

Case Histories of Significant Medical Advances: SSRIs and non-SSRIs (through 1999)

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Working Paper 20-135



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Funding for this research was provided in part by Harvard Business School.

SSRIs and Non-SSRIs ('Prozac' through 1999)

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Abstract: Our case history describes the development of Prozac, a blockbuster drug that transformed the treatment of depression – and became a cultural phenomenon in the United States. Specifically, we chronicle the: 1) prior treatments for depression and the research that provided a foundation for Prozac, before 1970; 2) development of Prozac, from 1971 to 1987; and 3) rapid adoption in the US after 1988.

Note: Prozac, like the other innovations in this series of case-histories, is included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a major impact on patient care. The case histories focus on advances in the 20th century (i.e. before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

SSRIs and Non-SSRIs ('Prozac' through 1999)

Depression, a debilitating mood disorder that produces persistent "sadness and loss of interest," can make patients "feel as if life isn't worth living."¹ According to the World Health Organization, over 260 million people worldwide suffer from the disorder, almost 800,000 of whom commit suicide each year.² Yet even diagnosis poses challenges. Depression can produce a range of mood changes, some which overlap with other kinds of mental disorders, rather than observable physical changes. Therefore, many physicians regard 'clinical depression' as a 'syndrome' of frequently co-occurring and coincident symptoms reported by patients and often rely on codified manuals, not laboratory tests or physical examinations, to make a diagnosis.

In 1986, American pharmaceutical maker Eli Lilly launched Prozac as a "breakthrough drug" to treat the illness.³ Previous anti-depressants required specialists to carefully adjust dosages for individual patients while monitoring effectiveness and sometimes difficult-to-tolerate side effects. Prozac in contrast, allowed general practitioners – the primary prescribers of antidepressants in the US – to safely prescribe standardized courses. It also led to a "new generation of antidepressants"⁴ that seek to elevate mood and reduce anxiety by increasing "serotonin" levels in the brain.⁵ By the end of the 1990s, over 15 million Americans took Prozac and other serotonin-increasing drugs for depression.⁶

Yet Prozac was and remains controversial because of concerns about excessive use and side effects. Furthermore, extensive medical research has not fully explained how serotonin affects mood and why Prozac and similar drugs work for some patients but not others.⁷

The next three sections of this case history describe 1) prior treatments and foundational research, from 1900 to 1970; 2) development and introduction of Prozac, from 1971 to 1987; and 3) rapid adoption of Prozac from 1988 to 2000.

1. Prior Treatments and Foundational Research (1900-1970)

Early diagnosis and treatments for depression. Depression puzzled physicians for thousands of years. The Greek physician Hippocrates attributed depression to an imbalance in the four "humors:" black and yellow bile, phlegm, and blood. Many later explanations attributed depression to moral or mental failure.⁸

Treatment through the 19th century included herbal potions or even witchcraft. Patients who did not improve faced imprisonment or banishment.⁹

Psychiatrists in the first half of the twentieth century attempted to define and diagnose depression more precisely and developed new remedies.¹⁰ Followers of Sigmund Freud tried to alleviate depression through "talk therapy." Others used muscle relaxants to sedate patients. In 1938, two Italian neuropsychiatrists developed a device to deliver "electroshock therapy" to stimulate the brain¹¹ (Physicians still commonly treat depression with stimulation of the brain, for instance, as in electroconvulsive therapy and transcranial magnetic stimulation).

Treating depression with tranquilizers. Accidental discoveries after the Second World War led to the development of "psychotropic" drugs to alter mood and behavior. These drugs, which came to be colloquially called "tranquilizers," were used to treat a wide variety of mental illnesses, many of which had not yet been precisely defined. Some, used to treat what would now be diagnosed as clinical depression, are still prescribed. Later, researchers learned that "tranquilizers" affected one or more of the chemicals that carry messages in the brain ("neurotransmitters"). At the time, however, little was known about neurotransmitters; instead, researchers studied how the drugs affected behavior.

In 1945, researchers at a British pharmaceutical company had synthesized a chemical to preserve penicillin (a vital wartime drug). They tested the safety of the chemical on mice, rats, and guinea pigs. Their tests showed that even small quantities “caused tranquillization, muscular relaxation, and a sleep-like condition from which the animals could not be roused.”¹²

In 1948, animal trials of a new French drug being developed for anesthesiologists (to prepare their patients for surgery) produced similar results. Soon after, safety tests on two new drugs for tuberculosis also seemed to sedate animal subjects.¹³ These animal studies then prompted systematic research of the effects of these drugs on human mood and behavior.

One study found that the new French drug made psychotic patients in a Paris hospital more manageable. Similarly, the two anti-tuberculosis drugs seemed to make patients more energetic and sociable. After researchers published their results in medical journals, newspapers followed up with reports of dramatic changes in patients¹⁴

Drug companies in Europe and the U.S. then tested other medicinal compounds. The compounds that produced calmness and tranquility in animals were tried on humans. Human trials showed that some drugs, initially formulated to treat tuberculosis and gout, calmed manic patients, energized depressed patients, lowered blood pressure, and improved appetite and sleep.¹⁵

Pharmaceutical companies developed more than twenty ‘tranquilizers’ from these compounds, including Thorazine (1953), Miltown (1955), Tofranil (1957), Marsilid (1958), and Valium (1963). The drugs secured widespread publicity in newspapers and popular magazines.¹⁶ Patients demanded tranquilizers from their doctors and soon general physicians joined psychiatrists in prescribing the drugs. In 1957, physicians wrote 35 million prescriptions for nearly 1 in 20 Americans.¹⁷

However, the newly developed psychotropic drugs posed many problems.¹⁸ Matching drugs to mental illness was hit or miss. Many drugs did not target specific illnesses and diagnoses required judgments based on symptoms reported by patients rather than objective tests or observations. Drugs often had to build up in patients’ bodies before patients experienced noticeable benefits, while unpleasant side effects could come first. Physicians therefore had to persuade patients to continue taking their drugs. To produce the necessary drug buildup while minimizing side effects, physicians had to gradually increase doses (through a process called “titration”). This required on-going monitoring of patients. But many general physicians who prescribed tranquilizers lacked the training and skill to choose the appropriate drugs and manage the process of their administration.

Moreover, even skillfully and carefully administered psychotropic drugs could produce serious side effects on their own or through interactions with other medications or even food. The side effects included reduced libido, allergic reactions, disrupted sleep, blurred vision, hallucinations, dizziness, dry mouth, fluctuations in weight, gastrointestinal problems, heart problems, and high blood pressure.¹⁹ They could also be addictive, produce thoughts of suicide, and provide the means for committing suicide; deliberate or accidental overdoses of fewer than a dozen pills could be fatal.

Studying serotonin. The wide use, benefits and limitations of psychotropic drugs spurred research, starting in the mid-1950s, to understand how chemicals influenced mood and behavior. As previously noted, some research suggested that many drugs produced desirable and undesirable effects by affecting neurotransmitters, the chemicals carrying messages in the brain.

One such neurotransmitter, serotonin, emerged as a candidate for affecting depression.²⁰ The chemical was already thought to affect neurological activity. In 1937, a pharmacologist at the University of Pavia, in Italy, had suggested it controlled muscle movement in the gut. In 1952, Cleveland Clinic researchers found the same chemical in the brain. They named it serotonin and demonstrated its role in carrying messages. In 1963 and 1964, psychiatrists Alec Coppen in England and Herman van Praag

in the Netherlands independently hypothesized that serotonin levels were linked to sadness and happiness. Studies published shortly thereafter reported low serotonin in the bodily fluids of depressed people and in the brains of people who had committed suicide.²¹

Meanwhile, researchers had found that neurons in the brain both produced and reabsorbed neurotransmitters (including serotonin). This suggested the hypothesis that serotonin levels could be increased, and mood improved, by reducing reabsorption (technically, “reuptake”) and not just by increasing production. In 1968, Swedish researchers at the University of Gothenburg and Karolinska Institute reported that some tranquilizers blocked reabsorption of serotonin secreted in the brain. These studies prompted drug companies to try “rational drug design” to try to synthesize molecules that would reduce serotonin reabsorption.²² Eventually, as we will see in the next section, researchers at the American pharmaceutical producer Eli Lilly synthesized a molecule that would be marketed as “Prozac.”

2. Developing and Introducing Prozac (1971-1987)

Lilly's serotonin research. Like many other pharmaceutical companies, Eli Lilly had developed and marketed a tranquilizer. However, its drug, introduced in 1965, had not enjoyed great success. Yet, the two pharmacologists, Irwin Slater and Robert Rathbun, who had developed the tranquilizer maintained their reputations within Lilly because of their previous research into a groundbreaking treatment for high blood pressure.* In the late 1960s, Lilly promoted Slater to Director of Pharmacological Research.²³

After Slater's promotion, Rathbun teamed up with chemist Bryan Molloy to develop molecules that targeted serotonin. The two then worked with two new hires, biochemist David Wong and pharmacologist Frank Bymaster, to find molecules that were effective in reducing serotonin reabsorption as well as “selective” in not affecting other neurotransmitters²⁴ (The researchers believed that selectivity could limit side effects). They identified first four, and then two, promising molecules from about sixty that they had synthesized.²⁵

Lilly researchers then synthesized more than thirteen variants of the two molecules which they tested on animals. The tests, completed in 1973, suggested that LY 110140 or “fluoxetine” was the most effective and selective of the thirteen variants.²⁶

The researchers presented their results to an internal committee, which included Rathbun's erstwhile collaborator, Slater, who now headed the company's pharmacological research. Lilly's researchers also presented their results at scientific conferences.²⁷

The two kinds of presentations produced different reactions. After the internal committee had reviewed the fluoxetine results, Lilly formed a research team, headed by biochemist Ray Fuller,[†] to turn LY 110140 into a clinically useable drug.²⁸ Outsiders, however, were skeptical. At the time, pharmacologists tested the calming effects of tranquilizers on stressed rodents. Researchers induced stress by exposing the rodents to extreme cold or prolonged periods of swimming in a narrow cylinder. Lilly's researchers had not reported the results of such tests. Rather, they had used experiments, recently pioneered at Johns Hopkins, that had shown that fluoxetine elevated serotonin levels in rodent brains for up to thirty hours.²⁹

* Lilly itself had not actually marketed a drug based on the discovery, however. Rather, the British pharmaceutical company, ICI, had successfully commercialized the research.

† Fuller, who had joined Lilly in 1963 to research tranquilizers, was a strong advocate for neurotransmitter research at Lilly. He went on to be well known and widely interviewed as the leader of the company's Prozac project.

Meanwhile, researchers from the Karolinska Institute had added to earlier evidence suggesting that tranquilizers raised serotonin in the brains of depressed patients. The Karolinska study reinforced the belief of Lilly's researchers and management that raising serotonin with fluoxetine (as the animal tests had found) could potentially treat depression. In any event, the fluoxetine team and Lilly's management disregarded the skepticism of outsiders about their animal tests and proceeded to the next phase of development.³⁰

Safety and Effectiveness trials. In 1975, Lilly's fluoxetine team started testing its safety on rats and dogs. However, researchers suspended the trials when they found rapid increases in fatty acids in the bodies of the experimental animals. Then, after reviewing possible causes, the Lilly researchers consulted the Neuropharmacology Division of the U.S. Food & Drug Administration (FDA).³¹

The Division encouraged Lilly to continue their fluoxetine project: FDA staff provided examples of other drugs that had also caused a buildup of fatty acids in animals but had not produced this effect in human trials and eventually secured regulatory approval.³²

Lilly's researchers took the FDA's advice, completed the animal trials, and, in 1976, started human trials. As they had hoped, fluoxetine did not produce a buildup of fatty acids in human subjects or show other safety problems.³³

The next stage in testing, small-scale human trials for effectiveness, produced unfavorable results: fluoxetine performed no differently than a placebo control. According to a Lilly researcher's recollections, this outcome discouraged fluoxetine developers until they learned that the trial had enrolled volunteers who had not responded to other antidepressants, perhaps because they may have been incorrectly diagnosed as depressed (when in fact they had other disorders or the mildness of their symptoms did not justify any drug treatment).³⁴

The fluoxetine team persuaded Lilly management to repeat the trials on depressed patients who had responded to tranquilizers; however, a psychiatrist hired to design the new trials soon left to start a private practice. Lilly management then put Slater in charge, along with a younger pharmacologist, Paul Stark, who also held a faculty appointment at nearby Indiana University.³⁵

In 1979, the first results of the redesigned trials showed that patients who had responded to tranquilizers also responded to treatment with fluoxetine. Some patients also experienced additional benefits, such as weight loss. In 1981, Lilly started larger-scale, Phase III trials to test fluoxetine against a placebo and six drugs then widely used to treat depression.

The large-scale trials, completed in 1983, suggested more effectiveness in treating depression than a placebo. Lilly also reported that in a few of its studies fluoxetine was, under some conditions, more effective than two antidepressants, Tofranil and Sinequan, that it had tested its drug against.³⁶

Fluoxetine offered a variety of advantages over many of the then commonly used antidepressants. It did not require physicians to gradually increase dosage: patients could start with and continue "therapeutic" levels of dosage (although, as with other drugs, it could take time to experience benefits). General practitioners could therefore more easily learn how to manage fluoxetine treatments.³⁷ Fluoxetine reduced the risks of self-harm; over a hundred doses could be taken at once with no risk to life. And, unlike some other psychotropic drugs, it did not seem to change the physical structure of nerve cells when taken over long durations.

Lilly immediately submitted its results to regulators, seeking approval to market its drug as a treatment for depression. As it happens, European regulators had previously approved a Swedish drug, "Zelmid," that also elevated serotonin levels and that had been withdrawn from the market in just two years after it produced dangerous side effects. (See **Exhibit 1**)

Notwithstanding the Zeldin experience, Belgian regulators approved fluoxetine in 1986, the U.S. FDA in December 1987, and British regulators in 1989. German regulators, however, declined to approve fluoxetine, citing concerns that the drug increased patients' risk of suicide.³⁸

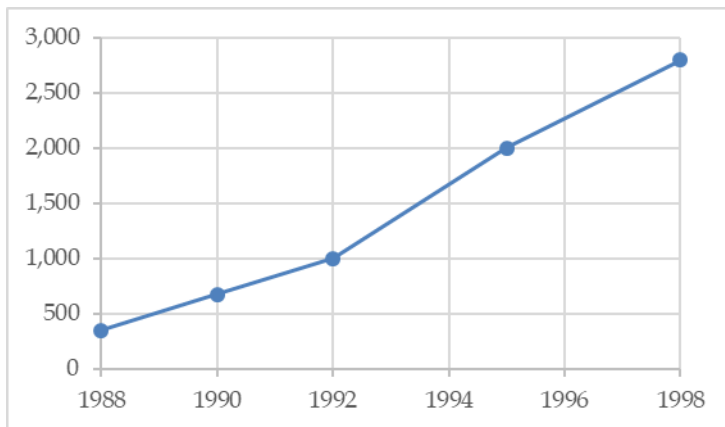
Lilly also tested fluoxetine as a treatment for obesity, hypertension, and alcoholism—uses that had been suggested by earlier animal trial results.³⁹ These trials, completed a few years after the antidepressant trials, would suggest that fluoxetine induced weight loss, alleviated severe pain, and quelled urges to smoke and drink alcohol. Lilly would then seek approval for some of these other uses.⁴⁰

3. Rapid Adoption (1984-2000)

U.S. launch. In 1988, Eli Lilly introduced fluoxetine as “Prozac” in the United States. It set a relatively high price: about \$1.10 per day, or 48 times the price of generic tranquilizers and four and a half times the price of brand name antidepressants. Lilly forecast yearly revenues of about \$70-100 million—less than a third of estimates made by outside analysts.⁴¹

However, Prozac's worldwide sales rapidly outpaced Lilly's and analysts' forecasts (See Figure 1). The United States accounted for most of these sales.⁴²

Figure 1 Sales of Prozac from 1988 to 1998 (\$ millions)



Source: Created using data from; “The Chemistry of Despair.” *The Economist*, June 16, 1990. The Economist Historical Archive, 1843-2015. Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac)”; Lopez-Munoz and Alamo, “Monoaminergic Neurotransmission”; Wenthur, Bennett, and Lindsley, “Classics in Chemical Neuroscience”; Eaton, Margaret. “Developing and Marketing a Blockbuster Drug: Lessons from Lilly’s Experience with Prozac.” Stanford, CA: The Board of Trustees of Leland Stanford Junior University, 2005.

As was then common with other new tranquilizers, Lilly supported its launch with advertisements in medical journals and an educational program for psychiatrists. However, Lilly also took some unusual further steps: it partnered with the American Psychiatric Association (APA) to create an educational program tailored for general physicians; Lilly’s sales force made calls to general physicians, and not just psychiatrists. Lilly also partnered with the U.S. National Institute of Mental Health to distribute branded brochures describing depression, its physical causes, and its treatment.⁴³

Diagnostic Guidelines. Prozac benefitted from new practices for diagnosing depression. American physicians had long relied on guidelines in *The Diagnostic and Statistical Manual of Disorders*, first published by the APA in 1952. In 1980, a new edition of the Manual included new guidelines for diagnosing depression: patients who reported symptoms for two weeks. Earlier guidelines had

specified diagnosis after a month of symptoms. The guidelines also now included patients whose symptoms followed major life events, such as the loss of a loved one, a terminal diagnosis, or divorce.*

According to some historians, these changes significantly increased the patients that physicians considered treating for depression;⁴⁴ the proportion of the U.S. population treated would triple between 1987 and 1997. By the end of the 1990s, as previously noted, over 15 million Americans took Prozac and similar antidepressants.⁴⁵ Blood tests, which might have contradicted clinical diagnoses of depression, had failed in development. Clinical diagnosis therefore remained the primary means of diagnosis.⁴⁶

Media Attention. Coverage of Prozac in the mass media included reporting on the television news program *Good Morning America* and a cover story in *Newsweek* (then an international mass circulation magazine).⁴⁷ However, some publicity was unfavorable. In 1989, a man from Louisville, Kentucky who had been taking Prozac shot and killed eight former colleagues and then himself with an assault rifle. The families of the victims sued Eli Lilly. Lilly settled during the widely publicized trial.⁴⁸

The Kentucky killings also provoked a campaign by the Church of Scientology, which opposed the use of psychiatric drugs. The Church's advocacy group published articles criticizing Prozac and advertisements in *Time* magazine and *USA Today* demanding Prozac's recall.

Yet front-page features in the *New York Times* (1993) and *Newsweek* (1994) reported no decline in Prozac's popularity. Rather, as the *Newsweek* article stated: "Compared with the anti-depressants of the past—obscure compounds that only psychiatrists and their patients could name—Prozac ha[d] attained the familiarity of Kleenex and the social status of spring water."⁴⁹ Peter Kramer, a psychiatrist at Brown University, encouraged use by even those who were mildly depressed in his 1993 book, *Listening to Prozac*. Prozac inspired episodes on well-known television series, such as "Frasier," "Sex and the City," and "The Sopranos." It inspired books, such as Elizabeth Wurtzel's 1994 memoir, *Prozac Nation* (which later became a film), and Lauren Slater's 1998 memoir, *Prozac Diary*. In 1999, *Fortune* named Prozac to its "Pharmaceutical Products of the Century" list.⁵⁰

Medical Controversies. As prescriptions grew, psychiatrists published medical journal articles about patients in whom Prozac had apparently induced suicidal thoughts and attempts.⁵¹ In response, the FDA convened a panel to investigate in 1991. However, the panel did not recommend more warnings on Prozac's label, much less any withdrawal of the drug.⁵² The Associated Press reported that the FDA had "found no evidence that Prozac is addictive and causes mood disorders, thereby rejecting a request to pull marketing approval for the drug. ... The FDA said clinical trials did not show any more suicide attempts among depressed patients on Prozac than among those being given placebos or other anti-depressants" and that "Prozac labels already note that violent behaviors have been reported among a small number of patients and that, in clinical trials, hostile behavior was observed at rates ranging from one in 100 to one in 1,000."⁵³

The FDA investigation did not, however, end questions about Prozac. Patients taking Prozac reported headaches, nausea, stomach problems, and reduced libido. One 1996 study of Prozac use by pregnant women found more fetal abnormalities, complications, and premature births than in a control group. Effectiveness was also controversial. Studies using new genetic technologies and brain scanners could not show a clear relationship between lower serotonin levels and depression (and thus could not validate the hypothesis that reducing serotonin reabsorption elevated mood).⁵⁴

* Previously, physicians often considered intense sadness, grief, or anxiety after significant losses as a normal reaction that could resolve itself in time without treatment, rather than clinical depression.

New marketing. In 1997, Lilly became the first company in the U.S. to take advantage of new FDA rules that allowed advertising drugs directly to consumers. For many decades, the FDA had restricted advertising to physicians, typically in medical journals. After the FDA allowed advertising aimed at consumers, Lilly immediately advertised Prozac in popular magazines, such as *Time* and *Reader's Digest*. The marketing campaign drew some criticism for projecting life on Prozac as natural; Lilly's advertisements featured the slogan "Welcome back" against a backdrop of sunshine and blue skies over forests and fields.⁵⁵

Lilly also sought to market Prozac to treat several conditions beyond depression. As mentioned, in the mid-1980s Lilly had tested Prozac as a treatment for obesity, severe pain, smoking, and alcoholism. After more clinical trials in the late-1980s and 1990s Lilly secured FDA approval to market Prozac as a treatment for panic attacks (1992), obsessive-compulsive disorder (1994), bulimia (1994), and anorexia (1997). In addition, veterinarians prescribed Prozac to aggressive animals, although Lilly did not promote such use. The prescriptions were "off-label," because unlike some of its competitors, Lilly had not sought or received FDA approval to market the use of its antidepressant for pets.⁵⁶

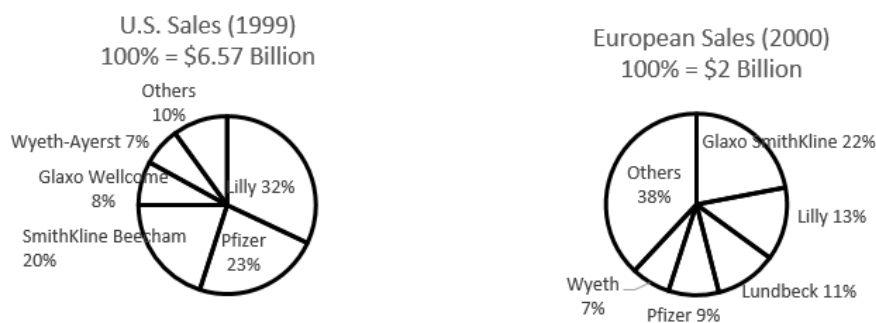
Usage in Europe and Japan. Although tranquilizers had been popular⁵⁷ in Europe, Prozac sales did not grow to the same extent there as in the United States. By the late 1990s, Prozac's European sales accounted for just an eighth of its U.S. sales. Lower sales may have reflected differences in guidelines and practices. European physicians usually used a different manual for diagnosing depression, and according to analysts, European physicians often prescribed Prozac in addition to tranquilizers, rather than as a substitute (possibly reducing doses or the duration of the prescribed courses). Also, herbal remedies for depression had become more popular in Europe than in the U.S.⁵⁸

Meanwhile, throughout the 1980s and 1990s, Lilly had not sought regulatory approval in Japan, where depression was highly stigmatized, and diagnosis and prescription standards were stringent.⁵⁹

The Competitive Situation in 1999

Other pharmaceutical companies had introduced antidepressants that targeted serotonin or elevated different - sometimes multiple - neurotransmitters throughout the 1990s (See **Exhibit 2**). Some competing drugs claimed fewer side effects or offered treatments for different kinds of symptoms. For instance, Effexor (which targeted both serotonin and norepinephrine) was marketed as a treatment for anxiety attacks and social phobias as well as depression.⁶⁰ The competing drugs reduced Prozac's share of the U.S. antidepressant market from over 50% in 1996 to about 32% in 1999. In Europe, where tranquilizers remained popular, Prozac's share was even lower.⁶¹ (See **Figure 2**).

Figure 2 Shares of Antidepressants sold in US (1999) and Europe (2000)



Source: Created using data from Frost & Sullivan, "U.S. Antidepressant Medications Markets" (7458-52) 2001, Chart 4.3, p. 4-19, and Frost & Sullivan, "European Psychotropic Drugs Market" (3776-52,) 2001, Chart 3.9, p. 3-52.

Prozac also faced a legal challenge to its U.S. patents. As mentioned, Lilly had progressively secured FDA approvals for several diseases and disorders (after testing for multiple conditions beyond depression). In the 1970s and 1980s Lilly had also used some of the test results to file for “secondary patents.” For instance, Lilly had filed a U.S. patent application for the drug as a treatment for irregular heartbeats in 1974⁶² and had then filed five additional applications for Prozac and its use in other diseases, such as anxiety disorders. The last Prozac patent was issued in December 1986.⁶³

In 1996, the generics producer, Barr Laboratories, sued to invalidate Lilly’s U.S. patents, on the grounds that Lilly had “double-patented” its drug. In January 1999, a federal district court judge had dismissed Barr’s claim at a pre-trial hearing. However, Lilly and Barr had already agreed to take their case directly to the United States Court of Appeals.⁶⁴

Exhibit 1 Astra's Zelmid

The Swedish pharmaceutical producer Astra had developed a drug to increase serotonin by reducing its reabsorption before Lilly. Astra had also started research in 1971. However, instead of relying on an in-house research team, as Lilly did, Astra collaborated with researchers at the University of Gothenburg and Karolinska Institute. These researchers had published an influential 1968 study of tranquilizers' effects on serotonin levels, and they identified a molecule a year earlier than Lilly's team—in 1972. Astra also completed development and trials in fewer years than Lilly did. In 1982, Astra introduced the drug as "Zelmid" in Europe to treat depression and phobias. And Astra partnered with longtime American pharmaceutical maker Merck to conduct the necessary trials to obtain FDA approval to market Zelmid in the United States.

Just two years later, however, Astra stopped selling Zelmid. The drug had increased suicidal thoughts in some patients, and, in rare cases, it induced a fatal disease in which the body attacked its own nerves, spine, and brain. Zelmid also produced flu-like symptoms. In 1984, Astra removed Zelmid from the European market, and it was eventually banned worldwide. Zelmid's abrupt collapse prompted Astra to shut down its antidepressant research program.

Source: Shai Mulinari, "Divergence and Convergence of Commercial and Scientific Priorities in Drug Development: The Case of Zelmid, the First SSRI Antidepressant." *Social Science and Medicine*, <https://doi.org/10.1016/j.socscimed.2015.06.020>, accessed November 2020.

Exhibit 2 Antidepressants introduced by Lilly's competitors from 1989 to 1999

Drug	Brand Name	Neurotransmitter Target(s)	Producer (Location)	Date introduced
Bupropion	Wellbutrin	Dopamine and Noradrenaline	Burroughs Wellcome (UK)	1989
Sertraline	Zoloft	Serotonin	Pfizer (US)	1992
Paroxetine	Paxil	Serotonin	Glaxo (UK)	1992
Venlafaxine	Effexor	Serotonin and Norepinephrine	Wyeth Pharmaceuticals (US)	1993
Nefazodone	Serzone	Serotonin and Norepinephrine	Bristol-Myers Squibb (US)	1994
Fluvoxamine	Luvox	Serotonin	Solvay Pharmaceuticals (Belgium) and Jazz Pharmaceuticals (Ireland)	1983 (Europe) 1994 (US)
Mirtazapine	Remeron	Serotonin, Epinephrine, and Norepinephrine	Organon International (Netherlands)	1994 (Europe) 1996 (US)
Citalopram	Celexa	Serotonin	Lundbek (Denmark) and Forest Pharma. (US)	1989 (Europe) 1998 (US)
Reboxetine	Edronax	Norepinephrine	Pfizer (US)	1997 (Europe) 1999 (US provisional)

Source: Compiled from *Wall Street Journal* (1996) Robert Langreth. "High Anxiety: Rivals Begin To Threaten Prozac's Reign." May 9, 1996, sec. Marketplace. <https://www.wsj.com/articles/SB831601811454975000>, Frost & Sullivan, "European Psychotropic Drugs Market" (3776-52,) 2001, Chart 3.9, p. 3-52, and Mulinari S. "Divergence and convergence of commercial and scientific priorities in drug development: The case of Zelmid, the first SSRI antidepressant." *Soc Sci Med.* 2015 Aug;138:217-24. doi: 10.1016/j.socscimed.2015.06.020. Epub 2015 Jun 18. PMID: 26123880.

Endnotes

- ¹ Mayo Clinic webpage on “Depression (major depressive disorder). Downloaded from <https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007> on November 9, 2020.
- ² Depression and suicide estimates are according to the World Health Organization’s (WHO) 2020 estimates. The economic toll of depression is also high: in 2014, researchers have estimated lost productivity, absenteeism, and treatment costs to be USD\$63 billion per year in the United States alone. See: Cody J. Wenthur, MeganR. Bennett, and Craig W. Lindsley, “Classics in Chemical Neuroscience: Fluoxetine (Prozac),” *ACS Chemical Neuroscience* 5, no. 1 (November 9, 2013): 14–23, <https://doi.org/10.1021/cn400186j>; David T. Wong, Kenneth W. Perry, and Frank P. Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac),” *Nature Reviews Drug Discovery* 4, no. 9 (September 2005): 764–74, <https://doi.org/10.1038/nrd1821>; “Depression,” accessed May 19, 2020, <https://www.who.int/news-room/fact-sheets/detail/depression>; “NIMH » Depression,” accessed May 19, 2020, <https://www.nimh.nih.gov/health/topics/depression/index.shtml>; “NIMH » Major Depression,” accessed May 19, 2020, <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>.
- ³ Cody J. Wenthur, MeganR. Bennett, and Craig W. Lindsley, “Classics in Chemical Neuroscience: Fluoxetine (Prozac),” *ACS Chemical Neuroscience* 5, no. 1 (November 9, 2013): 14–23, <https://doi.org/10.1021/cn400186j>, page 20.
- ⁴ Francisco Lopez-Munoz and Cecilio Alamo, “Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s Until Today,” *Current Pharmaceutical Design* 15, no. 14 (2009): 1563–1586, <https://doi.org/10.2174/138161209788168001>; Roberto Mandrioli, Michele Protti, and Laura Mercolini, “New-Generation, Non-SSRI Antidepressants: Therapeutic Drug Monitoring and Pharmacological Interactions. Part 1: SNRIs, SMSs, SARIs,” *Current Medicinal Chemistry* 25, no. 7 (2018): 772–92, <https://doi.org/10.2174/0929867324666170712165042>.
- ⁵ The category came to be known as SSRIs -- “selective serotonin reuptake inhibitor.” Later drugs designed to increase levels of other neurotransmitters or combinations of neurotransmitters are collectively known as “non-SSRIs” or by acronyms that indicate the chemicals involved. For instance, “SNRIs” increase levels of serotonin and norepinephrine (another neurotransmitter), and “NeRIs” increase only norepinephrine. See Mandrioli, Protti, and Mercolini, “New-Generation, Non-SSRI Antidepressants” and the sources in endnote 3 above
- ⁶ Clark Lawlor, *From Melancholia to Prozac: A History of Depression* (Oxford, UNITED KINGDOM: Oxford University Press USA - OSO, 2012), <http://ebookcentral.proquest.com/lib/bu/detail.action?docID=886553>.
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¹⁶ According to cultural and social historians, many of the publications were aimed at women. For instance, articles in *Cosmopolitan*, a popular women's monthly magazine published in the United States, explained tranquilizers would cure women who did not want sex or mothers who had breakdowns after the birth of a child. According to cultural and social historians, many of the publications were aimed at women. For instance, articles in *Cosmopolitan*, a popular women's monthly magazine published in the United States, explained tranquilizers would cure women who did not want sex or mothers who had breakdowns after the birth of a child. Jonathan M. Metz, "'Mother's Little Helper': The Crisis of Psychoanalysis and the Miltown Resolution," *Gender & History* 15, no. 2 (2003): 228–55, <https://doi.org/10.1111/1468-0424.00300>, pages 230, 239–240.

¹⁷ Lawlor, *From Melancholia to Prozac*; Metz, "'Mother's Little Helper'"; Lopez-Munoz and Alamo, "Monoaminergic Neurotransmission"; Kauffman, "The Discovery of Iproniazid and Its Role in Antidepressant Therapy."

¹⁸ Wenthur, Bennett, and Lindsley, "Classics in Chemical Neuroscience"; Wong, Perry, and Bymaster, "The Discovery of Fluoxetine Hydrochloride (Prozac)."

¹⁹ Lopez-Munoz and Alamo (2009), Lawlor (2012), Drugbank.com, and MayoClinic.org

²⁰ Some researchers believed that other neurotransmitters played a larger role. For instance, in 1965, a psychiatrist at the U.S. National Institute of Mental Health, Joseph J. Schildkraut, proposed that low levels of "norepinephrine" caused depression and high levels caused elation.

Elliot S. Valenstein, "The Discovery of Chemical Neurotransmitters," *Brain and Cognition* 49, no. 1 (June 1, 2002): 73–95, <https://doi.org/10.1006/brcg.2001.1487>; Patricia Mack Whitaker-Azmitia, "The Discovery of Serotonin and Its Role in Neuroscience," *Neuropsychopharmacology* 21, no. 1 (August 1999): 2–8, [https://doi.org/10.1016/S0893-133X\(99\)00031-7](https://doi.org/10.1016/S0893-133X(99)00031-7); Joseph J. Schildkraut, "The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence," *American Journal of Psychiatry* 122, no. 5 (November 1, 1965): 509–22, <https://doi.org/10.1176/ajp.122.5.509>; Lopez-Munoz and Alamo, "Monoaminergic Neurotransmission."

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²³ The compound lowered blood pressure by interfering with the function of the hormone epinephrine, which is closely related chemically to the neurotransmitter norepinephrine. A rival pharmaceutical company, Imperial Chemical Industries (ICI, located in Britain), filed a patent before Lilly researchers had refined their formulation, however, so Lilly could not secure a patent and did not bring the drug to market. Lopez-Munoz and Alamo, "Monoaminergic Neurotransmission"; Wenthur, Bennett, and Lindsley, "Classics in Chemical Neuroscience"; Wong, Perry, and Bymaster, "The Discovery of Fluoxetine Hydrochloride (Prozac)"; William H. Frishman, "Fifty Years of Beta-Adrenergic Blockade: A Golden Era in Clinical Medicine and Molecular Pharmacology," *The American Journal of Medicine* 121, no. 11 (November 2008): 933–34, <https://doi.org/10.1016/j.amjmed.2008.06.025>; R. C. Rathbun and I. H. Slater, "Amitriptyline and Nortriptyline as Antagonists of Central and Peripheral Cholinergic Activation," *Psychopharmacologia* 4, no. 2 (March 1, 1963): 114–25, <https://doi.org/10.1007/BF00413329>; Anthony Hordern, "The Antidepressant Drugs," *The New England Journal of Medicine* 272, no. 22 (1965): 1159–1169, <https://doi.org/10.1056/NEJM196506032722206>; Irwin H. Slater et al., "Pharmacological Properties of Recanescine, A New Sedative Alkaloid from *Rauwolfia Canescens* Linn.," *Proceedings of the Society for Experimental Biology and Medicine* 88, no. 2 (1955): 293–295, <https://doi.org/10.3181/00379727-88-21567>.

²⁴ Bymaster and Wong did much of the foundational neuropharmacology research for Prozac and were listed on all the publications together through the 1980s, with a changing cast of other Lilly researchers as co-authors. Bymaster then worked on other projects at Lilly in the 1990s, and so did not play a role in the promoting Prozac. Public attention then centered on his colleagues Fuller, Wong, and Molloy.

²⁵ Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac)”; Wenthur, Bennett, and Lindsley, “Classics in Chemical Neuroscience”; Lopez-Munoz and Alamo, “Monoaminergic Neurotransmission.”

²⁶ Lopez-Munoz and Alamo, “Monoaminergic Neurotransmission”; Wenthur, Bennett, and Lindsley, “Classics in Chemical Neuroscience”; Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac)”; Frishman, “Fifty Years of Beta-Adrenergic Blockade”; Rathbun and Slater, “Amitriptyline and Nortriptyline as Antagonists of Central and Peripheral Cholinergic Activation”; Hordern, “The Antidepressant Drugs”; Slater et al., “Pharmacological Properties of Recanescine, A New Sedative Alkaloid from *Rauwolfia Canescens* Linn.”

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²⁸ Wong states in his case history that the project team was formed in 1973, but he then references a timeline that dates the formation of the team to 1972. We are using the date from the main body of the article. Wong, Perry, and Bymaster.

²⁹ Wong, Perry, and Bymaster.

³⁰ Wong, Perry, and Bymaster; Marie Åsberg et al., “Indoleamine Metabolites in the Cerebrospinal Fluid of Depressed Patients before and during Treatment with Nortriptyline,” *Clinical Pharmacology & Therapeutics* 14, no. 2 (1973): 277–86, <https://doi.org/10.1002/cpt1973142277>.

³¹ Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac).”

³² Wong, Perry, and Bymaster.

³³ Wong implies, but does not state clearly, that Lilly’s toxicity trials went on to have similar results to the trials that the FDA had reviewed with the research team. That is, Wong suggests the toxicity that showed up in those first animal trials was temporary, and that the animals returned to a normal, healthy state after the trials were complete. Wong, Perry, and Bymaster.

³⁴ Wong, Perry, and Bymaster, page 770.

³⁵ According to Lopez-Munoz et al, for the position, Lilly chose John Feighner, who had won acclaim for his efforts to standardize European and American criteria for diagnosing mood disorders. However, before the redesigned trials started, Feighner left to pursue private practice. After he left Lilly, Feighner’s private clinic became a fluoxetine trial site. By the time of his death, Feighner reportedly had participated in over 200 clinical trials for 30 different antidepressants. During the development of Prozac, in 1984, Paul Stark started a company, the International Clinical Research Corporation, which specialized in designing and conducting clinical drug trials. Stark later helped found the Stark Neurosciences Research Institute at Indiana University. Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac)”; Lopez-Munoz and Alamo, “Monoaminergic Neurotransmission”; Facebook et al., “Dr. John Feighner Remembered for Groundbreaking Work with Antidepressants,” San Diego Union-Tribune, August 23, 2006, <https://www.sandiegouniontribune.com/sdut-dr-john-feighner-remembered-for-groundbreaking-2006aug23-story.html>. History | Stark Neurosciences Research Institute | IU School of Medicine,” accessed June 16, 2020, <https://medicine.iu.edu/research-centers/neurosciences/history>.

³⁶ According to a professor of psychiatry interviewed for this Note, “there are no persistently credible data to suggest that fluoxetine is significantly more effective than other antidepressants used in therapeutic doses.”

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