be an "antidepressant". In the patient group fluoxetine was later given to, benzodiazepines may well have been just as effective as fluoxetine itself.

In addition to early clinical trials aimed simply at trying to determine how tolerable fluoxetine was for psychiatric patients, Lilly was trying to establish whether there were any conditions for which it was a suitable treatment. The company persuaded clinicians to try it out in patients with atypical psychotic disorders as well as patients hospitalised with depressive disorders. It turned out to be ineffective in these groups. It made patients with psychotic features worse and it has never since been shown to work for hospital depression. The development of fluoxetine was at a crisis point. Irwin Slater, a veteran of drug development within the company, was drafted in to take over the clinical trials program. He tried fluoxetine out for pain syndromes, dystonia, and obesity, with no great luck[lxiv].

Senior management within the company opted to shelve the compound. Slater and Fuller were keen, however, to keep the project going. They pointed out that zimeldine was almost through a clinical trials program for depression and that fluvoxamine was not far behind. The hierarchy in the company relented. A clinical trial program began chasing milder depressions. Louis Fabre, who was later investigated by Upjohn for "recruiting patients from a half-way house for alcoholics",[lxv] was approached. He gave fluoxetine to five patients; all responded. This turned the tide.

With fluoxetine rescued the next thing to think about was how to brand it. Lilly turned to Interbrand, who later claimed they invented the "discipline of naming" in the late 1970s[lxvi]. The success of the name Prozac, in fact, played a part in shifting how drugs were named. James Singer, who later left Interbrand to set up his own NameBase/MediBrand, worked on the fluoxetine project[lxvii]. Prior to Prozac, drugs had a name that sounded scientific and referred in some way to the actual compound. Unlike Luvox or Zelmid, for instance, which clearly referred to the original pharmacological name, the name Prozac was seemingly designed to convey professionalism through its Pro- element, and the ability of the medication to target the right area for treatment through its –Zac element.

Prozac's close brush with extinction may have had one long-lasting consequence. Many clinicians have wondered why Lilly didn't bring in low doses of Prozac. With a 5 mg dose, for instance, some of the problems, which emerged at higher doses of Prozac, might have been minimized. The conventional explanation was that Lilly had a brilliant marketing strategy, which involved selling one pill at one dose -- something any fool could give. A later deposition of Richard Wood, in the Wesbecker case, a former marketing man, who became chief executive of the company in the late 1980s provides a great deal of evidence for the sales driven one pill fits all formula[lxviii].

But another possibility lies in the alarming early history of Prozac. In an effort to make this drug work, the company pushed the dose up to 80mg a day. In the mid 1980s, as FDA officials were finding it difficult to be certain that even high doses of Prozac worked, a Lilly study demonstrated that the new mild depression market they were investigating 5mg was as effective as 20 or 40mg[lxix]. Joachim Wernicke later in charge of clinical trials in Lilly emailed his colleagues: "How much do we want to say about the 5mg? I

hedged a little, with the thought that we may be able to show that 5mg is not as good on all measures. Some day we will have to report it if we ever want to use the information"[lxx]. In 1986 Stuart Montgomery reported that in milder depression, one per week was as good as 20mg a day[lxxi]. This study vanished quietly, even though in 2001, after Prozac had lost its patent, Lilly were to market a once-a-week form of treatment with Prozac.

Prozac and The Regulators

Lilly and Prozac were ultimately saved by two sets of changes in the clinical trial world. In the United States, federal support for psychopharmacology research had all but shut down by the end of the 1970s. Three things drove this[lxxii]. One was the financial crisis caused by the Vietnam War. Second, the Nixon administration viewed scientists with suspicion. Third, the administration was faced with escalating health service costs. The removal of federal support meant the end of independent clinical trials in psychopharmacology. For many investigators the only way to do research was to participate in industry run trials.

Industry paid clinical investigators up to $5,000 per patient entered into a study, and looked with favor on investigators who were able to recruit patients quickly. The earlier the trials were completed and submitted to the FDA, the better the chances of registering a compound early in its patent life and the better the returns on the investment. Naturally, industry would also look favorably on investigators who managed to produce the right results. This led by the end of the 1980s to a situation where some investigators were reporting on patients who didn't exist or on others who were professional patients who may have been on several investigational compounds at much the same time. In some instances, individuals other than clinicians were conducting both recruitment and ratings[lxxiii].

The second change occurred within the FDA. In 1981, Paul Leber, who had been formerly a pathologist and then a psychiatrist, disenchanted with clinical work in New York, moved to a job in the CNS division of the FDA[lxxiv]. He was quickly promoted to Division Head. Leber became a pivotal figure over the course of the next fifteen years. His first innovation all but brought the house down. Looking at the trials of antidepressants as they had been conducted up till then, Leber made the point that in a trial where a new antidepressant is compared to an older one and shown to be no worse than the older compound -- where everybody assumed that this meant that the new compound worked just as well as the old compound -- it was

quite possible that neither drug was working. It was possible that neither would have done any better than placebo. Proof that a new compound worked only came from trials against placebo.

There was uproar. Many companies had well-developed clinical trial programs for new compounds that did not include placebo trials. In some instances development was set back several years, at a considerable cost. Several new compounds, in particular mianserin, which was the best-selling antidepressant in many European markets, when compared against placebo in U.S. clinical trials, could not be shown to work. As it turned out the mianserin trials probably failed because they were conducted in a too mildly depressed group, where it is difficult to demonstrate that any antidepressant is superior to placebo. But the prospect had been raised that it might become increasingly difficult, indeed almost impossible, for new antidepressants to be registered, owing to difficulties in showing that they were superior to placebo.

This was a real problem for the emerging SSRIs, which couldn't be shown to work in hospital depression. Accordingly Prozac had to tread a tricky path between the Scylla of serious depression, where it didn't work, and the Charybdis of mild depression, where mianserin had come to grief. As an increasing number of the antidepressants coming on stream at this point were SSRIs and by this stage between five and ten years worth of development had already gone into some of them, Leber and the FDA as well as others must have been genuinely concerned that what appeared to be a necessary reform to the system was going to backfire. For a time no new drugs made it to the US market. As it turned out, this probably contributed significantly to the impact that Prozac had when launched in that it was the first antidepressant to hit the US market for what relatively speaking was an extraordinary length of time.

Leber's reforms required that a new drug show evidence from two pivotal studies that it worked and the majority of studies performed should go the same way[lxxv]. The term pivotal study had crept into use as an accepted code for a placebo controlled study.

In the case of Prozac, there were three placebo-controlled studies. Karl Rickels from Philadelphia conducted one and it was negative. A second was a six-centered study, called protocol 27, where Prozac was compared to imipramine and placebo. One of the investigators Lilly turned to was Jay

Cohn from Los Angeles. When it came to submitting the clinical trial portfolio to the FDA, Dr Cohn's study was removed at the request of FDA as the extremely favorable results that he reported were at odds with the other data generated[lxxvi]. Leaving Cohn's results out, when the other studies were combined Prozac was inferior to imipramine and barely better than placebo on a selected group of measures. On others it was no better than placebo. Three of the six centers failed to show it better than placebo. The final study by Louis Fabre was one in which there were only eleven completers on Prozac and the study period was effectively only four weeks in duration. It came up with a positive result for Prozac. With the Fabre study and counting protocol 27 as one study the score was two to one in favor of Prozac. If the component centers of the multi-center study were counted separately, the result was four centers in favor of Prozac and four against, hardly an overwhelming majority of studies.

The plans had been to launch Prozac in the United States in 1986. The FDA finally approved it in late 1987, after a scrutiny lasting over three years, during which serious flaws in the designs of its clinical trials were noted by the agency[lxxvii]. A pattern of approval of less effective antidepressants had begun. Since then it has not been uncommon for new drugs to be presented to the FDA where the new drug can only be shown to be superior to placebo in perhaps two out of six trials[lxxviii]. Rather than saying on balance that the new drug is simply not more effective than placebo or is of such minimal effectiveness that it's hardly worth permitting on the market, the FDA approach is to say that any trials in which the new drug is compared to an older antidepressant and this older drug appeared no different to placebo were failed trials. The trial rather than the new drug has failed.

Some of the ambiguities in the regulatory process came clearly to light with the application of Zoloft for a license. In this submission, only one of six studies stood out as clearly indicating a superiority of Zoloft over placebo. It did less well than amitriptyline when it was compared to that and it failed in two hospital depression studies[lxxix]. As Paul Leber ended up putting it: "how do we interpret.. two positive results in the context of several more studies that fail to demonstrate that effect? I am not sure I have an answer to that but I am not sure that the law requires me to have an answer to that -- fortunately or unfortunately. That would mean, in a sense, that the sponsor could just do studies until the cows come home until he gets two of them that are statistically significant by chance alone, walks them out and says he has met the criteria"[lxxx].

For those who believe that approval of a drug by the FDA means that it is in some sense good for you if taken properly, the situation is even more problematic than the above scenario might suggest. The two positive studies being referred to are not studies showing that the drug works for depression, they are rather two studies in which the drug can be shown to have an effect in depression. Whether it is a good idea to take any of these drugs is not addressed by any of these studies. These trials do not offer evidence in other words that the drug works in the sense that most people mean by the word "works" – that is clears the problem up.

Companies subsequently marketing their product do not have to reveal anything about the very weak evidence on which registration was based. The new compound can be sold with all the glossy slogans of rational engineering, hints of added benefits for weight loss or whatever, and celebrity endorsements. And since the end of the 1980s, companies have not had to bother about any questioning voices coming from independent investigators about just how good their compound really is. There are few independent investigators left in psychopharmacology[lxxxi].

Adopting the same principles in trials for mild to moderate depression, it would almost certainly be possible to show that stimulants such as dexamphetamine or methylphenidate are "antidepressants". It might even be possible to show that nicotine and a range of other drugs were antidepressants. Using these rules, in a population of mild to moderately depressed patients, the benzodiazepines would come out as "antidepressant". The fact that no one has done these trials owes everything to a business calculation. These older drugs are off patent, and no company stands to make money from them.

A key point to take from all this is the following. We have gotten used to the notion that our regulators, the FDA for instance, are looking after us. That they are acting in some sense as a consumer watchdog. But this is not their role. The role of a regulator is to adjudicate on whether this yellow substance meets minimal criteria for butter; to ensure for example that it is not lard injected with color. The regulators are not called upon to make any determinations as to whether the butter is good butter or not. Consumer watchdogs can do that. Within medicine, the physician is supposed to be the consumer's watchdog, which given that they never consume the product makes for an ambiguous situation.

Launch

Prozac was launched in the United States in 1988. In the United Kingdom, the plans had been for a launch in 1984, but it was late in 1989 before this materialized[lxxxii]. The U.K. was seen as quick to approve drugs at the time, with the FDA being widely criticized for taking much longer than other countries' regulatory authorities. Prozac bucked the trend.

In line with a strategy developed in 1983, the early sales pitch in most countries stressed that Prozac lacked the supposedly "nasty" anticholinergic and sedative side effects of the older tricyclic antidepressant drugs. That it was as efficacious as these drugs, but came in a convenient once-daily dosing[lxxxiii]. And borrowing from the mianserin story, there was a new emphasis on safety in overdose. Market surveys before launch had repeatedly asked people like me whether the fact that this new drug would not be associated with weight gain would influence our prescribing. I said no, completely miscalculating the response from patients when they heard about this feature of Prozac. By the time it was launched in Britain, word was filtering through from America that patients were lining up asking for Prozac by name, an experience that was new to American psychiatrists.

Over the course of the following few years, each of the companies with SSRIs ran clinical trials comparing their drug with the older tricyclic antidepressants. The marketing efforts were based on these trials. When all clinical trials were analyzed together, the SSRIs were no more effective in outpatient depressions than the older agents[lxxxiv]. As for the tolerability profiles of the SSRIs compared with the older drugs, the dropout rate of patients from clinical trials was almost equal – it would take over 30 patients assigned to either set of drugs before there would be one less dropout in the SSRI group, even though these trials were almost exclusively designed by SSRI companies, so that in over 30% of trials, the SSRI had been pitched against the tricyclic generally thought to have the most side effects -- amitriptyline.[lxxxv]. There was therefore an extraordinary contrast between the marketing hype and the trials underpinning it. When these studies were analyzed, the greatest predictor of the outcome lay in the sponsorship details of that study[lxxxvi]. Later in the decade it became clear that a large number of trials with less favorable results for the SSRIs were simply not reported and that the results on quality of life scales used in many of these trials were almost universally left unreported.

The trump card of the SSRIs has been that a greater number of patients are likely to be put on and remain on what is thought to be a "therapeutic dose" of drug than happens with other agents. But even here, the puzzle is that no more than 40% of patients take their drugs for more than few weeks[lxxxvii]. Something goes wrong with the other 60%. This "something" tempts clinicians to blame patients and tempts the "experts" in the field to blame the average clinician, who supposedly hasn't signed up to the need to stress to the patient the importance of remaining on treatment for six months or more. Nowhere in the literature is there any concession to the possibility that SSRIs may not suit up to 60% of those put on them.

How can this lack of clinical trial evidence for Prozac and other SSRIs be reconciled with clinical experience that suggests these drugs can work dramatically well for many patients? Surprisingly, a study done in my department was to end up producing more conclusive trial evidence that the SSRIs work than the trials that either Lilly or Pfizer had submitted to the FDA.

By the time Prozac got its licence, the crisis with the benzodiazepines had become severe. The psychiatric and primary care worlds were receptive to the idea that behind every case of anxiety lay a case of depression. No one was inclined to question the idea that antidepressants were a more scientifically rational treatment for many of the nervous states presenting in the community than anxiolytics. There was the extra benefit to the new antidepressants -- no one expected an antidepressant to produce dependence. Furthermore, compared with the older antidepressants, these new drugs were safe in overdose and therefore could be used safely in the treatment of suicidal patients. The fact that they had never been shown to work in a group of patients who were suicidal or in any group of patients who were severely depressed was quite another matter.

The plans had been to launch fluoxetine in Germany in 1984 but it took six more years for 'Fluctin' to reach the market there. There were probably very few people outside of Eli Lilly who knew of the view of the German regulators on fluoxetine as of May 1984: "Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression"[lxxxviii].

[i] Carlsson A, Wong DT. Correction. A note on the discovery of selective serotonin reuptake inhibitors. Life Sciences 61, 1203 (1997)
[ii] Wong DT, Bymaster FP, Engleman EA. Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. Life Sciences 57, 411-441 (1995)
[iii] Kielholz P. Diagnose und Therapie der Depressionen fur Praktiker. J F Lehmanns, Munchen (1971)
[iv] Blackwell B. The process of discovery In Ayd FJ, Blackwell B (eds.). Discoveries in Biological Psychiatry, Lippincott, Phila Pa., pp. 11-29 (1970)
[v] Arvid Carlsson was awarded a Nobel Prize in 2000
[vi] Carlsson A, The Rise of Neuropsychopharmacology: Impact on Basic and Clinical Neuroscience. In Healy D, The Psychopharmacologists vol 1. Arnold, London pp. 51-80 (1996).
[vii] The articles first demonstrating these biochemical properties are Carlsson A, Corrodi H, Fuxe K, Hokfelt T. European Journal of Pharmacology 5, 357-366 & 367-373 (1969)
[viii] The Zimeldine story and details of the drug can be found in Carlsson A, Gottfries C-G, Holmberg G, Modigh K, Svensson T, Ogren S-O. Acta Psychiatrica Scandinavia, volume 63, supplement 290 (1981)
[ix] See Iversen L. Neuroscience and drug development. In Healy D, The Psychopharmacologists Vol 2, Arnold, London, pp. 325-350 (1998)
[x] I owe some of these details to Sven Ove Ogren of Astra.
[xi] With figures like this, its difficult to disentangle true development monies from marketing and other costs.
[xii] The trade name for omeprezole in the US is Prilosec and in many European countries is Losec.
[xiii] Montgomery SA, McAulay R, Rani SJ, Roy D, Montgomery DB. A double blind comparison of zimeldine and amitriptyline in endogenous depression. Acta Psychiatrica Scandinavia 63, supplement 290, 314-327 (1981)
[xiv] Hellbom E, Humble M, Larsson M. Antihistamines, SSRIs and Panic Disorder. Presented at the 26th Annual Meeting of the Scandinavian Society for Psychopharmacology (1999)
[xv] Through the 1970s, many companies developed SSRIs. In some instances this was simply an academic exercise to produce a behavioral probe. Serotonin was not the fashionable neurotransmitter. The general consensus was that what was needed were norepinephrine reuptake inhibitors. Ciba-Geigy, for instance, produced a series of the most potent SSRIs ever synthesized but none were developed. Pfizer, Lundbeck and Lilly were all involved in producing norepinephrine reuptake inhibitors, a process, which coincidentally gave rise to SSRIs. Some of these SSRIs, including Prozac, on toxicological testing on dogs caused the appearance of vesicles in the lipid layers of the brain. No one was certain what this meant at the time. Some companies abandoned the development of their SSRI at this point, where others persisted. There appears to be no clear connection between this phenomenon in dogs and any comparable phenomenon in humans. However, drugs active on the serotonin system do appear, in what may be susceptible individuals only, to produce extensive pruning of nerve endings. This has been described clearly for Ecstasy and for some SSRIs. Any problems that occur with ecstasy, which acts on the serotonin system, may well also happen with SSRIs. Considerable efforts are put in by the scientific establishment to detecting the scary facts to do with illegal substances, with little effort to see whether comparable changes may be happening on therapeutic drugs. See Kalia M, O'Callaghan JP, Miller DB, Kramer M. Comparative study of fluoxetine, sibutramine, sertraline and dexfenfluramine on the morphology of serotonergic nerve terminals using serotonin immunohistochemistry. Brain Research 858, 92-105 (2000)
[xvi] On Indalpine – see CLRTP. The Birth of Psychopharmacotherapy; explorations in a New World, 1952-1968. In Healy D, The Psychopharmacologists Vol 3 Arnold, London pp. 1-54 (2000) & Simon P. Twenty-first century drug development. In Healy D, The Psychopharmacologists Vol 3, Arnold, London pp. 523-542 (2000)
[xvii] Naylor G, Martin B. A double-blind trial out-patient trial of Indalpine Vs Mianserin. British Journal of Psychiatry 147, 306-309 (1985)

[xviii] CLRTP. The Birth of Psychopharmacotherapy; explorations in a New World, 1952-1968. In Healy D, The Psychopharmacologists Vol 3 Arnold, London pp. 1-54 (2000)
[xix] Healy D. The Creation of Psychopharmacology. Harvard University Press, Cambridge Mass (2002)
[xx] On the mianserin and other "hysterias" see Pinder R. Approaching rationality. In Healy D, The Psychopharmacologists Vol 2, Arnold, London, pp. 581-605 (1998). See also Pinder R. The benefits of risks of antidepressant drugs. Human Psychopharmacology (1987)
[xxi] The company later brought out mirtazapine (Remeron), a closely related molecule, which at the time of writing had not achieved the same level of sales as mianserin.
[xxii] Pinder R. Approaching rationality. In Healy D, The Psychopharmacologists Vol 2, Arnold, London, pp. 581-605 (1998)
[xxiii] I owe many of these details and others to Klaus Bogeso, Roger Pinder, Arvid Carlsson or Jorgen Buus-Lassen.
[xxiv] Wakelin JS. The role of serotonin in depression and suicide. Do serotonin reuptake inhibitors provide a key? In Gastpar M, Wakelin JS (eds.). Selective serotonin reuptake inhibitors: novel or commonplace agents. Basel, Karger, pp. 70-83 (1988)
[xxv] Pichot P. The discovery of chlorpromazine and the place of psychopharmacology in the history of psychiatry. In Healy D, The Psychopharmacologists Vol 1, Arnold, London. pp. 1-21 (1996)
[xxvi] CLRTP. The Birth of Psychopharmacotherapy; explorations in a New World, 1952-1968. In Healy D, The Psychopharmacologists Vol 3 Arnold, London pp. 1-54 (2000)
[xxvii] Lopez-Ibor J Jr. In Healy D, The Psychopharmacologists vol 2, Arnold, London pp. 409-434 (1998)
[xxviii] Beaumont G, Healy D. The Place of Clomipramine in the development of Psychopharmacology. Journal of Psychopharmacology 7, 383-393 (1993). See Healy D. The Antidepressant Era, Harvard University Press, Chapter 6 (1997)
[xxix] Rapoport J. Children, phenomenology and psychopharmacology. In Healy D, The Psychopharmacologists Vol 3, Arnold, London pp. 333-356 (2000)
[xxx] Rapoport JL. The Boy Who Couldn't Stop Washing. EP Dutton, New York (1989)
[xxxi] Pedersen V, Bøgesø K. Drug Hunting. In Healy D, The Psychopharmacologists, vol 2, Arnold, London pp. 561-580 (1998)
[xxxii] Solomon A. Personal History. Anatomy of Melancholy. The New Yorker, January 12th pp. 47-61 (1998)
[xxxiii] Solomon A. Address to American Psychiatric Association, Chicago May (2000)
[xxxiv] This later became a book Solomon A (2001). The NoonDay Demon.
[xxxv] Berfield S (2002). A CEO and his Son. Business Week May 27th 2002, pp 72-80.
[xxxvi] Kirkpatrick D. Inside the Happiness Business. New York, May 15th pp. 36-43 (2000)
[xxxvii] Welch W. Discovery and preclinical development of the serotonin reuptake inhibitor sertraline. Advances in Medicinal Chemistry 3, 113-148 (1995)
[xxxviii] Woolley S. Science and Savvy. Forbes January 11th pp. 122-127 (1999)
[xxxix] On femoxetine see Buus-Lassen J et al. Comparative studies of a new 5HT (serotonin) – uptake inhibitor and tricyclic thymoleptics. European Journal of Pharmacology 32, 108-115 (1975); On paroxetine see Buus-Lassen J. Introduction to the development of paroxetine, a novel antidepressant. Acta Psychiatrica Scandinavia 80, supplement 350, page 13 (1989). The entire supplement is given over to development work on paroxetine.
[xl] Healy D, Leonard BE. Monoamine transport in depression: kinetics and dynamics. J Affective Disorders 12, 91-105 (1987). It is now clear however that this does not prove there is anything wrong with the serotonin system in people who are depressed.
[xli] Danish Universities Antidepressant Group. Paroxetine. A selective serotonin reuptake inhibitor showing better tolerance but weaker antidepressant effect than clomipramine in a controlled multicenter study. Journal of Affective Disorders 18, 289-299 (1990). See Bech P. Measurement and organization in psychopharmacology. In Healy D, The Psychopharmacologists Vol 2, Arnold, London, pp. 499-520 (1998), for an interpretation of this and related studies.
[xlii] The model company marketers had in mind around 1990 when the acronym was first coined was a model in which billiard or snooker balls being potted cleanly in pockets stood for the process of neurotransmission. This was a model that was to later recur in direct to consumer TV adverts for modern medicines put out by the Pharmaceutical Manufacturers of America. Intriguingly the first use of this model to describe the process of neurotransmission may have

been in a London Weekend Television series of programs called How to Stay Alive, which first aired in 1979 – details from Thelma Rumsey, a science researcher for LWT and later BBC..

[xliii] See Healy D. The Antidepressant Era, Harvard University Press, chapter 6 (1997)

[xliv] Healy D (2001). Have drug companies hyped social anxiety disorders to increase sales? Yes. Marketing hinders the discovery of long-term solutions; Response from David Sheehan. Western Journal Medicine 175, 364-365.

[xlv] Medawar C. The Antidepressant Web. International J of Risk & Safety in Medicine 10, 75-125 (1997)

[xlvi] The issue of physical dependence to all SSRIs was raised most clearly within Great Britain by Charles Medawar, who had been an active player in the benzodiazepine dependence story. Medawar wrote to the Royal College of Psychiatrists, the Committee of Safety for Medicines in Britain, the Medicine Control Agency and others noting the similarities in the emergence of a dependence problem with the SSRIs to the way the story had unfolded in the case of the benzodiazepines. His letters and their replies are laid out in fascinating detail on his website - Socialaudit.org.uk.

[xlvii] Healy D (2001). Deposition & Trial Transcript in Tobin v SmithKline. Available on request.

[xlviii] Rosenbaum JF, Fava M, Hoog SL, Ashcroft RC, Krebs W. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomised clinical study. Biological Psychiatry 44, 77-87 (1998). See also Socialaudit.org.uk.

[xlix] Among the insider takes on this I have heard it said that the dependence story began to play at a time when Prozac was at real risk of being overtaken by Paxil and/or Zoloft.

[l] Slater L. Prozac Diary. Penguin Books, Harmondsworth, Middlesex (1998).

[li] Healy D, Tranter R. Pharmacologic Stress Diathesis Syndromes. J Psychopharmacology 13, 287-290 (1999); with commentaries by H Ashton, A Young and N Ferrier, R Baldessarini, A Viguera and L Tondo, L Hollister, P Haddad and I Anderson, P Tyrer, pp. 291-298 & Reply by Healy D & Tranter R – In the shadow of the benzodiazepines p 299 See also Healy D The Creation of Psychopharmacology. Harvard University Press, Cambridge Mass (2001). See also Healy D (2001). Psychiatric Drugs Explained. Third Edition. Churchill-Livingstone, Edinburgh, chapter 8.

[lii] Glenmullen J. Prozac Backlash. Simon & Shuster, New York (2000)

[liii] Healy D, Tranter R. Pharmacologic Stress Diathesis Syndromes. J Psychopharmacology 13, 287-290 (1999); with commentaries by H Ashton, A Young and N Ferrier, R Baldessarini, A Viguera and L Tondo, L Hollister, P Haddad and I Anderson, P Tyrer, pp. 291-298 & Reply by Healy D & Tranter R – In the shadow of the benzodiazepines p 299. See also Healy D. The Creation of Psychopharmacology. Harvard University Press, Cambridge Mass, chapter 3 (2001)

[liv] Healy D. The Creation of Psychopharmacology. Harvard University Press, Cambridge Mass (2001)

[lv] Many of the details here come from depositions in the Fentress/Wesbecker trial (see chap 4), taken by Paul Smith and Nancy Zettler on Irwin Slater January 28th & 29th; Ray Fuller April 14th & 15th 1994, and David Wong January 12th & April 13th 1994.

[lvi] Wong DT, Horng JS, Bymaster FP, Hauser KL, Molloy BB. A selective inhibitor of serotonin uptake: Lilly 110140 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. Life Sciences 15, 471-479 (1974)

[lvii] It's failure, and that of other SSRIs, on this test, along with the fact that older antidepressants do not cause marked akathisia, retrospectively suggests that the reserpine test may in fact be a screening test for akathisia rather than for antidepressant activity.

[lviii] Mundy A (2001). Dispensing with the Truth. The victims, the drug companies, and the dramatic story behind the battle over fen-phen. St Martin's Press, New York.

[lix] See Lemonick M. How Mood Drugs Work .. And Fail. Time Sept 29th pp. 75- 82, for an account of this (1997)

[lx] Coppen A. Biological psychiatry in Britain. In Healy D, The Psychopharmacologists Vol 1, Arnold, London pp. 265-286 (1996)

[lxi] Meltzer HY. A Career in Biological Psychiatry. In Healy D, The Psychopharmacologists, Arnold, London pp. 483-508 (1996)

[lxii] Beasley C. Exhibit 7 in Deposition of Charles Beasley in Fentress Vs Eli Lilly (1994)

[lxiii] Fluoxetine Project Team Meeting Minutes, July 23rd 1979. Exhibit in Fentress Vs Eli Lilly.

[lxiv] Deposition of Irwin Slater in Fentress Vs Eli Lilly.

[lxv] Beasley C. Exhibit 7 in Deposition of Charles Beasley in Fentress Vs Eli Lilly (1994). On Fabre, see In Abraham J, Sheppard J. The Therapeutic Nightmare. Earthscan, London pp. 84. (2000)
[lxvi] www.interbrand.com/papers_review.asp?sp_id=39
[lxvii] Feuerstein A (2001). Meet the Street: How to Name a Blockbuster Drug. www.meetthestreet.com
[lxviii] Deposition of Richard Wood in Fentress Vs Eli Lilly (1994). There is no great reason to go for Wood's version of events even though he was the chief executive of the company in that he seems to have had a poor grasp of the clinical trial program.
[lxix] Wernicke J, Dunlop SR, Dornseif B, Zerbe R. Fluoxetine is effective in the treatment of depression at low fixed doses. Abstract prepared for CINP meeting in 1986; Exhibit in Fentress et al Vs Eli Lilly. Quotes and abstract in PZ1135 pages 678-681 (1994); Wernicke JF et al. Low-dose fluoxetine therapy for depression. Psychopharmacology Bulletin 24, 183-188 (1988)
[lxx] Exhibit in Fentress et al Vs Eli Lilly. Quotes and abstract in PZ1135 pages 678-681 (1994)
[lxxi] Montgomery SA, James D, de Ruiter M et al. Weekly oral fluoxetine treatment of major depressive disorder, a controlled trial. Presented at XVth CINP Congress, Puerto Rico (1986)
[lxxii] See Fink M.. A clinician researcher and ECDEU. In Ban T, Healy D, Shorter E (eds.). The Triumph of Psychopharmacology, Animula, Budapest (2000). See also Healy D. The Creation of Psychopharmacology. Harvard University Press, Cambridge Mass, chapter 6 (2001)
[lxxiii] Stecklow S, Johannes L. Questions arise on new drug testing. Drug makers relied on clinical researchers who now await trial. Wall Street Journal, August 15th, (1997). Eichenwald K, Kolata G. Drug trials hide conflict for doctors, New York Times May 16th pages, 1, 28, 29 (1999); A doctor's drug studies turn into fraud. New York Times May 17th pages 1, 16, 17. Boseley S. Trial and error puts patients at risk. Guardian Newspaper July 27th p 8 (1999)
[lxxiv] Leber P. Managing uncertainty. In Healy D, The Psychopharmacologists Vol 2, Arnold, London pp. 607-622 (1998)
[lxxv] Psychopharmacologic Drugs Advisory Committee. Twenty-eighth meeting, Thursday October 10th. The hearing this day was on Prozac (1985)
[lxxvi] Psychopharmacologic Drugs Advisory Committee 28th Meeting, Thursday October 10th 1985.
[lxxvii] De Ciccio T, Minutes of the "In-house meeting on fluoxetine" of the Food and Drug Administration. November 13th (1984)
[lxxviii] Moore TJ (1997). Hard to Swallow. The Washingtonian 33, 68-71 et seq.
[lxxix] Psychopharmacological Drugs Advisory Committee. Thirty-third meeting. November 19th (1990). This hearing was given over to Zoloft.
[lxxx] Ibid, p 90-91.
[lxxxi] Fink M. The Early Clinical Drug Evaluation Unit. In Ban T, Healy D, Shorter E (eds.). The Triumph of Psychopharmacology. Animula, Budapest, pp. 441-462 (2000)
[lxxxii] Minutes Pharmaceutical Product Strategy Meeting, April 6th 1983, Exhibit in Fentress Vs Eli Lilly.
[lxxxiii] Minutes Pharmaceutical Product Strategy Meeting, April 6th 1983, Exhibit in Fentress Vs Eli Lilly.
[lxxxiv] Anderson IM, Tomenson BM. The efficacy of selective serotonin reuptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. Journal of Psychopharmacology 8, 238-249 (1994)
[lxxxv] Anderson IM, Tomenson BM Treatment discontinuation with selective serotonin reuptake inhibitors compared to tricyclic antidepressants: a meta-analysis. British Medical Journal 310, 1433-1438 (1995).
[lxxxvi] Gilbody SM, Song F. Publication bias and the integrity of psychiatry research. Psychological Medicine 30, 253-258 (2000); Freemantle N, Mason J, Phillips T, Anderson IM. Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs. Meta-regression analysis. British J Psychiatry 177, 292-302 (2000)
[lxxxvii] Donoghue J. British Medical Journal in press (2000); Donoghue J, Taylor DM. Suboptimal use of antidepressants in the treatment of depression. CNS Drugs 5, 365-383 (2000)
[lxxxviii] May 25th communication to Lilly US from Lilly Bad Homburg by B v.Keitz containing a translation of an unofficially received medical comment on the Fluoxetine application to the German regulators.