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Risks of Prozac revisited

Drug's link to violence not studied by FDA, data show

By Anne C. Mulkern
Denver Post Staff Writer

Washington - Federal regulators knew as far back as 1986 that some people taking Prozac hanged or shot themselves, attempted suicide, or fantasized about murder.

Post / Craig F. Walker

Amber Hackett, above, of Parker, on her daughter, Holly Gerk. After being on the antidepressant Zoloft for about a year, Hackett says, the 15-year-old attacked and cut her with a knife.

The U.S. Food and Drug Administration said there was "no evidence to suggest" Prozac caused those events.

Eighteen years later, as studies have shown a possible link between newer antidepressants and a higher suicide risk in children, the FDA is re-evaluating its position, hinting it may force antidepressant makers to increase their warnings for the second time this year.

A revolution in the consumption of psychiatric medicine followed Prozac's approval in December 1987. Doctors last year wrote 142 million prescriptions for newer-generation antidepressants. In the intervening years, the FDA has repeatedly missed or ignored opportunities to scrutinize the wildly popular drugs, documents obtained by The Denver Post and a series of interviews show.

In its review of FDA oversight of newer antidepressants, The Post found that:

Despite repeated concerns about whether drugmakers had sufficiently examined the risk of violent reactions, the FDA never commissioned research that looked directly at the issue or instructed drug companies to do so.

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A key FDA administrator who for 20 years ran the psychiatric drugs division says second-generation antidepressants were approved by a regulatory process that requires only limited proof of efficacy and safety. "We don't know the risks that clearly. You're working in a sea of ignorance," Dr. Paul Leber told The Post.

Drug companies were aware of the need to sidestep the issue of suicidal and homicidal reactions, documents show.

"I think both the industry and the FDA have been irresponsible in not educating doctors and the public more," said Dr. Joseph Glenmullen, a Harvard University psychiatrist who wrote "Prozac Backlash."

"It's really clear the FDA dragged its feet for 15 years. They just let the whole thing get swept under the carpet until they got caught with their pants down."

British, Canadian alerts

The FDA acted after British and Canadian health authorities had already taken aggressive stances. The FDA issued its warning after word leaked that one of its medical officers wrote a report documenting that children taking the drugs had an increased risk for suicidal acts. Glenmullen and others believe new evidence about children reopens questions about risks for adults.

There was a series of opportunities to act sooner. Reports of Prozac patients' suicides came into the agency "in bunches" in 1990 and 1991. The FDA held a hearing and said there was no evidence to prove the drugs caused violence, but failed to ask for more targeted research.

Over the next few years, as Prozac copycat drugs came up for approval, the FDA saw reports that showed cases of self-mutilation, mania and suicide. The FDA asked drug companies for more data but did not force them to study the issue further. It failed to have drug companies standardize data for suicidal thoughts or actions, which meant that information couldn't be easily analyzed.

FDA officials refused repeated interview requests, saying they were awaiting hearings scheduled for this week to review a new study that shows a link between the drugs and higher risk of suicidal acts in adolescent children.

Last week, the House Oversight and Investigations subcommittee held a hearing to look at whether drug companies withheld data on the efficacy of the drugs. Another hearing Sept. 23 will examine the safety issue.

Long-term risks unknown

Based on the number of prescriptions written for Prozac, Paxil, Zoloft, Luvox, Celexa, Lexapro, Effexor,

Wellbutrin, Serzone and Remeron, most doctors clearly believe they are more helpful than harmful. Newer antidepressants are second only to codeine as the most commonly used prescription drug in the country, according to IMS Health, which tracks the drug market.

Dr. Richard Kapit, who worked at the FDA for 20 years and reviewed Prozac, said that compared with older antidepressants, Prozac has fewer side effects and is quite safe. Prozac may or may not cause suicide and violence, but those also were risk factors of the older drugs. Post-marketing studies should have been done, he said.

"Why weren't those studies done? I think it's basically that they didn't get around to it," Kapit said. "People have made decisions that other priorities came first."

Another former FDA administrator said the long-term risks also are unknown.

"I do have some doubts about their value in the big picture," said Leber, a psychiatrist. He is now a consultant to the drug industry, advising on psychiatric and neurological drugs.

Leber worked at the FDA for more than 20 years before leaving in January 1999. As director of the neuropharmacological drug products division for 15 years, he recommended the approval of Prozac, Zoloft, Paxil and others.

Leber believes the drugs are safe as defined by law but says little can be proved about relatively new drugs in terms of their risks. There aren't enough suicides to do a scientific study, he said.

Antidepressants have been a huge moneymaker for the drug companies, with the FDA reaping some of that revenue. Drug companies are required to pay fees to the FDA - a total of $215 million in 2003, up from $34 million in 1993, the first year they were collected.

Those fees were approved by Congress in part to hasten the drug approval process. The drug companies originally insisted that those fees not be used for studies of the drugs once they are on the market, Kapit said. That law was changed in 2002 and they cannot be used to study approved drugs where safety is an issue.

When Prozac and copycat drugs were up for approval from 1986 through the early 1990s, the drug companies appeared aware of the need to keep the suicide issue from mushrooming.

In a Feb. 7, 1990, Eli Lilly memo obtained by The Post, W. Leigh Thompson, a scientist in Lilly's clinical investigations unit, expressed concern after Leber asked Lilly to compare Prozac's rates of aggression and suicidal thinking with those of other antidepressants in a British health agency database.

"Lilly can go down the tubes if we lose Prozac and just one event in the UK can cost us that," Thompson wrote colleagues, expressing concern about a possible British review.

Other memos from 1990 show Lilly fought against having its label changed to include any suicide data. And company officials believed Leber was going to be there for them, court documents show.

Thompson called Leber at 6:15 a.m. on July 18, 1990, to talk about the suicide issue, according to a Lilly memo. Thompson noted that "Lilly and FDA are working together on the suicide issue."

In an interview, Leber said he was doing his job, which required him to ignore political pressures and evaluate drugs scientifically. "I like to believe that given the information I had at the time, I did what I should have done," he said.

"20 deaths in a report"

Naysayers within the FDA at that time appear to have been ignored. In a Sept. 11, 1990, memo, David Graham, an epidemiology director, charged a Lilly study with improperly excluding 76 of 97 cases when evaluating whether patients taking the drugs became suicidal.

Graham wrote that Lilly also used misleading comparisons and that "the firm's analysis cannot be considered as proving that (Prozac) and violent behavior are unrelated."

At the same time, reports of "successful suicides" were coming in to the FDA "in bunches," Martin Brecher, former FDA medical officer in the neuropharmacological drug division, testified in a March 13, 2003, court deposition. Brecher said that sometime in 1990 and the first half of 1991, he reviewed quarterly reports from Lilly documenting suicides by people who had been taking Prozac.

"It was really quite extraordinary, especially in comparison to other annual reports where, you know, you had 20 reports of a cold and maybe two reports of some liver enzyme elevations, and here you are with 20 deaths in a report," Brecher testified.

"The volume of reports of completed suicides with Fluoxetine (Prozac) raised questions as to the relationship ... and it in no way suggested an answer."

A spokesman for manufacturer Lilly noted that it is "one of the most studied drugs in the history of medicine and has been proven safe and effective."

The issue of suicide didn't go away as the FDA approved other Prozac-like drugs. In a Jan. 20, 1994, memo, Dr. Roger Lane of the Pfizer Co. told colleague E. Giller-Groton that his suggestions to try to study Zoloft for use in patients with aggression problems would be

"difficult to 'sell' within the company due to the problems Prozac has encountered."

"Marketing ... are very aware that a patient on Zoloft involved in an incident of mass homicide could severely affect the image and commercial success of Zoloft," the memo states. Pfizer spokeswoman Shreya Prudlo said that "Pfizer has studied the impact of Zoloft on the treatment of symptoms of anxiety and depressive illnesses and carefully monitors and evaluates all adverse events including suicide and violence."

Parker resident Amber Hackett, 34, blames Zoloft on her daughter Holly Gerk's violent outburst. Gerk, 15, took Zoloft for about a year and then began drinking and taking drugs, behavior her mother described as new. Gerk one day attacked and cut her mother with a 7 1/2-inch kitchen knife, saying she wanted to kill her, Hackett said.

"She was depressed before, but she could control herself," Hackett said. "She never acted violently until after she started taking the pills."

U.S. Rep. Diana DeGette, D-Denver, said more information is needed. "The concerns about prescribing antidepressants to kids are too important to remain unresolved," she said.

There are ample studies, most of them funded by drug companies, showing the drugs do work and are safe. However, most drug trials are short, running six to eight weeks. Patients who drop out because of serious adverse effects, including suicide attempts and mania, are not counted in the final risk percentages.

"In clinical trials ... from 15 to 21 percent discontinued the drug within six to eight weeks because of intolerable side effects," said Thomas J. Moore, analyst at George Washington University Medical Center in Washington. "It would be hard to find another family of drugs in common use with such an abysmal record."

An attorney who said she has seen internal drug company documents still protected by court seal said the drug companies have been successful in hiding data from doctors and in some cases the FDA.

"There's evidence ... to indicate the drug companies have known about a risk (of suicide and violence) since the 1980s," said Karen Barth Menzies, who is representing about 100 people suing drugmakers because of suicides in their families.

Doctors disagree on whether the FDA acted too slowly.

Dr. John March, professor and chief of child and adolescent psychiatry at Duke University Medical Center, said "the FDA's done exactly all the right things." March just completed the largest independent study to date of the generic version of Prozac and adolescents. British and Canadian health authorities "jumped to conclusions" while the FDA waited for a re-

examination of drug company data, he said.

Dr. Steven E. Hyman, who ran the National Institute of Mental Health and now is Harvard University's provost, said he believes the FDA has been cautious because the agency didn't want to send a "chilling" message that would keep people in need from taking the drugs.

Hyman believes that most people benefit from the drugs,but he said he is troubled that so much is unknown.

"I have a deep sense of disquiet that we really don't understand what's going on," he said. "We need government-sponsored trials. Truly objective and dispassionate trials."

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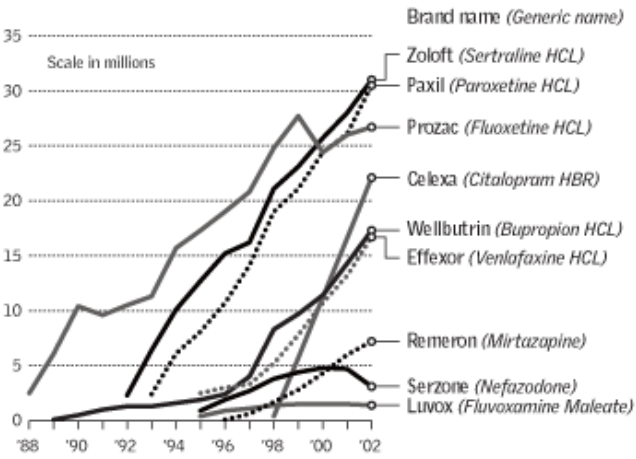
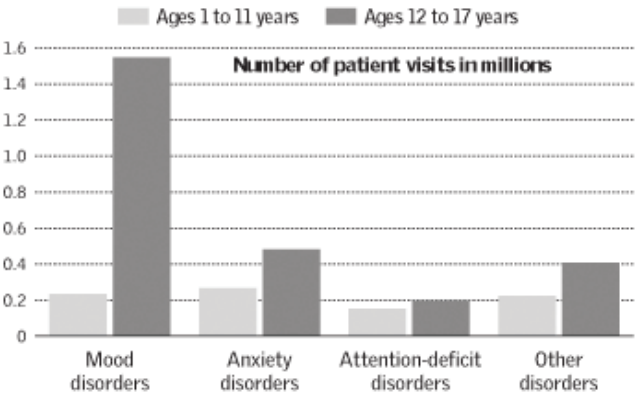
Antidepressant boom

The use of psychiatric medicine has soared since the FDA approved Prozac in December 1987.

Total U.S. prescriptions for selected antidepressants



What selected antidepressants were prescribed for in children, 2002



How antidepressants affect the brain

Drugs like Prozac allow a chemical transmitter, serotonin, to remain for longer periods in the space between nerve cells.

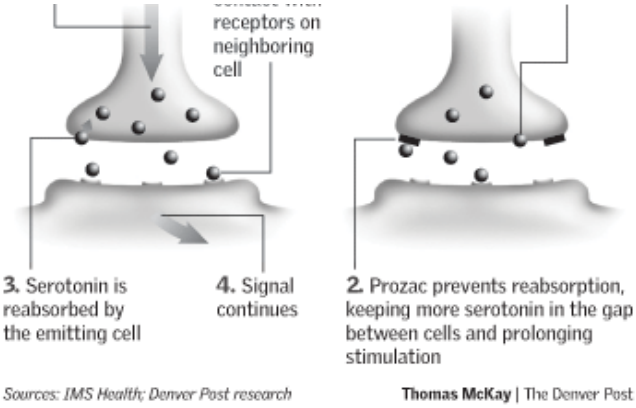
In a normal person

1. Signal travels down one brain cell

2. Serotonin is released and comes into contact with

In a depressed person

1. Less serotonin is released



Events that raised questions about risks of antidepressants:

1985: German health authorities raise concerns about Prozac's increased suicidal risk, which they say is five times that of older antidepressants. German health officials ultimately approve Prozac but with a stronger warning label than what will be approved in the U.S two years later.

1986: In a review of Prozac, prior to its approval, FDA Dr. Richard Kapit notes that the drug causes "anxiety, insomnia, agitation ... and psychotic episodes of a manic type." Among other adverse effects he lists "bizarre homicidal and suicidal behavior."

1989: During tests of Paxil, investigators for Beecham Laboratory (CQ) - part of what is now GlaxoSmithKline (CQ) - say Paxil "definitely" caused mania, suicide attempts, aggression and akathesia, or severe restlessness in some patients. Those reports were submitted to the FDA.

1990: Harvard psychiatrists Martin Teicher (CQ) and Jonathan Cole (CQ) publish study that indicates Prozac possibly increases risk of suicidal thoughts in 3.5 percent of patients.

1995: In a patent application, scientists working on a redesigned Prozac tell the government that their drug avoids Prozac's adverse effects of "severe anxiety leading to intense violent suicidal thoughts and self mutilation." (Eli Lilly in 2000 cancelled a $90 million deal to produce the drug. Generic Prozac remains on the market.)

1996: Pfizer, maker of Paxil, files report with FDA that says a drug-activated response is a "plausible" explanation for a manic reaction by a 9-year-old boy who choked himself with a tie and slashed his feet with a razor. The report otherwise blames depression as the reason for violent reactions seen in studies.

1998: The Journal Psychopharmacology publishes a study by Dr. Roger Lane (CQ) of Pfizer, which says selective serotonin reuptake inhibitors may produce

a report and memo to the FDA director of neuropharmacological drug products that concludes nearly all selective serotonin reuptake inhibitor drugs increase the risk of suicidal behaviors in children and adolescents nearly two-fold over those on a placebo.

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