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Prozac, Eli Lilly and the FDA

by Gary Null

Five years after the introduction of Prozac, there's no denying that this pharmaceutical has helped many people through a debilitating depression. Consider the case of a friend of mine, whose son was hospitalized for depression at the end of his first semester at college. The son received Prozac and was released one month later. When he became depressed again at age 19, treatment with Prozac allowed him to continue college. He eventually graduated summa cum laude and has since worked for three years without slipping back into depression.

Like this young man, many people have improved the quality of their lives with the use of Prozac. As with any complex issue, however, there's another side to the story on this drug - a side that has not yet received the widespread media attention focused on Prozac's "success" stories. The problem is not with the people who benefit from Prozac, but with those the drug may hurt. An extensive investigation shows that Prozac causes adverse effects in many people, and to those people who feel they are the victims of the drug they do not believe these effects have received adequate attention.

In today's marketplace, it's not enough merely to state that any new drug or medical procedure carries a risk/benefit ratio. This argument offers small comfort when the federal government, and specifically the U.S. Food and Drug Administration (FDA), has refused to give credibility to those who claim that Prozac has harmed them. In this report, then, we focus on the flip side of the Prozac story to illuminate the many voices that have previously gone unheard. These voices argue for a simple right - a forum in which to tell their side of the story.

The Flip Side

In the past few years, the use of Prozac has been implicated in many tragic murder cases. One of the most infamous of these occurred when Joseph Wesbecker, a pressman on psychiatric leave from his job, killed eight coworkers and injured a dozen others at his former place of employment. Wesbecker then turned the gun on himself and committed suicide.

At first, Wesbecker's rampage appeared to be another case of random workplace violence. But four months later, following a coroner jury's investigation, the facts of the case began to take a new turn. The jury ruled that Prozac may have contributed to Wesbecker's violence, and 10 of his victims petitioned congressmen to launch an investigation into the drug's role in the rampage.

This request came as quite a jolt. After all, Prozac had received glowing media coverage since its introduction in 1987. And in a few short years, it had become the leading antidepressant in the United States, garnering as much as 23% of the market. Some three million people have received prescriptions for Prozac (fluoxetine hydrochloride), and 800,000 prescriptions are written or renewed each month.

Behind this rapid growth was a highly effective advertising campaign by Eli Lilly & Co., the drug company that makes Prozac. In advertising its new drug to psychiatrists, Eli Lilly portrayed Prozac as safe, effective and easy to use. Indeed, Prozac was described as a new-generation drug - one that was "chemically unrelated to all other available antidepressants."

Prozac's potential side effects also promised to be much less severe than those of its predecessors - tricyclics such as Elavil

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In November 1991, Freda Howard of Kittery, Maine, killed her husband with an ax, set her home on fire and shot herself fatally. According to a blood test, Howard was on Prozac when she committed the murder/suicide. That same month, Barbara Mortenson of San Francisco, California, bit her mother 20 times, leaving "bite-sized pieces of flesh"on the floor. After her arrest Mortenson was quoted in the *San Francisco Examiner* as saying, "She made me mad, so mad, I've been taking Prozac for the last two weeks."

Prozac

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and monoamine oxidase inhibitors such as Nardil. These medications may cause hypertension, erratic heart beat, dizziness, sluggishness, constipation and weight gain, leading doctors to question whether the possible side effects are worse than the depression the drugs are intended to treat.

Meanwhile, Prozac's primary side effects included nausea, insomnia and anxiety. And unlike its competitors, which can cause people to gain weight, Prozac actually caused weight loss. Finally, the lethal level of Prozac would make it difficult to use the drug to commit suicide.

When the media discovered Prozac, the drug got a big boost in the consumer market. In major magazines, Prozac was referred to as a "wonder drug," a "hot yuppie upper" and a "breakthrough for depression." This positive publicity gave millions of people the impression that Prozac could drive depression from their lives - without causing harmful side effects in the process.

Consider an article that appeared in *New York* magazine's December 18, 1989 issue: There, an anonymous psychopharmacologist was quoted as saying, "Prozac is incredibly easy to prescribe. You can teach a chimpanzee to prescribe it." Likewise, Michelle Gersten, then assistant professor of child psychiatry at Mount Sinai School of Medicine, said, "It's much easier to think of prescribing Prozac for children because of the relative lack of side effects."

Akathisia and Violence

One of Prozac's potential side effects, however, is indeed a cause for concern. The drug can produce a condition called "akathisia," which comes from a Greek word meaning "can't sit down." In essence, akathisia is a drug-induced state of agitation that causes a person to pace or fidget continually. Few people outside the medical/psychiatric field have ever even heard of this condition.

In the product information sheet that accompanies Prozac, Eli Lilly acknowledges that the drug can cause akathisia. But the manufacturer claims that the condition occurs in less than 1% of Prozac users, while a medical report published in September 1989 tells a different story. This study estimated that 10% to 25% of Prozac users experience akathisia, making it a "common" side effect of the drug.

When this study was first published - at about the same time that Joseph Wesbecker committed mass murder - the significance of the findings were largely overlooked. But akathisia has since been recognized as a side effect that deserves close scrutiny. In medical literature dating back nearly 15 years, a number of articles describe the potentially damaging effects of akathisia. These reports include:

- In 1978, a man with drug-induced akathisia was described in an article by psychiatrist Walter Keckich of the University of Washington School of Medicine. The man, who was uncontrollably agitated, experienced "violent urges to assault anyone near him," according to the article, "Violence as a Manifestation of Akathisia." Eventually, he tried to kill his dog, a violent act apparently brought on by akathisia.
- In 1983, psychiatrist M. Katherine Shear and associates reported that two suicides might have been precipitated by akathisia-like symptoms from a different neuroleptic medication. This report appeared in the *Journal of Clinical Psychopharmacology.*
- Two years later, psychiatrist Robert E. Drake and another researcher linked two more suicide attempts to akathisia. In both cases, the patients had concluded that "life was no longer worth living" because their mental state had deteriorated so rapidly, when, in fact, it was the akathisia that had altered their mental state.
- Also in 1985, an article by Dr. Jerome Schulte, former director of medical education at Atascadero State Hospital in California, linked akathisia to extremely violent acts. This article, in the *American Journal of Forensic Psychiatry,* described one psychiatric patient who killed an old woman and attacked two others, a second patient who repeatedly stabbed a grocer, and a third who murdered his mother with a hammer.
- In 1986, akathisia was associated with suicidal and homicidal thoughts in a double-blind clinical trial, according to a report by several psychiatrists in the *Journal of Clinical Psychopharmacology.*
- In 1990, a two-year study on the link between akathisia and violence was published in *Psychopharmacology Bulletin.* The study found that people involved in violent acts had a higher akathisia rating than those who observed the incidents.

The Seeds of Violence

To this day, the survivors of Wesbecker's rampage do not know if akathisia played a role in his behavior because the investigation they requested was never carried out.

Even the investigation led by Dr. Richard Greathouse, the coroner, may have lacked complete information. During his investigation, Dr. Greathouse asked Eli Lilly if the company had received any reports associating Prozac with acts of violence. As Dr. Greathouse reported at the inquest, Lilly responded that two million people were using the drug, but that "they had not had any documented violent episodes occur, reported back to the company."

Documents suggesting otherwise have since been released by the FDA under the Freedom of Information Act. These documents show that Lilly had received reports of violent behavior in Prozac users. One such report, which Lilly sent to the FDA more than a year before the Wesbecker case, involved a patient who "became very aggressive while taking Prozac; after one week on the drug he had an argument with another motorist and attempted to run over him with his car."

The possible link between Prozac and Wesbecker's behavior has also been supported by a number of articles and letters in medical journals. In February 1990, for example, Dr. Martin Teicher, a Harvard psychiatrist, reported in the *American Journal of Psychiatry* that six patients who were depressed - but not suicidal - had "developed intense, violent suicidal preoccupation" within weeks of taking Prozac. Teicher suggested that Prozac "may induce suicidal ideation in some patients."

Some of the reports that followed Teicher's article include:

- In the November 1990 issue of the *American Journal of Psychiatry,* psychiatrist Krishna Dasgupta stated in a letter that a 38 year-old woman had become suicidal after taking Prozac for only 30 days.
- In a letter to the *New England Journal of Medicine* on February 7, 1991, two doctors from State University of New York, in Syracuse, reported that two patients had developed suicidal thoughts after taking Prozac. These patients were not suicidal before they took the drug, and their suicidal thoughts ended abruptly when they stopped taking Prozac.

- A group of researchers from the Yale Child Study Center in New Haven, Connecticut, reported that six adolescents had developed "self-injurious ideation or behavior" when they took Prozac. This report was published in the March 1991 edition of the *Journal of the American Academy of Child and Adolescent Psychiatry.*
- Dr. William Wirshing, a psychiatrist at UCLA, reported at the American Psychiatric Association's 1991 annual meeting that five patients appeared to have developed akathisia from Prozac. Dr. Wirshing believed the akathisia had "led them all to contemplate suicide."
- In December 1991, Dr. Anthony Rothschild, a Harvard researcher, described the effects of Prozac on three people who were "rechallenged" by taking the drug for a second time. All three patients developed akathisia and intense suicidal thoughts. Interestingly, none of the patients realized that their akathisia symptoms were caused by the drug, said Dr. Rothschild. Instead, they simply believed their mental condition was deteriorating.

The rechallenging process is an important tool in drug research. If a patient develops the same side effect both times that he or she takes a drug, the repeated response establishes a strong link between the drug and that particular reaction. Therefore, rechallenging allows researchers to study the side effects of drugs without conducting a clinical trial, which can be both costly and time consuming.

Suicidal Obsessions

Despite these reports on the potential side effects of Prozac, the medical community appears to be prescribing the drug with abandon. Prozac has been approved for use with depression only by the FDA, but the drug is being used for conditions such as weight loss, learning disorders, sleeping problems, cocaine addiction and smoking cessation.

In addition, many of the people who are taking Prozac for depression - its intended use - may simply be experiencing short-term feelings of depression or stress. Do these people need to take a potentially harmful drug at such times, or would they do just as well with emotional support? More important, how many Prozac users are told of the drug's possible side effects when it is prescribed?

What follows are a few examples of Prozac's effects on people who took the drug for depression:

• When Janet Sims and her husband went for marriage counseling, she was given Prozac to counter a "low mood." But Sims became aggressive on the drug and began to physically attack her husband. Sims' behavior put a tremendous strain on her marriage, which did not survive the Prozac episode. As Sims has stated: "As a result of my increased hostility and aggression which occurred while on Prozac, my marriage fell apart and my husband and I separated. I am convinced that Prozac created this hostility and made it impossible for my husband and I to work through the problems we were having."

Sims' violent mood swings continued, but she and her doctor never connected her behavior to the drug. Sims became obsessed with suicide as her mental state deteriorated, and she eventually received electric shock treatments at a psychiatric hospital. These treatments caused a severe memory loss - and all of this in a woman who originally wanted marriage counseling. "I had been trained in computers, but as a result of the shocks I have lost all my computer training," said Sims, who is suing Eli Lilly.

• Barbara Lynn Wilson had a similarly tragic experience with Prozac. In Wilson's case, the drug was prescribed when she "crashed into a severe depression" following a hysterectomy, even though the procedure commonly causes such feelings. Wilson became compulsively suicidal while she was in the hospital. She tried to hang herself, burn herself and jump from the window.

"While I was on the floor I began pacing and racing. I felt as strong as a locomotive," she said. "I felt like I could crash the walls or fly. I started to try to kill myself...taking every opportunity to use blood pressure cuffs, cords, and electrical cords to strangle myself, and towels from the bathroom and shower curtains around my face and just bizarre things." It was not until Wilson stopped taking Prozac that she realized the drug was responsible for her behavior.

• Likewise, Sharyn DiGeronimo received Prozac several years ago when she was feeling down. The psychiatrist described Prozac as a "great new drug...virtually free of side effects." "He did a complete sales pitch on me, [but] I really don't blame him because I think he was just as misinformed as I was," said DiGeronimo in a *Newsday* article.

Indeed, the doctor doubled DiGeronimo's dosage of Prozac when she became hostile and obsessed with suicide. "On Prozac, my whole personality did a complete change. I started becoming intentionally self-destructive although I didn't know why and I didn't care," she said. "As my behavior got stranger and stranger and more destructive, the doctor didn't see that the behavior changes were due to the drug, and he increased the dosage from one to two and then to an occasional third a day." DiGeronimo has since founded the Prozac Survivor's Support Group (PSSG) in New York State.

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The *Mortal Words* Birds *by* John Bryant

THE TERM *DOCTOR* USED TO REFER TO DELETERIOUS PRACTICES.

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Prozac

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These three women - Sims, Wilson and DiGeronimo - all took Prozac for depression, and all survived the experience. But other people with no history of depression are taking the drug for non-psychological problems, such as weight loss. In some cases, this has led to tragic results. Consider these two cases:

- Susan McGuiness, a 44 year-old woman, committed suicide after she took Prozac for a year and four months to lose weight. Susan's husband, Bill, said that she had "everything to live for" and that she believed the drug was helping her tremendously. Meanwhile, she was not losing weight and had begun to experience physical ailments.

"If Susan were alive today, she would be standing on a soap box giving the merits of Prozac.... But at the same time something was very wrong," said Bill McGuiness. "Her weight gain did not stop. And she was developing a mysterious pain deep inside her. We spent approximately $7,000 testing for every type of internal problem, and the doctors said 'nothing remarkable'."

McGuiness believes that Prozac led to Susan's suicide because the act was so completely out of character. "She was outgoing and empathetic and genuinely interested in other people," he said. "All of a sudden, on one Tuesday morning, to decide to leave work to go home and take a 38 revolver was something deeply out of sync with her character."

- Jennifer Wildman, a 19 year-old woman, also committed suicide after taking Prozac for about a year. Like Susan McGuiness, Jennifer took Prozac for weight loss. In November of 1990, she wrote suicide notes to her friends and then took her own life. Her mother, Linda, says that "Susan was a very loving girl, very happy, ready to go to college and had no thoughts of suicide or any suicidal tendencies before this."

As these cases illustrate, the improper use of Prozac for weight loss is a serious problem. In a *Newsday* article, Dr. Merton Kahne, a professor of Social Psychiatry at the Massachusetts Institute of Technology, suggested the drug's weight-reducing properties may be related to size of the dosage. "It is likely to turn out that at the lower doses you get only a slight weight loss. To get a more significant effect, you may have to overdose the person," said Kahne. Yet the same article tells us that one Dallas clinic offers Prozac as part of its weight-loss program. According to a nurse at the clinic, thousands of clients have received the drug since 1987, when Prozac was introduced.

Also vulnerable to the effects of Prozac are children, adolescents and elderly people. Although no studies on the drug have been conducted with these groups, psychiatrists continue to prescribe Prozac to such people. In an interview with the *Chicago Tribune* last year, for example, one psychiatrist said that the use of Prozac should not cause undue concern. "You're already dealing with people who are depressed and unstable and it could just as easily be the phases of the moon or their breakfast cereal that makes for an adverse side effect. In short, we're more careful, but we're not terribly concerned," said Dr. Robert Kowatch, associate director of in-patient psychiatry at Children's Medical Center in Dallas.

But Bonnie Leitsch, the national director of the PSSG, has a different story to tell. Based on her conversations with more than 600 people who had adverse reactions to Prozac, Leitsch believes the drug can cause considerable harm in children. "I am talking to widows and widowers and parents of lost children. They are starting Prozac on 9 year-old children who attempt to commit suicide and on 14 year-old boys who jump through windows."

Sadly, some of these adolescents succeed in ending their lives. One such teenager was Tracy Ann Ingstrom, a 17 year-old girl who received Prozac when she had minor relationship problems with her boyfriend. Tracy Ann's father, Rick Ingstrom, an investigator for the California Bar Association, says that Prozac caused a dramatic change in his daughter. "After approximately two months of taking this drug, her personality started changing drastically.... She started violent verbal and physical attacks on friends and would drive wildly. This was behavior that was never a part of her before," he said.

On January 24, 1991, Tracy Ann had a heated argument with her boyfriend. She told him that she was going home to shoot herself with a gun her father had hidden in the house. Her boyfriend did not take the threat seriously, and therefore did not try to stop Tracy Ann. Ingstrom continues: "At this, she drove home, kicked open a locked bedroom door, searched around my bedroom until she found a gun, and then shot herself in the mouth and committed suicide. The act was quick and violent and one that she would never, ever have thought of committing prior to taking the Prozac."

Another teenager, Chris Reed, was 18 years old when he took his own life - five months after he had started taking Prozac. Cornelia Reed, his mother, attributes Chris's suicide to Prozac's effects. "He should have never been put on Prozac. He was just having some problems in his life," she says. "My son would be alive today if he had not heard of Prozac.... I feel this is a very strong medication being given out easily."

Homicidal Rages

Unfortunately, people taking Prozac have also turned their rage on others around them - including their parents, spouses, and children. Following are some of the homicide cases that involved people who were taking Prozac at the time of the crime:

- In January 1989, Catherine Rouse of Dane County, Wisconsin, killed a friend and committed suicide while on Prozac.
- In February 1990, Raymond Hammerli of Mount Prospect, Illinois, murdered his ex-wife while on Prozac.
- In July 1990, Gail Ransom of San Jose, California, strangled her mother with a cord while on Prozac.
- In July 1990, Charles Gardner of St. George, Utah, killed a local nurse while on Prozac.
- That same month, Dr. Douglas Simmons of Sunfish Lake, Minnesota, killed his wife while on Prozac.
- In April 1991, Sandra Moneymaker, of Halifax, West Virginia, killed her two children and shot herself twice in the stomach after taking Prozac for three weeks.
- Also in April, Hank Adams, a former sheriff's deputy in San Diego County, murdered his wife and committed suicide while on Prozac. One of their five children witnessed the murder.
- In September 1991, Bill Coleman of Steamboat Springs, Colorado, killed his estranged wife and her male friend while on Prozac. Coleman also shot himself.
- In October 1991, Kristine Cushing of Laguna Niguel, California, shot and killed her two young daughters while on Prozac.
- In November 1991, Freda Howard of Kittery, Maine, killed her husband with an ax, set her home on fire and shot herself fatally. According to a blood test, Howard was on Prozac when she committed the murder/suicide.
- That same month, Barbara Mortenson of San Francisco, California, bit her mother 20 times, leaving "bite-sized

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pieces of flesh" on the floor. After her arrest, Mortenson was quoted in the *San Francisco Examiner* as saying, "She made me mad, so mad, I've been taking Prozac for the last two weeks."

Of course, Prozac's proponents maintain that the drug cannot be blamed for such tragedies. With the rising incidence of crime in our cities - and with nearly a million people taking Prozac - some of the drug's users are bound to be involved in violent acts. Prozac's defenders also point out that some of these people threatened violence before they started taking the drug. Therefore, they may have followed through on their threats regardless of whether or not they were taking Prozac.

But people who have studied the cases offer another line of logic. Michael O'Brien, director of research for the Citizens Commission on Human Rights (CCHR), a Scientology organization that investigates psychiatric violations of human rights, says that most of these people were not violent before they started taking Prozac. And given the intensity of the violence in many of the cases, he says, we must investigate the possibility that Prozac-induced akathisia played a role in the crimes.

Eli Lilly, in response to the violent crimes committed by Prozac users, points out that Prozac has failed as a defense in 30 criminal cases across the country. But in at least two cases that involved the use of Prozac, the defendants did not receive a prison sentence.

In one such case, defendant Larry Walters claimed that he killed his father, a Prozac user who had turned violent, in self-defense. Walters, of Saline County, Illinois, pleaded guilty to second-degree murder, but argued that he should not be sent to prison because he was defending himself.

In another case, Mildred Johnson shot and killed her husband while she was taking Prozac. The 76 year-old woman was tried for murder, but the jury convicted her of voluntary manslaughter. Johnson received a suspended sentence with probation.

In any event, the CCHR claims that the results of Prozac-related trials do not tell us whether or not the drug played a role in the violence. Many Americans believe that murder is murder. For these people, the reasons for the violence and the mental capacity of the killer do not carry much stock.

In fact, the CCHR opposes the insanity defense and the legal concept of diminished capacity, says O'Brien. The organization believes that guilty people should be punished for their acts. By policy, then, the CCHR does not testify on behalf of people who claim that psychiatric drugs prompted their violence. It simply provides information to interested parties upon request, including defense attorneys.

Meanwhile, Eli Lilly now faces more than 100 civil lawsuits from people who claim that Prozac can induce suicidal and violent thoughts or actions. To date, none of these suits has come to trial. Although some trial dates have been scheduled, they may not go to court for at least a year.

Nerve Disorders

While violent acts are the most alarming reaction linked to Prozac use, the drug may cause other problems as well. Among the most serious of Prozac's potential side effects is nervous system damage. In fact, some users say the drug severely impaired their nervous system, leading to disorders such as tardive dystonia or tardive dyskinesia. These health disorders, commonly called TD, cause involuntary muscle contractions that continue long after a person has stopped taking the drug. In some cases, the contractions never go away.

It's not news that psychiatric drugs can lead to TD. Many such drugs, including Haldol and Thorazine, are known to cause TD in about one-fifth of long-term users. Indeed, the manufacturers' prescribing information warns that the drugs can cause permanent brain damage.

Eli Lilly, by contrast, does not warn prospective Prozac users that the drug can cause permanent nervous system damage. Instead, Prozac's package insert merely cautions that users have developed dystonia, in which the muscles tense up involuntarily, and dyskinesia, in which the muscles move involuntarily.

To date, two Prozac users have sued Lilly on the grounds that the drug caused tardive dystonia or tardive dyskinesia. In one case, a woman in Texas claims that she suffered permanent neurological damage within 48 hours of taking two capsules of Prozac a day.

Cathy Churchill, another Prozac user, took the drug for eight days before she began to experience severe muscle spasms in her arms. Two years later, the Iowa resident still has TD and her ability to function has diminished.

The rapid onset of TD in Prozac users is a highly unusual disorder. While many psychiatric drugs cause nervous system damage, a permanent disorder such as TD generally does not develop until a drug has been used for a year or more. The name "tardive," in fact, means "late developing."

A number of reports linking Prozac to persistent dyskinesia or dystonia have been reported to the FDA. So far, however, the agency has not recognized that the drug may cause TD. If offers a variety of reasons for its "wait and see" stance, including insufficient information in the reports and some claimants' concurrent use of other drugs.

Most disturbing, however, is the FDA's rationale that TD symptoms have developed *too quickly* in Prozac users (within three months of taking the drug) to qualify as "tardive" disorders. In essence, the FDA appears to be saying that it will ignore TD that develops rapidly, since there is no word in our medical language to describe such a condition.

Prozac-induced TD may well be traced to the drug's akathisia side effects. In a 1988 article, Dr. L. Jarrett Barnhill of the University of North Carolina reported that he had found a link between akathisia and TD caused by other psychiatric drugs. In his article which appeared in *Clinical Psychiatry News*, Barnhill said that akathisia may precede the development of TD.

What is the connection between akathisia and TD? In the scientific literature, akathisia falls into a group of reactions that affect the "extrapyramidal" region of the brain. The feeling of restlessness produced by akathisia may be subjective, but it still resembles movement disorders such as dyskinesia and dystonia.

The causes of dystonia - and its development into permanent TD - are unknown. Nor does anyone truly understand the cause of akathisia. Without a doubt, however, akathisia exists and it does lead people to insanity. One could speculate, then, that some psychiatric drugs may cause permanent akathisia in the same way that they produce permanent TD.

The term "tardive akathisia," in fact, has already been linked with various psychiatric drugs in the medical journals. Imagine what this development means: Some people who take psychiatric drugs may be caught in a persistent web of insanity that drives them to destroy themselves and others around them.

No one knows whether Prozac can cause tardive akathisia. But the very possibility is

alarming. The controlled clinical trials for Prozac lasted for only six weeks, while some people have been using the drug for two years or more.

Clearly, the reports linking Prozac to TD must be studied carefully. Otherwise, we may discover years from now that many users of the drug have suffered serious damage to their nervous systems. This job should fall to the FDA, of course, which has the ultimate responsibility for resolving such issues.

The Experts Behind the FDA's Response

The FDA may not be up to the task, however, if its past actions on Prozac are any indication of its scientific rigor. In the fall of 1991, as concerns about Prozac and violence continued to brew, the agency assigned the topic to its Psychotropic Drugs Advisory Committee (PDAC). This committee met on September 20 to examine the evidence against Prozac and consider whether antidepressant drugs could initiate or escalate violent thoughts and actions.

But the deck appears to have been stacked from the start. Eight of the 10 panel members were psychiatrists, the very professionals who make a living by prescribing antidepressants, the class of drugs that are used to treat "depression." The ability to prescribe drugs is what distinguishes a psychiatrist from a psychologist.

Clearly, the practice of psychiatry would suffer considerably if an entire class of drug were to be linked with violent thoughts and behaviors. In fact, questions about the future of psychiatry have been raised for more than a decade now. In 1978, a well-known psychiatrist, E. Fuller Torrey, warned that the profession would be endangered as the medical community's understanding of mental problems continued to grow.

It's not surprising, then, that psychiatrists would want to protect antidepressants from negative rulings by the FDA. Tens of thousands of dollars are spent annually, *per psychiatrist*, to defend this category of drug. This leads to an obvious question: Should psychiatrists be the ones to decide on the safety of psychiatric drugs, as in the FDA panel on antidepressants?

Beyond this general concern, there are more specific questions about the panel members chosen to review Prozac. Half of these members had financial conflicts of interest due to their involvement with antidepressant manufacturers. These conflicts, which the FDA disclosed before the hearing, include the following:

- Psychiatrist Jeffrey Lieberman of Long Island Jewish Medical Center, had received $20,000 in grants from the Sandoz company at the time that he sat on the panel. Sandoz manufactures Pamelor, the second-biggest selling antidepressant in the United States.
- Psychiatrist James Claghorn owns Clinical Research Associates, a Texas company that has received $170,000 worth of grants from Sandoz and SmithKline Beecham, another antidepressant manufacturer.

(As a side note, it bears mentioning that Dr. Claghorn gave positive reviews to two other antidepressant drugs in the 1980s - zimelidine and nomifensine. Within two years of his review, both of the drugs proved to cause deadly anemias and other side effects. They were then pulled from the market.)

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Prozac

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• Psychiatrist Keh-Ming Lin disclosed a conflict involving a $95,000 grant from Merck, which manufactures an antidepressant/tranquilizer combination called Triavil.

• The wife of Robert Hamer, a biostatistician at the Medical College of Virginia, was employed at the time of the hearing by Bristol Meyers Squibb, another antidepressant drug maker.

• Psychiatrist David Dunner, of the University of Washington Medical Center, had financial conflicts totalling a half million dollars from four manufacturers of antidepressants. Remarkably, Dunner even had $200,000 worth of grants pending from Eli Lilly, Prozac's maker, when the hearing took place.

And that's not the end of it. In researching the panel members, the CCHR found that Dunner's conflict of interest waiver did not include several relevant items. This is a serious omission, since a failure to disclose such conflicts violates federal laws.

The conflicts of interest not disclosed in Dunner's waiver include the following:

• Two pending grants worth $250,000 from SmithKline Beecham and Pfizer, both manufacturers of antidepressants.

• An engagement to speak at a series of seminars funded by Eli Lilly. In his waiver, Dunner stated that he had no current commitments to speak.

Regarding Dunner, a final cause for concern is that he had received more than $4 million worth of research grants from antidepressant manufacturers in the eight years preceding the FDA hearing on these very drugs. Surely, say critics, this financial relationship would affect his opinion of the potential dangers of such drugs.

The other members of the panel, which the CCHR attempted to investigate, either own or work for private medical groups that have no obligation to disclose financial information. Thus, the Department of Justice or Congress would have to investigate the matter to obtain the relevant data.

But this much is clear about the FDA committee: Nine of the 10 members that met last September to review the evidence against Prozac either had financial conflicts regarding antidepressant drugs or were members of the psychiatric profession, whose livelihood depends, in part, on prescription drugs. The tenth panel member was Nina Schooler, a psychologist in the department of psychiatry at the University of Pittsburgh. Interestingly, Schooler also is a member of an organization heavily backed by Eli Lilly - the Scientific Council of the National Alliance for Research on Schizophrenia and Depression (NARSAD).

When the hearing drew to a close, what was the final verdict of this committee? The panel members voted 10 to zero that there was no evidence linking antidepressants with suicidal or violent thoughts and behaviors.

The FDA's Bad Science

Critics charge that the FDA's advisory panel left a lot of stones unturned. One major omission was its failure to recognize the importance of the "rechallenging" process, in which certain side effects can be closely linked to a given drug.

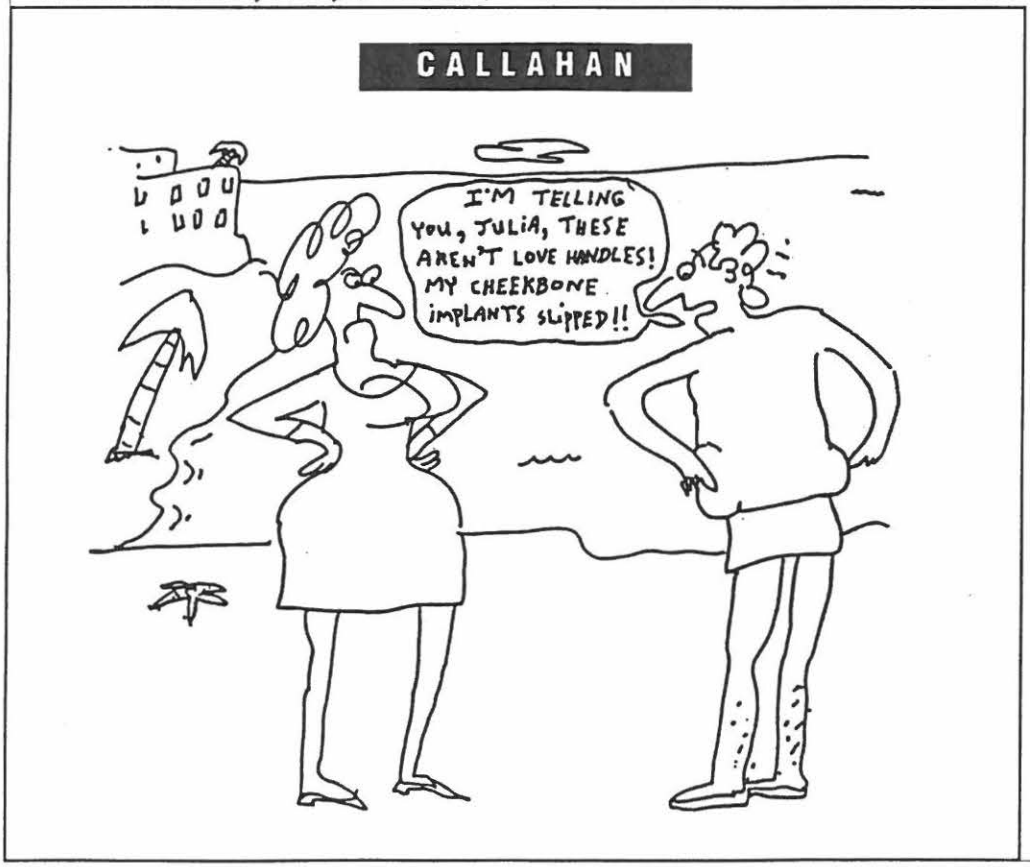
The rechallenging process applies to patients who have previously taken a drug and experienced a particular side effect, which abates when they stop taking the drug. These patients are then rechallenged with that drug to determine if the same side effect will reappear the second time around. If so, a strong correlation between the drug and the side effect is established.

This correlation becomes all the stronger as more and more rechallenge cases link a specific drug with a specific side effect. Eventually, the evidence that a drug and side effect are related becomes quite persuasive. Yet the FDA appears to underestimate the validity of this research tool.

At the FDA hearing, Dr. Martin Teicher, A Harvard researcher, informed the panel members of at least eight rechallenge cases that established a connection between Prozac and violent, suicidal thoughts. (The Rothschild study of three rechallenge cases, described earlier, was not available to the panel at the time.)

The panel was not interested in these findings, despite Dr. Teicher's comment that rechallenging could provide more definitive data in a shorter period of time than would a clinical trial. Indeed, the rechallenging process is relatively simple to carry out, when compared to the time and difficulty associated with clinical trials.

The panel also refused Dr. Teicher's request to present slides that linked Prozac to violent, suicidal thoughts. And yet, the committee allowed three slide presentations in defense of Prozac. O'Brien at the CCHR believes this was a highly questionable move. "It is not believable that a supposedly impartial panel entrusted with the lives and the health of millions of Americans would close its eyes to extremely important information like that," he said.



The National Institute of Mental Health (NIMH) presented one of the slide shows supporting Prozac on behalf of Frederich Goodwin, who was then head of the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA). Later, Goodwin was forced to resign from ADAMHA when he suggested that a study conducted with monkeys could be applied to people who live in America's inner cities. (Goodwin subsequently became head of NIMH.)

What was the thrust of the NIMH presentation? It estimated the total number of suicide attempts from all causes expected among Prozac users in one year, and compared that rate to the number of Prozac-related suicide attempts reported to the FDA in 1990. Apparently, the purpose was to demonstrate that Prozac could actually *prevent* attempted suicides.

Obviously, the number of suicides from all causes has nothing to do with suicide attempts that may have been caused by Prozac itself. When a person submits an adverse reaction report to the FDA, the agency assumes the person believes there was a direct relationship between the drug in question and the side effect being reported, confirms Dr. Paul Leber, head of the FDA's division of neuropharmacological drug products.

In essence, the NIMH used questionable means to build a case for Prozac and ask the panel to dismiss negative evidence against the drug. Dr. Teicher was the only person to question the logic of the presentation made on behalf of Frederick Goodwin, who also is a psychiatrist. Teicher, however, was not a member of the panel and therefore did not have a vote.

The FDA panel also failed to pursue a contradiction arising from a presentation by Jan Fawcett, a psychiatrist at Rush Presbyterian, St. Luke's Medical Center in Chicago. Fawcett's presentation, which was sponsored by Eli Lilly, discussed some of the common risk factors associated with suicide, including anxiety, panic attacks, insomnia and poor concentration. In addressing the panel, Fawcett said that anxiety was a short-term predictor of suicide that often occurred within one year.

Meanwhile, Eli Lilly's prescribing information for Prozac lists anxiety as one of the most common side effects noted during the drug's clinical trials, affecting 9% of trial subjects. (This side effect was not observed in subjects who took placebos.) Likewise, insomnia occurred in 13.8% of the trial participants.

When Dr. Teicher pointed out this contradiction, the FDA's panel chose not to pursue it, even though Dr. Teicher stressed that thoughts of suicide have been linked to many of the side effects of antidepressants - such as insomnia, anxiety, akathisia, panic attacks and mania.

The bottom line, according to critics, is that the FDA panel received more than enough evidence about the link between Prozac and violence to take action against the drug. But the panelists may have abstained from doing so because of their own conflicts of interest with drug manufacturers.

To date, both the CCHR and Ralph Nader's Public Citizen Health Research Group have requested that the FDA take action against this drug. The CCHR's call for a ban on Prozac was denied by the FDA, while Nader's petition for a stronger warning about the drug's side effects is still pending.

In light of the FDA's recent ban on tryptophan, a natural tranquilizer product, its support of Prozac seems especially suspect. The agency called for a voluntary ban on tryptophan in 1990, after a contaminated batch of the amino acid was linked to a number of deaths and illnesses among consumers. While this incident was tragic, the contaminated tryptophan was traced to a single foreign manufacturer. An investigation into five other tryptophan makers found no contamination.

Tryptophan, of course, was a competitor of highly profitable drugs such as Prozac. For more than 40 years, people had used tryptophan as a safe and natural alternative to pharmaceutical tranquilizers. With tryptophan, there are no side effects such as akathisia or aggressive behavior because the amino acid affects the body's chemistry in a balanced way.

When the FDA banned tryptophan, critics such as the *Townsend Letter for Doctors* called the agency's motives into question. In its May 1990 issue, the newsletter stated: "The most important issue from a consumer safety viewpoint, according to the FDA, is to protect the public from exposure to tryptophan. Whether tryptophan itself is the cause of the illness, or a contaminant contained in the product [is the primary cause], is considered irrelevant by FDA officials."

What's With the FDA?

Some critics would say that the FDA's decision not to take action against Prozac is par for the course. Over the years, the agency has approved the sale of many dangerous drugs, proving itself to be a big supporter of the multibillion-dollar pharmaceutical industry.

Two years ago, for example, a detailed report on 198 drugs sold to Americans was released by the General Accounting Office (GAO). Of these drugs, which the FDA had approved between 1976 and 1985, a staggering 52% - 102 of the drugs - proved to have "serious post-approval risks." Among the possible side effects were disabling health disorders and even death. Serious post-approval risks were twice as likely to occur with drugs prescribed to children.

Meanwhile, a Congressional investigation revealed in 1989 that FDA officials had accepted bribes from generic drug makers to speed their new products through the agency's approval process. This investigation was carried out by the Subcommittee on Oversight of the Energy and Commerce Committee, which is chaired by Congressman John Dingell (D-MI).

During the investigation, one example of the FDA's cozy relationship with drug makers came from the Inspector General of Health and Human Services. He told of "conferences' in exotic locations where FDA employees were wined and dined by members of the very industry they are entrusted to regulate. Accepting favors from the drug industry was so common, said some FDA staffers, that they assumed it was a standard, acceptable practice at the agency.

The generic-drug scandal eventually led to the conviction of five companies and 22 individuals for corruption or fraud. Among those convicted were five former officials of the FDA.

In addition, job hopping between the FDA and the drug industry dates back many years. In 1964, it was reported that 10% of the 800 people who left the FDA during the previous five years went to work in the drug industry. And during the Nixon administration, many officials appointed to the FDA had previously worked for drug companies or for consulting and legal firms that serviced the pharmaceutical industry.

More recent examples of such ties are not hard to come by:

- Mark Novitch, former deputy commissioner of the FDA, left the agency in 1985 to join the Upjohn pharmaceutical company, where he is now vice-chairman. Novitch was a 13-year veteran of the FDA, where he had held the position of acting commissioner on two occasions.
- John Norris succeeded Novitch at the FDA as the agency's second in command. Three years later, he joined Hill and Knowlton, a top public relations firm that represents major drug companies, as executive vice president.
- Wayne Pines, the FDA's associate commissioner of public affairs until 1982, now works at Burson Marsteller, the leading public relations firm in the drug industry.

Politics and Pills

If money equals power, then the drug industry is powerful indeed. But how does that play out in the real world? According to some critics, the FDA's continuing support of Prozac suggests that perhaps no regulatory agency could remain impartial in the face of such influence.

When the first lawsuit was filed against Eli Lilly on the grounds that Prozac caused suicidal thoughts, the FDA came to the drug's rescue. Lilly's stock value had dropped after the suit was filed, losing about 10 points in two weeks. In response, the FDA issued a statement in support of Prozac, claiming that its database of adverse reactions to Prozac did not include any reports of intense suicidal thoughts.

More than six months earlier, however, the FDA had already released reports to the CCHR under the Freedom of Information Act correlating suicidal thoughts with Prozac. In essence, then, the FDA was assuring the public that Prozac was safe, while its computer printout of adverse reactions - which is clearly listed by category - showed that the drug could cause dangerous side effects.

Today, the Biffle case in Texas is at the forefront of the Prozac controversy. The suit against Eli Lilly claims that Michael Biffle committed suicide because he took Prozac, and the judge has ordered Eli Lilly to submit the names of all physicians who reported that their patients on Prozac had developed suicidal thoughts or behaviors. The names of the doctors only - not the patients - are covered by the order.

With this list of names, the plaintiff attorneys hope to prove that Eli Lilly knew of problems with Prozac early on but chose not to take action on the doctors' reports. But if the FDA has its way, the names will not be released. The agency's Dr. Carl Peck wrote a letter, to be presented to the judge, arguing that other physicians would hesitate to report adverse reactions if the reporting doctors' names were submitted to the attorneys. This letter, according to a confidential source, was sent after Dr. Peck received a communication regarding the Biffle case from a rather influential source - former vice president Dan Quayle.

Quayle, it seems, had developed a reputation as a drug industry supporter in his home state of Indiana, where Eli Lilly is based. According to an August 1991 article in *The Nation,* Quayle maintained a "continuing flow of campaign contributions" by catering to the drug industry and other special interests in Indiana. And the *Boston Globe* reported in its November 13, 1991 issue that Mitch Daniels, vice president and director of corporate affairs at Eli Lilly was Quayle's "closest advisor."

According to Daniels, Quayle's office was never approached by anyone at Lilly and he never personally discussed business with the vice president. In the *Globe* article, however, an anonymous executive at Eli Lilly said that a lobbyist for the firm did speak with Quayle's top aides about "issues of vital importance to the company."

Oddly enough, Quayle was not the only recent link between the White House and Eli Lilly. Former President Bush had a seat on the company's board of directors before he resigned to run for vice president in 1979.

Eli Lilly and other manufacturing giants that pollute the environment stood to benefit from Quayle's actions as chairman of the Council on Competitiveness. Under the banner of improving the nation's "competitiveness," this White House panel seriously diminished the impact of our anti-pollution regulations. In fact, our level of air pollution may actually become *worse,* says *The Nation,* due to Quayle's reversal of pollution laws.

For all of this, are there any tangible signs that Quayle's committee increased our competitiveness? According to Rep. Gerry Sikorski (D-Minn), a member of Waxman's committee, the answer is a resounding 'no.' In the *National Journal,* Sikorski was quoted as saying, "They can't point to a single item that has made American industry more competitive. What they can point to is a bunch of backdoor, secret decisions that bailed special interests - business interests."

Of all the companies that will benefit from more lax pollution regulations, Eli Lilly is near the top of the list. Its Tippecanoe laboratory in Indiana ranks as the country's eleventh worst polluter of substances that are suspected or known to cause cancer. In February 1991, an Eli Lilly attorney complained to the EPA that the company needed greater freedom to emit air pollutants under certain circumstances. What's *good* for Lilly in terms of pollution standards, of course, is undoubtedly *bad* for the public health.

Finally, Quayle's Council on Competitiveness also worked to speed up the drug-approval process at the FDA - a change that would benefit companies such as Eli Lilly. In November 1991, the Department of Health and Human Services issued a press release from Quayle and HHS Secretary Louis Sullivan stating that the Council on Competitiveness had asked the FDA to alter its drug oversight procedures to "significantly speed the development and availability of new medicines."

An article in the *Legal Times* reports that Eli Lilly representatives met with the Council on Competitiveness several months before this announcement was made to discuss the FDA's drug-approval process.

Lilly's future depends on its ability to get new products to market. But the company's well of new products is rather dry at this time, according to an article in *Barrons.* Eli Lilly had counted on approval from the FDA to market Prozac for weight loss - at triple its starting dosage for depression.

As *Business Week* reported in a June 1992 issue, however, it is highly unlikely that Prozac will ever be approved for such use. But to market new products, Lilly would have to spend years developing and testing the drugs, a potentially calamitous delay for the drug maker. Unless, of course, the Council on Competitiveness succeeds in speeding up the process.

Quayle's maneuvers, however, began to draw the attention of Congress. Quayle and Allan Hubbard, the executive director of the Council on Competitiveness, were investigated when they took actions to weaken the clean air laws. The investigation, initiated by Congressman Waxman (D-CA), examined allegations that Hubbard had helped to alter the regulations to benefit his own company. The investigators also attempted to uncover more data about the secret activities of Quayle and the council.

Quayle, for his part, fought off Congress's attempts to delve into his communications with agencies such as the FDA, arguing that these communications were exempt from disclosure due to his position as vice president. Quayle refused to show up, for example, when summoned by the House Government Operations' subcommittee on human resources. He also ordered Kessler, the FDA commissioner, not to submit certain documents requested by the subcommittee. Kessler was ordered to turn over the documents through a congressional subpoena.

Quayle's claim of presidential immunity was put to use on other occasions as well. When Congress summoned him to answer questions about his secret actions with the FDA and other agencies, Dan Quayle did not show up.

Drugs and Iatrogenesis

And what of Eli Lilly's track record with drug safety? Over the years, this pharmaceutical giant has produced some extremely dangerous products - and it has knowingly withheld information about negative side effects. Some of these drugs have left their users with far worse health problems than those they originally took the drugs to treat. Some examples:

- **LSD** - This drug was originally created by Sandoz; Eli Lilly then completed the synthesis of LSD. For many years, psychiatrists promoted the use of LSD. Unfortunately, their audience was a generation of people who did not know how to handle such a powerful hallucinogenic drug.
- **Methadone** - After Nazi scientists developed methadone, Lilly brought it to the U.S. as a treatment for heroin addiction. Methadone not only failed at this task, but it also turned out to be much more addictive than heroin.
- **Darvon** - When Lilly introduced Darvon, it was promoted as a safe, non-narcotic pain killer. Years later, Ralph Nader's Health Research Group called it "the deadliest prescription drug in the United States," according to an article in *Time* magazine.
- **Oraflex** - Once again, Lilly marketed this drug as a safe and effective treatment for arthritis. And once again, the opposite was true. In 1985, Lilly pleaded guilty to criminal charges for failing to report four deaths and six illnesses in Europe related to Oraflex. Before the Oraflex fiasco had ended, more than 100 deaths had been associated with the drug. Lilly's penalty was a $25,000 fine, the maximum allowable under the law.
- **Diethylstilbestrol (DES)** - This "wonder" drug, produced by Eli Lilly and other manufacturers, was prescribed to millions of pregnant women to prevent miscarriages. While the drug makers claimed that the product was safe one researcher noted in 1950 that DES tended to promote premature labor. Decades later, the daughters of women who took DES developed cancer due to the drug's use. Eli Lilly, it was discovered, had withheld facts about the drug's side effects.

As these examples show, the company has a disturbing tendency to ignore evidence of tragic and even fatal results until the damage is done. And this leads us to a final question: what does Eli Lilly intend to do with Prozac - the most lucrative drug ever put out by the company?

The Profit Incentive

When Prozac was launched in early 1988, it hit the market with a bang. Eli Lilly's stock, which stood at about $40 per share, climbed to a high of nearly $90 over the next 18 months. However, the stock began to decline when the first lawsuit concerning Prozac was filed against Lilly, costing shareholders billions of dollars in lost value.

The company - and stock analysts - had pinned a lot of hope on Prozac. As the *Economist* reported in its October 1989 issue, Lilly's troubles before the Prozac controversy and its low stock value made it a takeover candidate. Prozac, with its huge sales potential, was expected to boost the company's flagging stock.

To date, the drug has made a tremendous amount of money, but the reports of suicidal and violent side effects have put a damper on future projections. In 1989, its second year of sales, Prozac generated $350 million in revenue. In 1990, sales doubled to $700 million, accounting for 12% of Eli Lilly's revenues. One financial firm predicted Prozac sales of $1.5 billion in 1992 and $2.3 billion by 1994.

Today, however, Prozac sales have flattened and the drug has seen an actual decline in the number of prescriptions sold. Originally, Eli Lilly was expected to make as much as $20 billion from Prozac by 2001, when the patent expires. Now, that expectation has been reduced by half. In fact, Eli Lilly could lose a total of $15 billion if Prozac were to be pulled from the market in the next year or two.

In the end, the Prozac scandal raises some serious questions for Americans to consider. How closely connected can we allow the FDA to become to its designated charge - the powerful and lucrative drug industry? And, more important, if we allow conflicts of interest to undermine our country's drug approval and oversight function, can we live with the consequences?

Clearly, we need to address the Prozac controversy in a more responsible manner, through an impartial forum that will not be influenced by the mammoth drug industry. With Prozac on the market for nearly five years, and with many questions unanswered, it seems that Congress should step in to help get the issue resolved. ◆