Optional Background Reading on Prozac for Homework 8 Web Problem #1

Prozac® is the registered trademark for the drug fluoxetine hydrochloride (see Figure 1). Fluoxetine hydrochloride may be prescribed for a variety of conditions including mild bulimia and obsessive-compulsive disorder. However, Prozac® is best known as an antidepressant, and over the last decade has become the most widely prescribed drug in the history of psychiatry. Prozac® is currently prescribed to more than 54 million people in over 100 countries².

Fluoxetine hydrochloride was the first of a new class of drugs for treating mental illness known as selective serotonin re-uptake inhibitors. These drugs help to alleviate depression by increasing the levels of the neurotransmitter serotonin (see Figure 2) in the brain. Serotonin is a chemical that is exchanged by cells in the brain, and is thought to influence sleep, appetite, aggression and mood.

Prozac® is also the first prescription medicine to become a cultural phenomenon. During the early and mid-nineteen nineties, Prozac® was the subject of intense media scrutiny, being vigorously – if not particularly deeply – discussed on popular television talk shows, magazine articles and

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1 Image source: [http://organic.chem.wisc.edu/](http://organic.chem.wisc.edu/)
best-selling books (see Figures 3 and 4). In March of 2003, the film adaptation of Elizabeth Wurtzel’s 1997 novel, *Prozac Nation: Young and Depressed in America*, was released, starring Christina Ricci and Jason Biggs (the pie guy from *American Pie*). This movie tells the story of a woman’s struggle with depression during her freshman year at a prestigious university, and her interactions with parents, room-mates, psychiatrists and ultimately Prozac®.

Figure 4: A very small selection of the books that have appeared on the subject of Prozac® over the last ten years.

Prozac® was initially approved for medical use in Belgium in 1986 for the treatment of depression, and was approved by the FDA in 1987. In a very rapid rise to popularity Prozac® achieved its most-widely prescribed psychiatric drug by 1990, a position that it has maintained ever since. According Eli Lilly and Company⁴ (the manufacturers of Prozac®), the safety and effectiveness of the drug have been “…thoroughly studied in clinical trials with more than 11,000 patients.” Eli Lilly and Company further comment, “There have been more than 3,500 publications on Prozac® in medical/scientific journals.” This is a surprisingly lukewarm testament to Prozac®’s effectiveness and safety.

The *Physicians’ Desk Reference* (PDR) lists critical information on prescription drugs. In the section on “Adverse Reactions,” under the entry for Prozac® the PDR devotes approximately one page to simply listing the adverse reactions to the drug that were encountered during the clinical trials alone. Since the conclusion of the clinical trials, tens of thousands of Prozac® users have reported adverse reactions, ranging from occasional diarrhea to attempted murder/suicide. A number of patients who were prescribed Prozac® have sued Eli Lilly and Company. Recently (November 30, 2002) Eli Lilly settled a major case out of court. The plaintiffs, Diane and Melvin Cassidy of Monroeville PA sued Lilly for $4.84 million in damages, although the actual amount of the settlement has not been made public.

The Cassidy case alleged that Prozac®, prescribed to Diane Cassidy for weight loss, produced suicidal thoughts and eventually led Ms. Cassidy to attempt suicide. The suicide attempt left Ms. Cassidy paralyzed on one side of her body and mentally impaired. The PDR casually mentions “suicide attempt” (in only one place) as an “infrequent whole body” adverse reaction to the drug.

A number of other recent cases involving Prozac® have been troubling both for the human tragedy involved and also for some of the tactics employed by Lilly officials. One such incident was the product liability trial following the 1989 workplace shooting/murder-suicide of Joseph Wesbecker in Louisville, KY.

Mr. Wesbecker had a long history of severe depression and was prescribed Prozac® in 1989. Approximately one month after he began to take the drug, Mr. Wesbecker obtained an AK-47 assault rifle and entered the Standard Grauve building in Louisville, KY, where he had been previously employed. Mr. Wesbecker opened fire on former co-workers, killing eight and wounding twelve before turning the gun on himself. In the aftermath, the Jefferson County coroner performed an autopsy on Mr. Wesbecker’s body and determined that Mr. Wesbecker had a therapeutic level of Prozac® in his system at the time of the shooting.

Victims of this rampage sued Eli Lilly and Company, and the trial took place in 1994. A key strategy for the victims’ attorneys was to demonstrate that Eli Lilly and Company had a history of reckless disregard by bringing drugs with potentially dangerous side effects to the market. A key example in establishing this history was Lilly’s failed anti-inflammatory drug, Oraflex®, introduced in 1982 but withdrawn only three months later. Suspiciously, the victims’ attorneys failed to introduce this into evidence during the trial. With the jurors unaware of the Oraflex® information, Eli Lilly easily won the trial (with a 9-3 jury verdict) and subsequently and publicly claimed that it had been “…proven in a court of law…that Prozac® is safe and effective.”

The trial judge, Justice John Potter, conducted an independent investigation of the attorneys’ failure to introduce the Oraflex® evidence during the trial and discovered that Eli Lilly made a secret deal with the victims’ attorneys, paying both the attorneys and the victims not to use the Oraflex® information in court5. In 1997 the verdict in the case was changed (with very little public attention) from an Eli Lilly victory to “dismissed as settled.” It is quite astonishing from an ethical point of view, that even though they had interfered with the trial, officials at Eli Lilly nevertheless claimed that the verdict demonstrated that Prozac® was “safe and effective.”

At the end of 2002, President Bush signed the Homeland Security Act into law. In a further drug-related controversy, a provision was anonymously6 inserted into the bill – too late for debate by the House of Representatives – blocking certain lawsuits against large pharmaceutical corporations, principally Eli Lilly and Company. Specifically, the legislation protected large pharmaceutical companies against lawsuits brought by parents who believed that their children had been harmed by thimerosal7, which Eli Lilly developed and manufactured for more than forty years. Senator John McCain (R-AZ) characterized this provision of the Homeland Security Act as “among the

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6 For several weeks following passage of the bill, and in spite of repeated requests from the news media, no member of the House of Representatives acknowledged a role in adding this provision. Finally, on December 12, 2002, House Majority leader Dick Armey (R-TX) told CBS news that he was responsible for the provision. Armey explained to CBS News that it was “…a matter of national security. We need their vaccines if the country is attacked with germ weapons.” For more, see: http://www.cbsnews.com/stories/2002/12/12/eveningnews/main533886.shtml
most inappropriate” of the entire piece of legislation and commented to reporters, “…this language will primarily benefit large brand-name pharmaceutical companies which produce children’s vaccines – with substantial benefit to one company in particular. It has no bearing whatsoever on domestic security.” In November 2002, no less than forty-five lawsuits had been filed against Eli Lilly by parents alleging that their children had suffered neurological disorders as a result of exposure to thimerosal.

Thimerosal (also referred to by its trade name of Merthiolate®) is a mercury-based vaccine preservative that has been used in many vaccines given to children. Some pediatric vaccines continue to include “trace levels” of thimerosal. Some medical researchers have postulated a link between vaccines containing thimerosal and autism, although no definite links have been demonstrated to the satisfaction of the medical and scientific communities. In 1998 the Food and Drug administration (FDA) banned the use of thimerosal as a preservative in over-the-counter (OTC) pharmaceutical products and the following year, both the FDA and the American Academy of Pediatrics urged vaccine makers to stop using mercury-based preservatives such as thimerosal.

This specific provision of the Homeland Security Act provoked a public outcry and was repealed after approximately three months.

In the latest episode of this disturbing story, suggestions have begun to surface that officials at Eli Lilly and Company, manufacturers of Prozac®, may have been aware of potentially dangerous side effects for some time. Several internal Lilly documents (some dating to the 1980’s and stamped “confidential”) have been described in the British Medical Journal and furnished to news organizations (such as CNN) by US Representative Maurice Hinchey (D-NY). These documents seem to indicate that Eli Lilly officials not only knew that Prozac® had potentially troubling side effects, but that they sought to minimize the impact of this information on physicians’ prescribing of the drug.

Since its introduction in the mid-1980’s, Eli Lilly and Company’s controversial drug Prozac® has been implicated in a number of deaths – some put the number in the thousands, as shown in Figure 5 – that occurred in circumstances like Ms. Cassidy’s. However, there have been very few deaths that can be attributed to overdose of the drug.

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In the United States, thimerosal has been removed from many pediatric vaccines. This has been possible through re-packaging the vaccines in single-use vials rather than in large, multi-use vials. Some vaccines administered in the United States, such as Fluzone manufactured by Aventis, are still distributed in multi-dose vials and still contain some level of thimerosal. In many other countries, especially in the developing world, pediatric vaccines are still distributed in multi-dose vials and contain comparatively high levels of thimerosal.


See: http://www.aap.org/policy/jointhim.html


See: http://www.house.gov/hinchey/

Source: http://users.actweb.net/
in a purely biochemical sense. That is, deaths that resulted directly from chemical interference between fluoxetine hydrochloride and the human body’s natural chemical processes, as opposed to neurochemical effects that produced homicidal or suicidal behavior on the part of the patient taking Prozac®.

Prior to the introduction of Prozac® into the United States in 1987 there had been only two deaths as a result of acute fluoxetine overdose, and these were both in combination with either alcohol, powerful painkillers or illicit drugs. In the first case, the person was determined to have taken 1800 mg of fluoxetine. Although it was not possible to determine the actual amount of fluoxetine taken by the other person, measurements made during the autopsy were consistent with a dose of 760 mg.

Fluoxetine hydrochloride is a chemical that has an unusually long half-life (5 days) in the human body. (Fluoxetine hydrochloride is broken down by the liver to form a chemical called norfluoxetine, which has an even longer half-life – about 14 days – in the body.)

Until recently, Prozac® was only available in capsule form, with each capsule delivering 20 mg of fluoxetine hydrochloride (see Figure 618). The dosage guidelines in the PDR clearly state in several places that the maximum safe dose of Prozac® is 80 mg per day.

In this web problem you will work out how the scientists at Eli Lilly, Prozac®’s manufacturer, could have arrived at this figure for the maximum daily dose.

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18 Image source: [http://adbusters.cool.ne.jp/prozac.jpg](http://adbusters.cool.ne.jp/prozac.jpg)