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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

PSYCHOPHARMACOLOGICAL DRUGS

ADVISORY COMMITTEE

Friday, September 20, 1991

Conference Rooms D/E
Parklawn Building
Rockville, Maryland

C O N T E N T S

PROCEEDINGS

CALL TO ORDER: WELCOME AND INFORMATION

DR. CASEY: Good morning. I would like to call this meeting to order and to welcome everyone to the 34th meeting of the Psychopharmacologic Drugs Advisory Committee. My name is Dr. Daniel Casey and I am from the V.A. Medical Center and the Oregon Health Sciences University in Portland, Oregon. I have the pleasure of being the chairman of this committee.

I would now like each member at this table to identify himself. Dr. Leber, first.

DR. LEBER: I am Dr. Leber, I am Director of the Division of Neuropharmacological Drug Products.

DR. TEMPLE: I am Dr. Robert Temple. I am Director of the Office of Drug Evaluation I.

DR. CLAGHORN: I am Dr. James Claghorn, Clinical Research Associates in Houston.

DR. LIEBERMAN: Jeffrey Lieberman, Long Island Jewish Medical Center, Albert Einstein College of Medicine, New York.

DR. SCHOOLER: I am Nina Schooler with the University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania.

DR. CASPER: I am Regina Casper with the University of Chicago, Department of Psychiatry and Committee on Human

Nutrition.

DR. HELLANDER: I am Ida Hellander with the Public Citizen Health Research Group in Washington, D.C.

DR. MANN: John Mann, Department of Psychiatry, University of Pittsburgh.

DR. DUNNER: Dr. David Dunner, Department of Psychiatry and Behavioral Sciences, University of Washington in Seattle.

MR. BERNSTEIN: Michael Bernstein, the Executive Secretary to this committee.

DR. TEICHER: Martin Teicher, McLean Hospital and Harvard Medical School.

DR. STANLEY: Michael Stanley, Department of Psychiatry, Columbia University.

DR. MONTGOMERY: Dr. Stewart Montgomery, Department of Psychiatry, Saint Mary's Hospital Medical School in London, England.

DR. REGIER: Darrel Regier, Director of the Division of Clinical Research at the National Institute of Mental Health.

DR. LIN: Keh-Ming Lin from UCLA Medical Center, Director of the Research Center on the Psychobiology of Ethnicity.

DR. ESCOBAR: Javier Escobar, University of Connecticut Health Center in Farmington, Connecticut.

DR. HAMER: Robert Hamer of the Department of Psychiatry and Department of Biostatistics, Medical College of Virginia, Virginia Commonwealth University.

DR. TAMMINGA: I am Carol Tamminga from the Department of Psychiatry at the University of Maryland in Baltimore.

DR. LAUGHREN: Tom Laughren, Group Leader for Psychopharmacology at FDA.

DR. CASEY: Thank you. Welcome to the new committee members and to the invited guests of the committee.

Mr. Bernstein, the committee's Executive Secretary, has requested time to make a number of administrative announcements. Mike, please?

OPENING COMMENTS

MR. BERNSTEIN: Thank you, Dr. Casey. I wish to welcome each of the committee members to this, the 34th meeting of the Psychopharmacologic Drugs Advisory Committee. Additionally, I would like to welcome three of our new members of the PDAC, Dr. Lin, Dr. Casper, and Dr. Schooler.

My name is Michael Bernstein and I am the Executive Secretary of the committee, which functions within the Division of Neuropharmacological Drug Products. Please bear with me while I make a few administrative announcements.

On the table by the entry are handouts of the agenda, question list, and roster of committee membership. I

hope that everyone has picked up a copy. Also on this table is an attendance sheet which we hope everyone in attendance has signed. If today's meeting is to serve the public interest, the cooperation and good will of all participants is critical. Let me explain.

Ordinarily, open public hearings are held immediately prior to the formal session and are limited to one hour's duration. This time limitation is intended to strike a reasonable balance between allowing individual citizens to make statements before the committee and the absolute need of the committee to have sufficient time to conduct its official business in a comprehensive and deliberate manner.

However, in light of the intense public interest and emotion surrounding the item on today's committee agenda, the chair of the PDAC, Dr. Casey, who has the legally delegated authority to do so, has agreed to expand the open session to allow as many as 50 individuals the opportunity to make a brief verbal statement of five minutes or less in duration. Those who could not be accommodated as speakers are respectfully invited to submit their statements in writing for the record.

Even with the imposition of limits on the number of individuals who may speak and the maximum length of any individual statement, the open public hearing is expected to take approximately four-and-one-half hours. We can ill afford

to extend the duration of the open session any further, because it would surely compromise the ability of the committee members to hear the formal agenda presentations and provide the high quality of discussion and advice we all seek.

It is the chair's intention that the total duration of the meeting should not exceed 10 hours; that is, Dr. Casey plans to adjourn the meeting at 6:00 p.m. Accordingly, all participants in the meeting must adhere conscientiously to the time allotted, be they participants in the open public or regular sessions.

To ensure an efficient use of time in the open public hearing the following system will be employed. There will be two active microphones. The 50 individuals have been granted an opportunity to make a public verbal statement. Specifically, the first 50 to apply to the Executive Secretary have been arranged in alphabetical order and given an assigned number. Those with odd numbers will use the microphone at the right, those with even numbers, the microphone on the left. When a speaker at one microphone completes his or her statement or when five minutes elapse, whichever occurs first, that microphone will be turned off and the speaker at the alternate microphone will be asked to begin his or her statement.

The speaker should identify him- or herself prior to speaking. Any speaker who is not present at the microphone

when his or her name is called, his opportunity to speak will be lost. If, as the morning proceeds, a speaker discovers that the point he or she wishes to make has already been made, it would be helpful to all if that speaker would elect to relinquish his or her allotted time slot. The speaker, of course, could still submit his or her comments in writing.

I trust that all speakers will understand the necessity of placing limits on the extent of individuals' participation in this meeting.

In the event that any person at this hearing becomes uncooperative or disrupts this meeting in any way, he will be escorted out of the building by our security force.

(Administrative announcements)

As this is an open hearing, a reminder that the proceedings may be tape-recorded, but the recording is considered to be unofficial until it has been approved by the Commissioner of the Food and Drug Administration. A review of the agenda by Committee Management Branch personnel indicates that no committee member requires limitation on his participation at today's session based upon reported interests as of September 19, 1991.

The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. The purpose of this meeting is a scientific investigation into

suicidal ideation, suicidal acts, and other violent behavior reported to occur in association with the pharmacological treatment of depression.

In accordance with the prepared agenda, there will be no specific issues dealing with a specific product or sponsor presented to the committee for review and evaluation during this meeting. Therefore, it has been determined that all committee members may fully participate in today's meeting without the risk of any conflict of interest, as defined in 18 USC.

In order to preserve the integrity of the objectives of the agenda and to preserve fairness, all members and consultants are requested to limit any issue discussed to class action considerations at this meeting. However, while it is not the objective of the meeting to advise FDA regarding possible actions that could potentially affect all manufacturers of antidepressant products, it is possible that such recommendation could result from this meeting. Therefore, FDA has taken the additional precaution of granting class action waivers for members and consultants who have any reported active financial interest in any manufacturer of antidepressant drug products.

Class action waivers have been granted to the following members: Keh-Ming Lin for his interest in Merck; Jeffrey Lieberman for his interest in Sandoz; Robert Hamer for

his interest in Bristol-Myers-Squibb; David Dunner for his interest in Sandoz, Burroughs-Wellcome, American Home Products, including Wyeth Labs and A. H. Robbins, Eli Lilly, Pfizer, Ciba-Geigy, Warner-Lambert, including Parke-Davis, SmithKline Beecham, and Bristol-Myers-Squibb.

Class action waivers have also been granted to the following consultants: James Claghorn for his interest in Sandoz and SmithKline Beecham; Michael Stanley for his interest in Merck, Pfizer, and Eli Lilly.

A copy of these waiver statements may be obtained in the agency's FOI office in 12A-15 of the Parklawn Building.

In regard to FDA's invited guests, John Mann would like the record to reflect that he participated as an unpaid consultant to Eli Lilly on May 2, 1991. Stewart Montgomery would like the record to reflect that he participated as principal investigator in a placebo-controlled study of fluoxetine in prophylaxis of suicidal behavior from 1988 to July, 1990. Martin Teicher would like the record to reflect that he has a financial interest in Burroughs-Wellcome for the product Wellbutron, and he is negotiating a contract with Cepacor to study fluoxetine. He received a consulting fee from Cepacor. He receives speaker fees directly and indirectly from Upjohn for talks on diagnosis and treatment of seasonal depression. He participated in the Wellbutron advisory panel in December, 1990. He serves as a consultant

to attorneys in various litigations against Lilly or in cases where criminal defense was related to the use of Prozac.

The agenda reflects only Eli Lilly under the topic "Pharmaceutical Company Presentation." It should be stated that all manufacturers of antidepressant drug products were invited by the FDA to present data at this portion of the meeting and all but Eli Lilly declined the invitation. However, some have made submissions of material to the record concerning their interest in this subject.

In the event discussions involve any other products or firms not already on the agenda for which an FDA participant has financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Lastly, the emergence and/or intensification of suicidal thoughts and acts and/or other violent behaviors in association with antidepressant drug use will be the only issue discussed by the committee at this meeting.

Thank you for your attention. This concludes my comments.

DR. CASEY: Thank you, Michael.

The open public hearing will be held first and is now in progress. Fifty individuals have contacted Mr. Bernstein and requested an opportunity to address the committee. The first speaker is Maryles Allen.

(Administrative announcement)

OPEN PUBLIC HEARING

MR. BERNSTEIN: Is Maryles Allen here?

(No response)

DR. CASEY: Next will be Burton Appleton.

(No response)

DR. CASEY: Marian Badovinac?

(No response)

DR. CASEY: Sally Barrett?

MS. BARRETT: My name is Sally Barrett and I am here with my husband, Al Barrett. We both live in San Diego, California. We are members of the San Diego chapter of the Prozac Survivors Support Group. Al and I have traveled many miles to be here before the Pharmacologic Drugs Advisory Committee members, to testify before this committee, to tell a story that is very painful and difficult to relate, but a true story that needs to be told.

This story has to do with our youngest daughter, Jennifer, and our experience with the drug Prozac. On January 25, 1970, Jenny entered our lives and captured the hearts of her mom and dad, like her older sister had. She was a child

who always did well in school with no pushing from her family. Jenny was a naturally self-motivated young lady and she was an achiever, and she remained so all of her elementary school days and on through high school. She graduated with honors at the top of her class. We always felt she had the greatest talent and potential of anyone in our family.

However, at age 17 she developed an eating disorder called anorexia. Her doctor placed her on a number of antidepressants with no positive results. By the end of 1989 her condition had improved and her weight was normal. We were much encouraged by this change. In January, 1990, however, she was placed on the antidepressant Prozac. Several weeks later she took an overdose, which was her first suicide attempt.

Jennifer herself could not understand why she would do such a thing, nor did we. For the next four or five months after she was taken off of this drug she did not talk about suicide nor attempt it. However, she was heavily sedated under the effects of another drug, called enafranil [phonetic] and she was then placed on Prozac to counteract the effects of enafranil. The doctor said she had never prescribed this combination before. Her evaluation of Jennifer was that she was mildly depressed. This occurred in July of 1990.

In 1990, after starting Prozac, Jenny's behavior became more agitated and aggressive and hostile. Jenny

started having terrorizing nightmares, frightening the whole family with her outcries. Jenny's behavior began to change dramatically and drastically. She started shoplifting in the stores, a strange and unusual act which we could not understand, especially since she had quite enough money to make the purchases herself.

It was at this time that she began spending money wildly and impulsively. She began overeating at this time and gained 75 pounds. The second month after Jenny was again -- the second time that she was placed on Prozac she secretly purchased a gun on August 25 and shot herself in the head and died on August 27.

Since Jenny's death we have been trying to rationalize and understand how and why this happened. Jenny was a happy girl and an honors student and she had many friends. As we tried to put the sequence of this bizarre chain of events together, we realized that the change in our daughter's behavior occurred after Jenny started taking the drug Prozac.

My daughter and our family were totally uninformed or warned of the dangers and the risks involved with the use of this drug Prozac. Are we not entitled to an educated, intelligent, and informed choice when we take such powerful and mind-altering drugs as these? If we had been fully informed, we would never have allowed our daughter and our

loved one to use this drug.

I believe anyone who knows the truth about the risks involved would come to the same conclusion we have, that it just is not worth the risk. I really wonder what is happening in the United States when human life, our most precious commodity, is expendable in the pursuit of corporate profit and greed. I think it is time for America's most vulnerable citizens to stop being used as uninformed guinea pigs for Eli Lilly's wonder drug.

I respectfully request that this drug be taken off the market so that no other child or family will suffer the loss and the devastation that we have. Thank you for your time and attention to this most important matter. This bizarre chain of events had led us to believe that she had a very strong reaction to the drug she has been on.

The following was added by my husband. He said, "I truly believe that my daughter's executioner was Eli Lilly, who, through the killer drug Prozac, carried out the sentence given her when Prozac entered her unsuspecting body and mind. She carried out the death sentence herself, death by Prozac."

Al and I received a death sentence for life, too, but our sentence is for the rest of our lives. Eli Lilly murdered my soul with the drug. Now we are facing a life sentence without Jenny here to share it with us. Thank you.

DR. CASEY: Thank you. Next is Melynda Bavmann,

please.

(No response)

Dr. Peter Breggin, please?

(No response)

Pallie Carnes?

MS. CARNES: Good morning. My name is Pallie Carnes. I am the Director of the Prozac Survivors Support Group of Covington, Georgia.

I was put on Prozac for weight loss, since I had had a baby the year before and I was having a hard getting the stubborn pounds off. I was put on it for weight loss and only three days after being put on Prozac I started having terrifying nightmares. I would wake up screaming and the nightmares always had something to do with death.

I couldn't laugh or I couldn't cry. I started having headaches and forgetfulness. I had no emotions at all. Soon after, I started having suicidal thoughts, followed by a suicidal attempt. I was always very agitated with the people I had to deal with on a daily basis. My friends and family were very concerned about me. My children didn't understand what was happening to their mother. I didn't realize what I was putting them through. And to top it off, I gained weight.

Then, from watching a T.V. talk show, I learned that Prozac was an antidepressant drug and not a weight loss aid

and that a lot of people who were taking Prozac were having the same symptoms that I was having. I quit taking Prozac that day and, soon after, I started feeling like my own self again.

Although I still have the headaches, fatigue, and forgetfulness which first appeared when I was taking Prozac, I consider myself lucky to be alive. I was only taking Prozac for three weeks. I often wonder what would happen if I had continued taking this drug. Why is it so hard to admit that a mistake had been made when Prozac was released to the public? After all, we're only humans and humans make mistakes. Can we not correct this mistake and take Prozac off the market before any more damage is done or any more lives ripped apart, or is Prozac profit the only voice being heard?

Please listen to the survivors here today. We know, firsthand, the truth. I wonder how many doctors who believe in the power of Prozac would take it? After all, it's given to patients for everything from a pick-me-up to a weight loss aid. Are they just a bit nervous from taking this drug themselves but they would not hesitate to give it to an unsuspecting patient like me?

I was a different person while I was taking Prozac. I was a zombie. I would sit and stare. I was completely without emotions. If you can only realize how this feels, not

to be able to laugh or cry and not know why. I didn't have the patience to help my children with their homework or the energy to play a game with them like I usually do. But I didn't care. I only knew that I did not want to be around anyone and that included my family. I was not the loving mother and wife any longer.

If Prozac can affect me, a 27-year-old healthy mother of five children, in just three weeks, what could it do in a couple of months? Given the history on Prozac and the way it has already affected me, I hate to think what could have happened.

I am a different person now. I am the loving and caring mother and wife and I will never forget how Prozac affected my life. I only hope my children will forget the uncaring, selfish, and physically ill person that Prozac turned me into when all I wanted to do was lose weight.

Eli Lilly calls Prozac the wonder drug, and I wonder why. Thinking back on how this drug affected me, does a wonder drug rob you of a conscience? Does a wonder drug make you forget the difference between right and wrong? I no longer wonder about this so-called wonder drug; I now know that I wouldn't be here today if I continued taking this killer drug.

I'm pleading with all of you who sit on this committee, who have the power the remove this drug, at the

same time considering approving Prozac's sister drug, Loban, for a weight loss aid, remove Prozac from the marketplace and save lives, not approve Loban and release yet another killer. Haven't there been enough deaths to prove to the Food and Drug Administration that Prozac is killing America and its people?

This is hard for me, because I tried to commit suicide in front of my five children. I didn't know what I was doing and don't remember exactly what happened. All I know is that my husband took the gun away from me and my children were looking from the other room. What would have happened if these children had seen their mother commit suicide? I was only put on it for weight loss -- weight loss. Is it worth it? Is it worth it for my children to be motherless today because of a drug that has no side effects, I was told -- had no side effects -- but yet it brought me to the brink of holding a gun to my head and almost killing myself. If my husband wasn't there, I wouldn't be here. The children wouldn't have a mother.

My husband stuck by me, my family and friends have stuck by me. They have seen what it's done to me and it's just not worth it. I plead for you to just take a second look at this drug and see what it's doing. Don't the numbers count for themselves? Don't the people here today, average normal people speaking, have anything to do with your votes and what you're going to decide?

DR. CASEY: Thank you very much. We appreciate your comments. Next is Dennis Clarke, please.

MR. CLARKE: Good morning, Mr. Chairman, my name is Dennis Clarke, President of the Citizens Commission on Human Rights International.

Our Commission was involved for several years in investigations into the effects of many psychotropic medications on individuals who have committed some rather heinous crimes in this country, including such individuals as Patrick Purdy, who shot up a school in Stockton, California, shooting 34 children and a teacher -- the man had been on Elavil for the previous two years; Lorrie Dann, who shot up a school in Winnetka, Illinois, who was on, at the time, an experimental drug called enafranil; James Wilson, who shot up a school in Greenwood, South Carolina, he had been on antidepressants and was being withdrawn from Xanax under a psychiatrist's care at the time; and such people as John Hinckley, Jr., a Valium addict who, according to experts, testified at his trial was in a Valium-induced rage when he shot President Reagan, Jim Brady, and the two police officers in Washington, D.C., in 1981.

That investigation led us to look into the Westbecker massacre in Louisville, Kentucky, in September of 1989. The perpetrator of that crime was found to be, by the coroner, with high therapeutic levels of Prozac in his blood

at the time of the massacre. An initial review of the existing data publicly available on the drug led us to request of the FDA, in October of 1989, through the Freedom of Information Act, any data that the FDA might have on the drug.

The data that we received pointed to the startling possibility that Joseph Westbecker and the eight others who died in Louisville and the 12 who were left wounded and crippled and their families were, in fact, the victims of the irresponsible and negligent promotion and sale of an inherently dangerous and defective product.

Evidence compiled since that massacre in Louisville has only confirmed the certainty that, in fact, Prozac is flawed as a product and must be removed from the market. That this has not happened in spite of the overwhelming evidence in the files of the FDA to support that action, indeed, raises some serious questions about what might be going on within the FDA and with this committee here today.

Before I expand on this point, let me point out to you that in the last week the Council of Europe, representing 23 member countries in Europe, has, by written declaration, called for the discontinuance of Prozac in Europe. In Holland this week an advisory commission for the side effects of drug started an official government investigation into the problems with Prozac. In addition, the government agencies in Sweden and Norway have refused to register Prozac for sale in their

country.

The real questions which we are now pursuing answers to are not whether the drug should be taken off the market, which it should, but why it was allowed on the market in the first place and why it is still on the market. According to the FDA documents which our Commission obtained through the Freedom of Information Act, Prozac has been linked to more deaths and more suicide attempts in a shorter period of time than any drug in history.

According to FDA sources, this is now over 500 deaths documented in the files of the Food and Drug Administration. We estimate that number to be 10 to 20 times that in total in the society. So why is this drug still on the market? It is our belief, and we have attached evidence in writing to prove that, in fact, the decisions which have been made and are being made on Prozac and which will be made in the foreseeable future are being made by individuals who are appointed by the Food and Drug Administration and who have a vested interest in having and keeping Prozac on the market.

While the American people, by and large, feel that the FDA has tested Prozac and found it to be safe and effective, the truth is, this agency has never tested the drug and has never done its own independent study of the drug.

As the time for testimony is quite limited, what we have to say about the perceived conflicts of interest will be

in writing. We strongly recommend that this committee recuse itself from reviewing this matter and that a new committee, made up of a broad spectrum of medical professionals and consumer representatives free of conflicts of interest, be empaneled to independently investigate the facts and evidence already on hand at the FDA.

We also recommend that you listen closely to the voices of the representative American victims of this inherently dangerous product who have put their lives on hold to come here before this committee today to tell you their tragic experiences with Prozac. Listen well.

DR. CASEY: Thank you very much. We appreciate your comments. Next is Mrs. Del Shannon, please.

MS. SHANNON: Lee Ann Westover.

DR. CASEY: Excuse me, are you Mrs. Del Shannon?

MS. SHANNON: I am Mrs. Del Shannon, yes.

I am the widow of Charles Westover, also known as Del Shannon. My husband was given Prozac on January 24 of 1990. On the evening of February 8, 1990, he killed himself. I am told his death was instantaneous, but I believe his death actually began the moment he took his first dose of Prozac.

Before Prozac, my husband was very involved with people, our family, and his work. He was very much in charge of his business. But within days after he started taking Prozac I noticed a personality change in him. He showed signs

of restlessness, akathisia, agitation, pacing, and his appearance was very drawn. He developed severe insomnia, extreme fatigue, chills, racing heart, dry mouth, and upset stomach. His hands would shake uncontrollably at times. This really alarmed him. I would ask him what was wrong and his only reply was, "I don't know, I don't know."

At this time my husband's career was better than ever. He was just finishing a new album and was at his utmost creative peak. Many good changes were happening rapidly in his life. On January 24, due to these changes, he went to a doctor for counseling, as he was experiencing some stress. He was given Prozac. Two weeks later I found him dead in our home.

He told me, when he came home from the doctor, that he was given a new drug, "It's not even a drug, it's a chemical, it's very safe. It's supposed to help me over the hump I'm in." The drug was Prozac. Charles was very much against suicide. He counseled people against suicide. To him, and I quote, "Suicide is a permanent solution to a temporary problem."

I want you to know suicide was totally out of character for my husband. There was no note and no goodbye. The day he died he had made appointments for the following afternoon and evening. He had booked future gigs.

On February 8, my daughter and I were going to the

market. He asked for some vitamins and other items that he wanted from the market. He kissed me, smiled, and we said, "See you later." There was absolutely no warning of suicide or anything violent.

I know with absolute certainty that if Charles had any idea of the side effects of Prozac he would never have taken it. This drug is most assuredly responsible for any torment or suffering and the eventual suicide of my husband. I want people to be aware of what can happen when you take the drug Prozac. Thank you.

DR. CASEY: Thank you. Mr. Richard D'Alfonso, (No response)

Sharyn DeGeronimo, please.

(No response)

Susan Dime-Meenan, please.

MS. DIME-MEENAN: Mr. Chairman and members of the advisory committee: My name is Susan Dime-Meenan and I am Executive Director of the National Depressive and Manic-Depressive Association. I am here today representing over 35,000 members who are patients with depressive illness. The National Depressive and Manic-Depressive Association is the only patient-run organization, membership-based, in this country. Through our 250 local chapters we aim to increase research, education, and public welfare. We aim to end stigma and discrimination against those who suffer from these

medical, treatable disorders.

I am suffering from manic-depressive illness, and seem to be trembling, since I'm so nervous about being here. I understand all too well the difficulty associated with these illnesses. I understand all too well how difficult it is to be properly diagnosed and receive treatment for this debilitating illness.

Only recently has medical science found evidence that manic-depressive illness is a biochemical illness. Only recently has it found that it's a chemical imbalance in the brain. I'm here this morning to tell you, Mr. Chairman, that the National Depressive and Manic-Depressive Association is opposed to any opposition in labeling for antidepressant medication in general and Prozac in particular.

Scientific evidence from around the world has found no causal linkage between antidepressant medications and the emergence or intensification of suicideality or violent acts. Suicideality is a symptom of depressive illness. It is a common experience among those 80 percent of us patients, as are sleep disorders, feelings of worthlessness, and eating disorders. In fact, suicidal behavior occurs in 15 to 40 percent of us and 15 percent of the untreated patient population does commit suicide, the fatal act.

Any change in labeling, especially when there is no scientific evidence to support such action, would generally

harm the patient community and make it more difficult to be treated with these life-saving medications. Physicians would hesitate to prescribe them and some patients may discontinue taking their medication abruptly, without consulting their doctors, resulting in relapse into their illness.

A change in labeling is not an abstract concern to us. It could cost us lives. We believe that the most important step a patient can take on the road to recovery is to seek appropriate treatment and medical attention. Almost all clinically depressed people can be helped substantially. Unfortunately, depressive illness is also among the least recognized mental illnesses and only 30 percent of the patients ever receive any kind of treatment.

It's important that all of us, including this committee, do everything we can to remove barriers for treatment for those of us whose lives have been saved by antidepressant medications. We must discourage the stigma associated with mental illness and not discourage people to seek treatment.

I find it extremely dangerous that these unfounded, nonscientific allegations about antidepressant drugs have reached this level of public concern. This entire controversy is fiction. It's been organized and funded by an anti-psychiatric cult, the Church of Scientology, which has waged a campaign against medical care of the mentally ill. They

have exploited the pain and the suffering and misled people about the chemical nature of these diseases.

Mr. Chairman and members of this committee, I urge you to base your labeling decisions on science and not scientology, on fact and not fanaticism. The patient community is looking to you to protect our access to care. The patient community is looking to you to protect these life-saving medications and help us receive the medical treatment necessary for us to continue our lives. Thank you very much for your consideration.

DR. CASEY: Thank you. Mr. Mike Donnelly, please.

MR. DONNELLY: I am Mike Donnelly. It is a matter of moral responsibility that I am here today. I'm a successful business- and family man from south Florida. I'm a Christian and do not belong to the Church of Scientology. I've always been mentally healthy and well blessed.

Two years ago I sustained a massive head injury due to a car accident. After months of treatment and rehabilitation I tried to go back to work and run my business. I became frustrated by my inability to function as I used to. My doctor recommended I see a psychiatrist to help me through this anxiety.

I met with this psychiatrist and he had me fill out these mental test forms in which one question asked if I had thoughts of killing myself. Well, this question shocked me

and I checked no. It went on to ask several more questions. I filled them all out. He then graded these tests and gave me a high score on them, what you would call, perhaps, an A on my mental condition at the time.

He then declared, through no scientific test, that I had a chemical imbalance in my brain due to the head trauma and which could be corrected by taking America's new wonder drug, Prozac, and showed me Newsweek magazine proclaiming this statement on the cover.

I have found psychiatrists abuse this generalized statement of a chemical imbalance of the brain as a way to prescribe these psychiatric drugs and a way to start the psychiatric revolving door, just go in and out, in and out, and sometimes the problem is you never come out.

The first week taking Prozac I felt no effects. The second week my anxiety increased, I could not make decisions, and I had trouble eating and sleeping. The third week I became agitated and could not sit still. I began pacing through my house and had more trouble eating and sleeping. The fourth week I had total loss of appetite, complete insomnia, anxiety was literally pouring out of my ears. After not sleeping or eating the entire week, I was incapable of any rational thinking and reduced to a pathetic shell of a person with nothing inside. I felt like I literally lost my soul, incapable of any emotion whatsoever.

At this time I did not attribute these effects to Prozac but merely saw my head trauma from the car accident was getting worse. My anxiety became humanly intolerable and I became convinced I was never going to be the same, that the only way to have peace and serenity again was to die. This is how I became intensely suicidal.

I would like to describe intensely suicidal for you. I wanted to throw myself under our large company dump trucks as they were pulling out for work. I fantasized about drinking weed killer, throwing himself on high-voltage power lines, running across a police practice gun range in full fire, wrestling a gun from a policeman's belt while in a crowded store, jumping off the balcony of his parent's 10th floor condominium, and many more suicide fantasies.

I realized I needed help at this point and went back to the psychiatrist, who recommended I double my dose of Prozac. I committed myself to an institution, where I would be safe and could be properly monitored. After visiting two institutions, with my bags packed, ready to commit myself, I lay down on the bed in a room that would have been mine. I remember staring up and looking at the ceiling for several minutes. Then I got up, I walked over to my wife and I said, "I can't do this, I'm leaving."

I walked out the door and got in the car and left, as a passenger -- I couldn't even drive a car. On the way

home my wife yelled at me and said I had to listen to the doctors, I had to stay in the hospital, and I did not even want to help myself. On the way home I got a glimmer of what might be happening to me, and when I returned home I walked straight into my bathroom, opened up my medicine cabinet and took out the bottle of Prozac and said, "This stuff is killing me," and flushed it down the toilet.

This is after two months of taking it. I said, "I'm not taking this drug anymore, see a psychiatrist, or commit myself to an institution. I'm taking vitamins and start working out." Then I barged out my front door and made a feeble attempt at jogging around the block.

For the next month and a half this nightmare raged on. I still had insomnia, high anxiety, and suicidal thoughts and was not sure it was definitely Prozac causing this. Little by little my anxiety subsided. I began sleeping again and suicidal thoughts subsided.

Once again I was capable of rational thinking. I read some literature about the tremendous adverse reactions that can be caused by Prozac and it was like reading about what I had just gone through. I realized that this was Prozac that pushed me to the brink of self-destruction and I could be normal again.

To think this psychiatrist wanted to double my dose of Prozac and institutionalize me is a blatant inhumane

atrocity.

DR. CASEY: Mr. Donnelly, could you please sum up?

MR. DONNELLY: Yes, I would like to. I need one more minute, please.

I would have committed myself -- I believe if I would have committed myself to this institution I would still be there to this day or I would be dead, a definite wasted life, another statistic. This drug is too dangerous to be given out like candy. Psychiatrists, Eli Lilly, and the FDA should be held directly responsible for ignoring these overwhelming abundance of facts and accountable for all the atrocities that are directly linked to this drug that I've read about.

Eli Lilly has presently petitioned the FDA to approve Prozac, fluoxetine, as a diet pill under a disguised name called Loban. Loban will have 60 mg instead of 20 mg that is the standard dosage being prescribed as an antidepressant. I can see it already on the cover of national magazines, "America's New Wonder Diet Pill, Loban," for people dying to look --

DR. CASEY: Mr. Donnelly, in fairness to the other people, I will have to ask you to make just one more sentence.

MR. DONNELLY: In fairness? I'm a taxpayer. I need 30 more seconds to finish.

(The microphone is turned off)

DR. CASEY: Mr. Donnelly, thank you very much for your comments. We appreciate your time. Miss Irene Dotson?

MS. DOTSON: Good morning. My name is Irene Dotson. I came with my 10-year-old son and my sister from Jefferson City, Missouri, to share a personal experience that I had while taking Prozac.

In 1989 I was working at a very high-pressure job. I was working for the Missouri Department of Social Services. I was managing an apartment complex and I was working on my master's. Things were going pretty good but it was very stressful. I finally just decided I've got to go the doctor and talk to my doctor and find out why I'm not being able to handle this. I've handled much more in the past.

The doctor told me that this wonderful new drug Prozac would really get me through this rough time that I was having and just to bear with it. He said it's sort of slow, you know, getting it started. It may take two or three weeks before you see any help, but once you do, you'll feel much better.

Before taking the Prozac -- my husband and my son and I, we all work together at managing this apartment complex, we work side by side day after day -- we had a very healthy, happy family. Once I began taking the Prozac that all changed. I underwent this complete personality change. I became paranoid, I wanted to avoid everyone -- I stayed in

my bedroom -- I wouldn't answer the phone, I wouldn't answer the door, I didn't go to work. I just couldn't deal with anyone, not even my son or my husband.

When I started having these nightmares of dying -- and it was always of me dying, different ways, it was almost like a videotape, like a horror movie being run through my head every night, so then I didn't want to go to sleep. I just wanted to stay up all the time. That didn't help.

I didn't know what to do about it, so I decided that I was just going to go ahead and take care of myself and that everyone else could just forget me. I was just going to take care of myself and get through this. And that is not typical of me and it's not typical of me to ignore my friends and my family, and I was putting them through a very, very bad time.

It seemed like everyone was trying to push me over the edge. In citing one incident, which became a very violent time, my husband and I had what would have been a minor disagreement, say, six months before taking Prozac. I attacked him with a kitchen knife. Luckily, he's bigger and stronger than I am and he defended himself, but I did this right in front of my son. Whenever I was stopped, I thought, "I can't believe what I'm doing. I don't believe what I'm doing. This is wrong."

Then I decided that I was going to kill myself. My doctor had prescribed nerve medicine for me -- I think it was

Ativan. I had just had the bottle filled that day and had a hundred pills in it. And so I went and I took all hundred pills, right in front of my son and right in front of my husband. I was really lucky, because my husband forced me to go to the emergency room, but I was already completely knocked out by the time we got to the emergency room.

They saved me. They told me that I could have had brain damage severely. We have put our life back together, but I'm sure that those incidents were caused by Prozac. It just seems like nothing like that had ever happened to me or my family until I started taking that drug. Thanks.

DR. CASEY: Thank you. Debra Douglas?

MS. DOUGLAS: Debra Douglas. Back in 1988 I sought psychological help for a reactive depression after the sexual assault of my three-year-old son and subsequent court proceedings.

Prozac, new on the market, seemed a perfect drug for me, or so said my doctor, because of the minimal side effects, namely, weight loss. I began taking 20 mg of Prozac and soon found myself feeling very much back to my old self, energetic and feeling good, but slowly felt as if it were wearing off and I was gaining weight.

I questioned the doctor each time I went for my prescription renewal how this could be; my eating habits hadn't changed. I was originally told I could expect a weight

loss. In trying to obtain the desired effects, my doctor kept increasing the dosage, with little apparent concern for adverse effects.

By the end of a year and a half on Prozac my doctor had me taking the maximum dosage rate of 80 mg. I questioned and complained each visit that other problems I was having I was sure were related to Prozac, only to be told that there was no relation.

My gynecologist had referred me to the University of Miami with my chart, across which was written "I give up." I had lower abdominal pain accompanied by a spotty brown discharge from my uterus that led to chronic bacterial infections. I underwent diagnostic surgery, laparoscopy, and D&C under general anesthesia. It was later suggested I have a hysterectomy.

Trusting the doctors and their knowledge, I accepted their answers that Prozac could not be related. At 80 mg I was having the desired effects, according to my doctor. My life was very much in order, things were going very well, except for the continuing saga of the gyn problem.

I had finished my work day at the port for the cruise line which I have worked for, for almost four years now, and love working for, met my family at the ballfield for my son's baseball game. The game was fun, as usual, and when it ended I left in my car. About two blocks from home I had

a seizure-like attack that came on suddenly. I somehow reached home, collapsed in the door, and once my husband reached home I was rushed by ambulance to the hospital.

I was having what they called an explosive headache episode and was in extreme pain, totally out of control. Many tests were taken, with no real findings. After four days I was released with pain medication in hand. My psychiatrist had been advised of my hospitalization and of my request to be taken off the Prozac.

I was given a slow schedule of reduction from the 80 mg. The next day after my release another explosive headache episode occurred, with the same intensity, out of the blue, as the first one. I was again rushed to emergency, more tests, and a longer hospital stay. Again, no real findings other than the suggestion by the neurologist that these headache episodes were emotion-related.

After nine days of being on I.V. Demerol every four to six hours and suffering another attack while there, I was released, sent home this time with a stronger barbiturate for pain. I could not function normally. I tried going back to work but the constant head pain that the pills didn't relieve was overwhelming. I became a desperate person.

One pain pill after another didn't work, so I took a handful one night. I woke up the next morning very sick. My head hurt so badly I could barely hold it up. My husband,

sympathetic as he was, and not knowing I had taken an overdose the night before, felt very helpless and left me to sleep that morning after he'd seen the boys off to school. He kissed me goodby and said he'd be back in an hour, he had to run to the bank.

For me to take the next step, a sudden impulsive action that overrode all rational thoughts, needing to get up, reach into the gun cabinet on the closet shelf, and make this headache go away. I had to get the gun. I took the 9-mm automatic, sat down on the bed, and put the gun to my head. I wasn't clear on how to shoot the gun, so I lowered it and pulled the trigger. It fired into the bed. As I went to hold it back up to my head, the feather-touch trigger had tripped after that first shot and I blew a four-inch hole out the back of my arm instead of my head.

That gun, I later learned, was loaded with hollow-point bullets, and I shudder to think what could have happened. I also know how lucky I am to be here today. After arm surgery and a one-week hospitalization, I spent another three-and-a-half weeks in a private psychiatric hospital recuperating.

My entire being felt shook up, turned inside out, dumped out, and I had to pick up all the pieces and put me back together again. After I was released, I began seeing publicity surrounding Prozac. I started putting this together

as well. No longer was I bothered by the lower abdominal pain. I was free of infection. I hadn't had a headache in several weeks, and I had also been off the Prozac for a month then.

My gynecologist sees no reason for doing hysterectomy, as my gyn checkup is completely normal. To this date I've not had a recurrence of the gyn problem and I've not had one headache episode or head pain that I feel certain Prozac caused. Prozac did this to me. Had someone looked further into Prozac, believe me, even mentioned early on of the so-called remote possibility that Prozac could cause any of these adverse effects, especially the act of putting a loaded gun to my head, to want to die so violently, steps could have been taken to avoid it. Thank God I was a lousy shot.

As you hear the many stories today, you can see we are real people, not small percentage numbers of a minority suffering these silenced adverse effects. Please look at us, listen to us, take this Prozac off the market until it can be proven 100-percent free against violent turns in personality, until Eli Lilly can give assurance that the psychiatrists and general practitioners that are so quick to hand out this prescription are aware of all side effects, and information is passed down to all patients. Thank you.

DR. CASEY: Thank you. Cathy Eckstein?

MS. ECKSTEIN: My name is Cathy Eckstein. I reside at 197 Jousters Lane in Lawrenceville, Georgia.

I was prescribed 60 mg of Prozac by my physician during a period of grief that followed my son's suicide. The suicide occurred during the first few weeks of his withdrawal from the prescribed drug Ritalin. I have been trying to come off Prozac since February, 1991, and have only managed to reduce the dosage from 60 to 40 mg.

Since I've been on Prozac I've experienced the following adverse reactions: a drug-induced insanity that has caused several self-destructive outbursts, there was an extended period of anger, rage, and hostility, and it turned into terrible feelings that suicide was the only answer. I remember screaming at my family that I now know how my son Brad must have felt before he hung himself. I knew that I needed help but I didn't know where to go, I didn't know what to do, and I didn't know how to deal with it.

I was taken to the doctor that had prescribed the Prozac and was told that there was no reason for me to try to stop taking it and that I should increase the dosage to the original 60 mg. In addition to these outbursts, there have been headaches that feel as though burning pain went from the base of my neck to the top of my head. There have been many episodes where I could not pronounce words clearly or correctly and a tremendous loss of physical strength, leaving

me unable to function in my normal activities for days and sometimes weeks at a time.

In my own research of Prozac I have learned that withdrawal only occurs after an addiction to the drug has occurred. Prozac is an addictive drug that has caused me harm. I have yet to get off this horrible drug and to date have found no adequate medical facilities to successfully remove it from my life. I was never informed of its true side effects.

I want to see Prozac taken off the market. I am concerned as to what other effects or reactions I am now to expect in the future as a result of taking this drug. The drug has falsely been promoted to me as safe and a miracle drug.

My son died as a result of Ritalin. Others are now dead or dying because of Prozac. How many deaths need to occur before the FDA is convinced that this drug is not safe and is not a miracle and the American people are tired of being guinea pigs because of the pharmaceutical companies' need for profit? No person deserves to experience what I have and am experiencing on Prozac. I am requesting that you take Prozac off the market. Thank you for letting me speak.

DR. CASEY: Thank you. Mr. Leonard Finz, please.

MR. FINZ: Thank you. Dr. Casey, Mr. Chairman, distinguished members of this committee: My name is Leonard

L Finz, a former New York State Supreme Court Justice and an attorney from New York City, the senior partner of a law firm that represents many Prozac victims throughout the country.

I ask that the FDA direct Eli Lilly to update its warnings on Prozac now. This is not a radical request but one that is totally consistent with protecting the public interest. While Prozac may be safe for many, we say that as to a small percentage Prozac is responsible for suicidal ideation, actual suicide, violent behavior, and, in some cases, even homicide.

We contend that the manufacturer, Eli Lilly, has always known of the potential of fluoxetine to act as a stimulant, thereby exerting a harmful influence upon the health of certain patients. Fluoxetine's capability of producing negative effects which substantially include anxiety, nervousness, and agitation, is no secret to Lilly or to the FDA.

Indeed, Dr. Cappett, in a safety report to the FDA's advisory committee, such as this one, on October 10, 1985, stated, quote: "Fluoxetine is more of a stimulant." Has Lilly included this in its warning label? The answer is no. Further, Dr. Cappett stated, quote: "Fluoxetine may create liabilities, in particular, fluoxetine causes nervousness, insomnia, diminished appetite, and weight loss. These are symptoms from which depressed patients frequently suffer as a

result of their primary illness and it may be that fluoxetine treatment may at least temporarily aggravate some of these problems." Has Lilly included this in its warning label? No. Further, in reviewing certain studies, Dr. Cappett stated, quote: "The most frequent reason for termination or drop-out in the clinical trials of Eli Lilly was anxiety and nervousness." Parenthetically, nervousness, anxiety, akathisia, agitation, are all forerunners of uncontrollable and involuntary conduct by the patient. Has Lilly included this in its warning label? No.

But, further, Dr. Cappett stated, quote: "Anxiety and nervousness is a problem that may not go away with time and possibly might get worse." His prophecy unfortunately has ripened to fact.

At that very same meeting of this committee held in October of 1985, a little more than three years before fluoxetine was approved by the FDA, Dr. Lee Thompson of Eli Lilly, Medical Director, in fact, agreed with the concern that Dr. Cappett was expressing, when he, Dr. Thompson, stated, quote: "We agree with the very comprehensive analysis of, amongst others, Dr. Cappett." But let me go just one step further. What, then, did Lilly do to address that concern in its warning label? Absolutely nothing.

Indeed, since its first label was published, Lilly has been extraordinarily silent as to the concern set forth by

the FDA in 1985. To date, Lilly has produced a number of labels, the latest of which, to my knowledge, was revised just a few months ago. Up until May of 1990 there was no warning or report by Lilly of any association between Prozac and suicidal ideation or violent behavior.

On May 24, 1990, for the first time, its label included a reference to suicidal ideation and violent behavior under the remote heading of "Post-Introduction Reports," camouflaged with other items without any prominence attached by way of size of print or boldness of lettering.

This is ludicrous when compared to Lilly's description under contraindications, et cetera. I have got just about two more pages, but I am going to go right to the closing because of the time limitation, Doctor. Thank you.

DR. CASEY: Thank you.

MR. FINZ: Surely. I have this prepared and I will present it to the committee.

Dr. Teicher found 3.5 percent of emergent suicidal ideation. Dr. Rosenbaum found 3.5 percent, the exact percentage. Has that been included by Lilly? I daresay that that is an outrage, that the public interest was not protected in knowing that there are such retrospective studies. The public has a right to know and they have not been told.

In order to protect the public interest, the FDA must direct that Lilly's warnings be updated to reflect the

reported concern of significant adverse reactions.

Prozac is being prescribed by family practitioners and others for manic depression. Lilly never had any clinical trials on manic depression. Obsessive-compulsive disorders: No clinical trials on that. Diet control: No clinical trials. Alcohol abuse: No clinical trials. Drug abuse, smoking habits, PMS, cocaine addiction, migraines, and panic disorders: Has Lilly warned against such use in its label, despite its actual knowledge that Prozac is being prescribed by others than psychiatrists for such conditions? The answer is no.

In 10 seconds I will wind up. Prominent and bold box warnings are needed now. The public interest, Mr. Chairman and committee members, might deserve more, but under no circumstances is it entitled to less. And the FDA should do now what its own safety report suggested more than six years ago, and such a course by the FDA would be a responsible, conservative, and prudent course, and nobody would be hurt by the printed word, but perhaps lives would be saved by them.

Such a warning, Mr. Chairman, should, in the public interest, be directed that Lilly do it now. Thank you very much for your consideration.

DR. CASEY: Thank you. Ms. Laurie Flynn, please.

MR. FEDELI: Mr. Chairman, my name is Fred Fedeli

and I am substituting today for Ms. Flynn.

MR. BERNSTEIN: Sir, just a minute, please, while we review the policy on that.

(Mr. Bernstein consulted with officials.)

I have been advised that the policy is that individuals had been approved to make presentations rather than agencies, so if Ms. Flynn is not here, we should proceed to the next speaker.

MR. FEDELI: We had already informed the panel that there would be a substitute for Miss Flynn.

MR. BERNSTEIN: Did you notify me? No one ever called me.

DR. CASEY: In that case, since there is some ambiguity, please go ahead. Five minutes.

MR. FIDELI: Thank you very much.

I would like at the outset to associate my remarks with the very courageous testimony of Ms. Meenan and the subsequent testimony of the American Psychiatric Association.

The National Alliance for the Mentally Ill, as many know, represents more than 130,000 family members of persons with serious mental illnesses as well as those persons themselves. Let us state at the outset that in the United States presently more than 20 million people will develop a mood disorder, depression or manic-depressive illness, during their lifetime. Each individual has a personal story to tell

about the devastation associated with his or her untreated condition.

Thankfully, during the past 20 years congressional appropriations for research at the NIMH have allowed the nation's finest medical researchers to better understand the nature of these disease disorders and to find more effective means of treating them. Modern treatments today are very safe and effective, allowing persons with recurrent mood disorders to live useful and productive lives.

The National Alliance for the Mentally Ill believes that the issue of whether warning labels on products are appropriate should be determined solely through scientific research and clinical trials. Anecdotal data or sensational distortion of the truth is not an appropriate cornerstone for public policy in this field or any field of government.

At this time, millions of Americans are being successfully treated with antidepressant medications to alleviate the more prevalent negative symptoms associated, problems in thinking, concentration, and decision making, excessive fatigue, loss of self-esteem, inappropriate feelings of guilt and unworthiness, loss of interest in pleasure, and sleep and appetite disturbances. The newer medications have proven to be remarkably effective in relieving these symptoms and with far fewer and milder side effects.

Some suggest that the side effects are tragically

severe and life-threatening, causing suicidal ideation and successful suicide. The new medication Prozac is only the most recent target of these allegations. We believe that the charges are false. What is tragic is the cost of untreated depression, both in human and in economic terms. It is estimated that mental illness, according to the NIMH, costs the U.S. economy $73 billion a year, $40 billion for treatment and premature death, and $28 billion more in reduced work effort and absenteeism.

A recent television program in which several persons alleged suicidal symptoms from the use of Prozac contributed to several patients stopping use of the drug. Who knows how many more were dissuaded against even beginning Prozac therapy? Our toll-free 800 telephone line at the National Alliance headquarters tells us that these numbers are substantial.

The alternative will surely be foregone treatment and later costly hospitalization. Ironically, the failure to access modern, proven effective medical interventions could heighten, not alleviate, the recurrent thoughts of death or self-harm which often characterize a major depressive episode. Access to necessary medication will only be diminished if irrational and nonscience-based product labeling is to be required for all medication.

On behalf of our membership and the millions more

who have been successfully treated with antidepressant medication, we urge this agency not to proceed further with this proposal unless the scientific and clinical outcome data so warrant for the protection of the public safety. Thank you, Mr. Chairman.

DR. CASEY: Thank you. Suzanne Lovett Francis, please.

MR. BERNSTEIN: Suzanne Francis, Sonja Lovett, and Mark Lovett.

(No response)

DR. CASEY: Dr. Burton Goldstein, please.

DR. GOLDSTEIN: My name is Burton Goldstein. I am a professor of psychiatry and pharmacology at the University of Miami School of Medicine. I also chair the United States Pharmacopeia Drug Information Service, the disease panel on psychiatric disorders.

The USPDI Service was established in 1970 to provide clinically relevant and established information to physicians, pharmacists, and patients with regard to medications they might be prescribing or taking. At this time, with no data to scientifically support a causal relationship between antidepressant drugs or any members of the antidepressant drug class and suicidal thoughts or behavior or violent thoughts or behavior, we will not change the information we provide to professionals and to the consumer. We will continue, however,

to review data as they become available. Our review process is ongoing.

The second comment, Mr. Chairman, I would like to make is a very personal comment which comes from my experience as a clinician, a physician, for over 25 years, and as an investigator in the field of clinical psychopharmacology. I have a very grave concern that any label change for antidepressant medications, including Prozac, will have an adverse and regressive effect on physicians, especially the nonpsychiatric physicians, in the recognition and treatment of depression.

Over the past 10 to 15 years, academia and the National Institute of Mental Health, professional organizations, and the public organizations have recognized that depression is a major chronic, relapsing, debilitating illness, with over 70 percent of its patients seen by the nonpsychiatric physicians in the general medical setting.

In 1988, the "Depressive Awareness Recognition and Treatment Initiative" was launched by the National Institutes of Mental Health to educate physicians and the public. Even with this concerted effort by so many very dedicated and talented people, physicians now only recognize 42 to 51 percent of depressive disorders, based on the medical outcome studies, which was published in The Journal of the American Medical Association in August of 1989. It is estimated that

only 20 to 25 percent of depressed patients are treated.

The seriousness and high-disability aspects of depression were cited in another segment of the medical outpatient studies. Twenty-one percent, or 2400, of over 11,000 patients from nearly 400 medical practices throughout the country met the criteria for major depressive illness or severe depressive symptomatology.

Let me take just a moment to quote: "Patients with a depressive disorder or depressive symptoms had decreased physical, social, and role functioning as well as poor perceived health and high bodily pain scores. All of these impairments were comparable to or worse than those reported by patients with the most chronic of physical conditions studied."

The concern that I have is that because of this era of sensationalism and all of the unfortunate situations that we have heard today, which do not make a causal linkage, will cause some change in present labeling, which generically, certainly, covers suicidal behavior with all the antidepressant drugs and, in the case of fluoxetine, suicidal ideation is mentioned.

I am terribly concerned that any labeling change of antidepressant medication without scientific data to justify such a change will adversely affect patients and physicians needlessly. Who would want to prescribe and who would want to

take a drug that the federal government says may be associated with suicidal thoughts or behavior?

What I predict will happen is that the level of awareness, detection, recognition of depression will diminish. Only those patients with depression which is so severe and so obvious will be treated with antidepressant medication. The syndrome of depression won't be recognized and, therefore, won't be treated, and won't be treated adequately, so what will result will be the symptoms of depression will be treated, so that insomnia, a symptom of depression, will be treated with hypnotics, anxiety with anxiolytics, the anergia, loss of interest, and fatigue may be treated with stimulants. This will be a tragedy.

If the data supported a labeling change, it would be morally, legally, and ethically wrong not to modify the labeling. But it is equally wrong to modify labeling when there are no scientific data. Thank you, Mr. Chairman and members of the committee.

DR. CASEY: Thank you. Mary Guardino, please?

MS. GUARDINO: My name is Mary Guardino and I am the Executive Director and Founder of Freedom from Fear, a nonprofit organization that is dedicated to aiding and counseling individuals and their families who suffer from fears, phobias, anxiety, and depression.

Our mission is multidimensional, and besides

consumer mental health education and advocacy, Freedom from Fear is actively involved in neuropsychiatry research. At the organization's headquarters in Staten Island, New York, the New York State Psychiatric Institute conducts many neuropsychiatric studies in the area of anxiety and depressive disorders. Also, it is the site of an anxiety and depression research center for children and adolescent disorders, funded through the National Institute for Mental Health.

Every year thousands of suffering individuals from across the country seek help and treatment from Freedom from Fear. I am grateful for the opportunity to be here today to express to this committee the opinions of my organization and of people who come to us for help, and hopefully to influence you to make appropriate recommendations to the FDA regarding any proposed labeling changes for antidepressants.

Millions of Americans have received safe, effective treatment from pharmacotherapy for depressive illness. Because of your expertise in the field of neuropsychiatry, each committee member is well aware of this. Unfortunately, recently a misinformation campaign against antidepressants, particularly the drug Prozac, has been launched by an organized group, and the media hype which resulted from this, not any new scientific information, has brought us here today.

Those who attack the drug as inducing murder and suicide base their scant evidence on an anecdotal report, a

long-standing war on psychiatry, and fear. The research data strongly suggest, instead, that Prozac is highly effective, even preferred to other antidepressants.

Yet what depresses me and my organization the most in all the national hoopla and media attention over the unsubstantiated side effects of Prozac is the continuing degradation which it is bringing to people with long histories of depression, fully treatable depression.

On the one hand, the adverse publicity is stigmatizing further a great body of our population who experience psychiatric disorders. Those who are in treatment may regress, either because the stigma is too great or because they are switched to medications less effective or, in some instances, with greater risks than Prozac. Others, who may have sought legitimate treatment, are now frightened away.

What is even more frightening is that some suffering individuals may discontinue their therapy without proper medical supervision. Consequently, they may be at risk for serious problems. With few exceptions, the media prefers to spend more time transmitting flimsy information about psychiatric disorders than it invests in educating the public about the legitimate treatments that are available to millions of Americans who suffer daily from a variety of psychiatric disorders.

A recent survey conducted by Freedom from Fear of

245 of its members nationwide found that 78 percent of the people felt that the media has a great to moderate influence on public understanding of psychiatric disorders and 69 percent felt the media often represents a sensationalized view of psychiatric disorders. When asked to give an example of this, the key incident cited was the media attack on Prozac.

Regarding the unfortunate instances reported in the media about individuals suffering from unusual symptoms which they are attributing to treatment with antidepressants, all the scientific evidence indicates no linkage between these symptoms and Prozac and antidepressants in general.

Members of the committee, perhaps these symptoms came about not because of medicine but in spite of medicine. In my own case, I fortunately have been in remission for more than six years from my own battle with panic disorder and depression. When I did relapse last year, I welcomed treatment with Prozac, because I have been able to observe closely its efficacy and low side-effect profile in controlled studies that are being done at Freedom from Fear by the New York State Psychiatric Institute since 1986.

Prozac has enabled my son to return to college after a bout with major depression. Success stories like mine are being replicated by the millions across the country and in the world because of advances in science and the treatment of psychiatric disorders.

Not only is modification to any antidepressant labeling not warranted, based on scientific data but, also, this act will place the FDA in a position of stigmatizing further an already fragile population. Likewise, it will impair sufferers' opportunities to receive appropriate and safe treatment. In a recent FDA ruling, spokesman Steve Asparais stated: "There was concern that a very bad precedent could be set if scientific standards were lowered."

Committee members, put aside the media hype, forget the hysteria, the American public depends upon you. There is no scientific data to warrant any labeling changes. Thank you.

By the way, on a lighter note, I think that my other recommendation is to have some water for the speakers in the future.

(Laughter)

DR. CASEY: Thank you for your comments. I believe there is water outside available.

Melinda Harris, please?

MS. HARRIS: Melinda Harris. Let me state one thing, that listening to the opposition has made me stronger -- hopefully I won't cry. I'm not against all psychiatric drugs and I'm not against all antidepressants, but I'm against Prozac, because it killed my father.

I'm a full-time airline secretary, part-time model,

sales rep, and a maid. My father took Prozac, I think he started taking it around May of 1990. Consequently, in September of 1990 something very, very bad and very violent happened. A lot of the people that I've talked to that have taken Prozac start out feeling a good perky upbeat feeling. Then a terrible change starts to occur.

Unfortunately, with my dad we didn't have time to notice too many changes, except that he became withdrawn and agitated. But by that time it was too late. He got up at 9 o'clock in the morning, took a 12-inch butcher knife out of the kitchen drawer and stabbed himself violently in the abdomen once and then proceeded to do it twice.

His girlfriend's son caught him in the process and dialed 911. My dad suffered three miserable months in the University of Michigan with wounds so severe that he had tubes stuck in all pertinent areas of his body. My father told the nurse he was sorry he did it.

I know my dad was sorry he did it. I know my dad did not want to die. All his medical records say that he was not suicidal and had no thoughts in that way. My dad did not like pain. If my dad ever wanted to die, I know he would have done it in a quiet, easy way.

To watch an 8-inch-long wound about 3 or 4 inches wide heal from the inside out is something most common people don't see. They had a sheet of plastic over his wound and I

could see his intestines. Did it scare me? No. When you love someone, nothing matters.

I will talk any time about Prozac negatively and I will do anything I can to help put a stop to this drug. You may think my talk is rather morbid or radical but it is not. It is plain fact and truth and my testimony to make you people realize what a dangerous drug this is. I have talked to numerous people about this drug and no one except maybe 5 percent has anything positive to say about it.

If Prozac were ever to stay on the market, it would have to stay in the hospital, with patients under constant supervision.

Someone made a statement to me the other day about Prozac and said what if Prozac got out on the streets and drug users on the street starting take it. That thought scared me almost more than anything in my entire life. Can you imagine people taking double and triple doses on the streets, getting violent, aggressive, and cutting people up? Yes, Prozac patients usually have a fetish with knives.

At one time I thought maybe if Prozac was monitored closely, things would be okay. But, no, I am sorry, my neutral attitude has withered, I have heard too many stories.

There is a lady, Marilyn, in Michigan, a couple of towns from me. Marilyn was too sad to come today. Her husband had no previous mental or emotional illness. He

suddenly got depressed and went to the doctor and the doctor said, "I have a miracle drug for you." Three weeks later her husband shot himself and suffered for five weeks. Marilyn and I were not alone, and I'm sure there are many more people like us. That is why I came today, to meet other people who know the pain, and to put a stop to the pain Prozac creates.

I believe Prozac does alter the mind. I also know people have picked at the Scientologists, since they are against psychiatric drugs. I am not a Scientologist, but I do hate Prozac. You cannot label the Scientologists anymore, because there are many others who hate the drug, too.

No one can bring my father back at the young age of 55, but I can help others live and I can talk about it. I know my dad would have liked me coming here today and he would have said, "That's daddy's little girl." No one can justify the violent suicides and murders Prozac has provoked. This is a real story, and God bless the people who believe and understand that Prozac does kill. Thank you.

DR. CASEY: Thank you. Shirley Jarrott?

MS. TRACY: Hello. I am speaking for Shirley Jarrott. She had an emergency in her family and could not make it from Oregon. My name is Ann Tracy, from Salt Lake City, Utah.

DR. CASEY: Excuse me, please. Mr. Bernstein, do we have any record of the representation?

MR. BERNSTEIN: No, we do not.

DR. CASEY: Ma'am, do you know if Miss Jarrott had contacted the agency?

MS. TRACY: As far as I know, she had, and I have all the forms that she faxed to the agency.

DR. CASEY: Do you know if she contacted about her substitution with you today?

MS. TRACY: Yes, it has my name specifically on the paper work.

DR. CASEY: Could you submit that to the agency after your presentation?

MS. TRACY: Certainly.

I'm the Utah Director for the Prozac Survivors Support Group and have been in constant contact with Shirley and know of her case and the problems that she has had and, in representing her, I would like to discuss the severe problems that she has had in her health in the use of Prozac which was directly related to severe liver damage.

The suicidal tendencies, of course, were there as well, but her concern is the damage to her liver that she has to live with constantly. This is something that I have been extremely concerned with. I'm alarmed at the high incidence of liver impairment that seems to be being reported to you, and the biggest reason I am concerned is because that is directly what regulates the amount of Prozac within the body.

If we have the Prozac rising to higher levels, of course, we're going to have some very severe problems, and I think that that might be one reason why we're seeing what we're seeing.

Prozac has directly affected my life. I was engaged last year to a young man who was on Prozac. He was put on Prozac in early 1989, prescribed for stress and some depression related to business failure. The personality changes came quickly. I couldn't even begin to describe the horror that happened to him for the next two-and-a-half years of his life.

He looks back now, after being off three months -- he would have come, but he's too sick -- after three months of being off, he looks back at the last two-and-a-half years and cannot remember much. He doesn't know what was dream and what was real. There's no detection there of reality.

I would like to encourage your committee to start looking at brain-wave patterns in the use of antidepressants. When you look at brain-wave patterns of somebody on Prozac I see a total anesthetic sleep state with eyes open. That, to me, is frightening. I think that is why so many families are describing their loved ones as being gone, just completely gone. They're no longer there. There's really no other way to describe someone that you've loved so much who's changed so drastically.

I believe that this is also one reason why the patients are unaware of what is happening to them and unaware of the effects, and that is why families tend to be the ones that notice the effects rather than the patients themselves.

Prozac works on the mood center of the brain to remove depression, but in doing so I believe that it also removes other feelings that are extremely vital to life. So many people are saying that they cannot feel guilt, they have no conscience, they cannot love, they cannot feel empathy or compassion. To me, that's alarming. To have individuals walking around that cannot feel guilt? Of course, we would have more violent behavior.

Another thing that really alarms me in what I have seen with so many patients -- and Utah has got some very severe problems with this particular drug, it's very widely used -- is the fact that so many people that tend to have a tendency toward alcoholism are reverting to alcoholism with the use of Prozac. I would like that investigated. I would like to know why people who have worked for years to overcome this particular addiction in their lives are reverting to this. Dr. Teicher noted that in one of his cases. To me, that is really frightening.

I would like you please to take another look at Prozac. Consider all the shattered lives and shattered families that are out there and, believe me, they are

everywhere. All you have to do is start asking. Thank you.

DR. CASEY: Thank you. Suzanne Johnson, please?

MS. JOHNSON: My name is Suzanne Johnson. I am standing here before you today, my government-appointed judge and jury, pleading not only for my life but literally thousands of others. As I stand before your firing squad, I must cry to be heard. I don't deserve this. Nobody does. Only God has the power to pick who lives and who dies. Who do you think you are? God?

My Prozac nightmare is beyond description. There is no known vocabulary to describe what has happened. Prozac has altered the entire course of my life. I'll never, ever be the same. Prozac has destroyed every hope of me having any kind of normalcy in my life. Gone are my carefree days, never, ever to return.

I was told that Prozac had no side effects, except for possible weight loss. No withdrawals and no addictive potential. I literally quote my physician, quote: "Suzanne, sometimes patients lose 5 percent of their body weight, but then we can never be too rich or too thin, can we?"

Looking back, the emotional side effects began immediately. My wild spending started within a week of my ingestation of Prozac. I began lending sums of money to people when I didn't have the money to spare. I went on credit card binges that will takes years to pay off. I even

purchased a opera length black gamma mink coat.

Also, here come the mood elevations and irresponsible behavior. I had become impervious to any type of normal thinking. I was totally out of control. My friends were aghast at my deteriorating mental state, but were afraid to speak to me about it because of my agitated state of mind. In my own thoughts I had become superior, almost godlike. All my semblances of religious faith were torn to shambles, literally nonexistent. Now my love of God was masked, totally masked by darkness, by Eli Lilly's devil Prozac.

During this time it is a miracle I did not harm myself or others. I had become a menace to society, and the FDA is allowing this to happen. I want to know why. On September 3, 1991, the United European Parliament recommended to the member countries where Prozac is authorized to look into Eli Lilly's killer drug and recommend discontinuation of Prozac in its present form. What happened to America, the beautiful land of the free? This totals 23 -- 23 -- western European countries. Do they care more about their people than you care about yours? We've become so money-oriented that it's the money, the money, the money, let's have the money. I don't understand.

The FDA is calling for retraction of various food products, citing false and misleading advertising. What about false and misleading advertising concerning Prozac? Look at

this brochure. It's a school teacher. She can't sleep, so she's going to take Prozac so she can function properly. You open your mouth, you pop a pill, and the world becomes rose-colored again. I wouldn't want anybody on Prozac to teach my children. I don't think you would, either.

Allen Gellsberg from your office sent around a fax on July 2, 1991, and stated that since Prozac was introduced in 1988, more adverse side effects have been reported than any other drug. I wish you would stop this atrocity now. How many more people are going to be killed and maimed before you do something? You have the power to change things. You have the power to listen to what we say and investigate what we say. We need help.

My nightmare continues. Each step I take today is a borrowed step from God. Last November I was hospitalized with an hematocrit of 9000, a hemoglobin of 2500, and a white count of 1100. I come here today at great personal risk with a white count of 740. Monday morning I received three more units of packed red cells, bringing my transfusion count today to 40. During my ingestation of Prozac my bone marrow was being eaten up. I was so high on Prozac that I noticed no physical symptoms.

Please take Prozac off the market. Imagine my dismay when I was alerted to the fact that bone marrow donors are being accepted that are on Prozac therapy. When someone

undergoes a transplant, the young mother, the father, the child, and the cause of death is listed as complications of bone marrow transplant, when in fact it could have been caused by marrow that --

DR. CASEY: One minute, please.

MS. JOHNSON: This madness has got to stop. You are holding, you guys are holding a loaded gun in my hands at my temple. You're playing Russian roulette with my life. Maybe the next time the chamber won't be empty. Without a medical miracle, it's too late for me now. Withdraw Prozac from the market before it harms anybody else, before other blood is on your hands, because my blood is already on your hands.

DR. CASEY: Thank you. Kathleen Kessen?

(No response)

Ron Klemme?

(No response)

Bonnie Leitsch?

MS. LEITSCH: I am the National Director for the Prozac Survivors Support Group, an organization consisting of Prozac survivors and the families of people who did not survive. I personally have interviewed and talked with over 400 people who have been prescribed Prozac for various reasons, for weight loss, to stop smoking, and the scenario is the same. They are free of suicide before they go on the drug and when they are on the drug they become suicidal. They go

off the drug and they are no longer suicidal. Well, I'm not a doctor, but I wouldn't think you would have to be a mental heavyweight to soon figure that Prozac played a part in the suicidal ideations.

Doctors say that this problem with Prozac, all that is needed is for this drug to be monitored. But what I'd like to know is how do you monitor a patient when suddenly and without warning they try to take their lives? Such as the woman in North Carolina who was cooking supper, had a load of clothes in the washer and dryer, no indication that she was going to commit suicide but, indeed, she did. She hanged herself with a belt in the middle of cooking supper. Now, how can you monitor that?

Likewise, the man in Arizona, laid out his medication for the day, played gin rummy with his wife, made plans for the day, and while she was taking a shower he killed himself. How do you monitor that?

And myself, my own case. I was making icing for a Father's Day cake when suddenly, without warning, it seemed like a swell idea to kill myself. Did I consider the consequences of that? No. Did I shoot myself? No, because a gun wasn't handy. Had it been handy, I'm sure I would have done that. I was, however, dead on arrival to the hospital. Had it not been for the emergency team, I would not be here today.

What I'm curious about is the people who seem to think it's perfectly okay to have this drug on the market are people who have a vested interest. I question why this is happening. Well, we know it's impossible for the doctors to monitor these patients, because if they had, there would not have been 800 suicides, 500 deaths associated with this drug.

And if all of this isn't tragic enough, we are referred to as anecdotal. What does that mean? Does that mean that the people that died on this drug is not equally as dead? Does it mean that Sally Padoor, who's grieving the loss of her son, is not just as grieved? I think not. What that really means is that we were not in the paid-for studies of Eli Lilly. We are the real people. Anecdotal are the real people. This is the people that you have unleashed this drug on.

The FDA responsibility -- now, maybe we need to make this a little more clear -- is to protect the general public, not to stuff money into doctors' and into Eli Lilly's pocket at the expense of the general public. How dare you? You were put here to protect us. We are the general public. And who said it's okay, who in the world said it is okay to kill one person so that another feels better? Who gives anyone here that right?

Where in this country is it all right for you to say it only kills 3.5 percent? Gentlemen, if you want to be that

3.5 percent, fine, have at it. But the general public does not want to be that 3.5 percent.

DR. CASEY: Thank you. Dr. Michael Lesser, please?

DR. LESSER: My name is Michael Lesser. I am a psychiatrist in private practice in Berkeley, California. I'm here today to report about a high-benefit, low-risk alternative nutritional therapy for suicidal depression and other forms of mental and even physical illness.

I call this nutritional medicine. It's a very old form of therapy; it goes back to the days of Hippocrates, who said "Let thy food be thy medicine and thy medicine be thy food." But it's also an extremely new medicine in that the vitamins and many of the subparticles, the molecular particles, of nutrition have only been discovered in recent years.

I believe that nutritional medicine has three distinct and important advantages over currently available drug therapy. First, nutrients are not alien to the body. They are substances which are normally present in the body and the body is used to handling these substances. Therefore, when skillfully applied by a knowledgeable physician, there are no side effects with the use of nutrients in treating mental illness.

Secondly, nutrient therapy is effective at getting at the cause of the illness. No one has ever claimed that

psychiatric depression is due to a deficiency of a drug, but there have been numerous studies which have shown that psychiatric depression can be due to a nutrient deficiency. As an example, take the case of vitamin B1 thiamine. Back in the 1940s, I believe, the Mayo Clinic did a study on thiamine with human volunteers -- at that time it was possible -- and found that in some cases they had to stop their study of thiamine deficiency, where they had made these volunteers deficient, because they were developing suicidal depression.

Prompt restoration of thiamine to their diet resulted in a complete improvement of their symptoms. Similarly, we have the example of niacin deficiency with that other very severe mental illness, schizophrenia, or the psychoses. Dr. Joseph Goldberger of the United States Public Health Service was assigned, in 1914, to discover why 200,000 people in the United States at that time were suffering from pellagra, which was causing a schizophrenic psychosis. He eventually discovered that there was a deficiency of a nutrient in their diet for their needs, namely, niacin of B vitamin. When they were put on niacin, they recovered from their mental illness and were able to leave the mental hospitals. There has been no claim that schizophrenia is due to a deficiency of tranquilizers.

The third major advantage of nutrient therapy for the treatment of depression and other mental illnesses is that

there is no suicidal risk, absolutely no suicidal risk. There is no reported case in the medical literature that I am aware of, of anyone who has ever successfully committed suicide by taking an overdose of a nutrient. On the contrary, my common clinical experience with patients who are depressed and angry is that after they've been on the nutritional and vitamin therapy for a period of several weeks is that not only does depression disappear but anger is greatly ameliorated and disappears.

With such great advantages, one would wonder why is nutritional therapy not more widely employed? There are some drawbacks. First, there is not a financial incentive for drug companies to employ nutritional therapy, because nutrients are not currently considered prescriptive items and are not patentable. Perhaps a change is needed in regulation so that nutrients in high dosages be used as prescriptive items so that they could be subject to IND investigational studies and there would be a financial incentive for companies to employ them as therapies.

Secondly, it's a complex therapy. It requires usually taking several nutrients and changing a person's diet and, therefore, it will always have some limit, because many people are unable to follow such a complex change in their life.

The other reason this is not currently widely used

is because insurance companies are not paying for this treatment, and here I think it would be very easy to mandate that insurance companies do pay for this treatment when it's prescribed by a physician.

DR. CASEY: Would you please conclude?

DR. LESSER: That concludes my remarks, ladies and gentlemen, as to why I believe nutritional and vitamin therapy should be more widely employed to treat these serious conditions.

DR. CASEY: Thank you. Heidi Lovett?

MS. LOVETT: Good morning. My name is Heidi Lovett and I'm here this morning to present testimony on one single instance of a suicide in which I believe Prozac played a significant role. I'm referring to the suicide of my husband of 28 years, James Donald Lovett. It is not easy for me to talk about my husband's suicide, not simply because I miss him but because I think that by focusing on the circumstances of his death it is easy to lose sight or distort the healthy, vibrant part of his character.

James was a good husband, a good father, a good brother to his sister, and a proud grandfather. His children and his grandchildren were very close to him. They enjoyed being in his company and admired him in many ways. But this hearing is not about the husband I knew, but the victim of suicide that he became. So I must confront in this public

testimony a question I face privately every day: Why did my husband take his own life?

I realize that I will never know the complete answer to this question, but I'm not completely ignorant about it, either. I'm convinced that my husband's suicide was a complex product of two factors. Throughout his life he struggled with episodes of acute and, I can assure you, exceedingly painful depression. To ease the pain, my husband did what millions of victims of depression do; he sought professional help.

It was this treatment regimen that became the other factor in my husband's suicide. I should like to note that I considered my husband's willingness to seek out psychiatric treatment to be his and my greatest asset in the war against his depression. Not everyone who suffers from depression can summon the courage it requires to acknowledge that there is a problem and to pursue a course of treatment. Yet my husband did.

Counseling was part of his treatment and in April of 1988 Prozac was the other primary component of his therapy. His physician psychiatrist put him on 20 mg of Prozac twice a day and that's what he was taking up to the day of his death.

Like many victims of depression, my husband was no stranger to occasional thoughts of suicide. However, he did not hesitate to signal the fact of suicidal thoughts to me or to his sister and others close to him. Aware of his

depression, we did not take these warnings lightly, but we did take some comfort in the fact that he was at least warning or signaling his problem and that he had never, in fact, even attempted to commit suicide.

This is one reason why his suicide on the eve of last Thanksgiving is so terribly vexing to me. Neither I, his children, nor anyone to whom he was close had an indication that James was suffering from suicidal tendencies. When my daughter returned home from school to find his body on the bathroom floor of our home, she thought for a few fleeting moments that he might be playing a practical joke on her. The grim truth that shocked us then shocks us still.

Partly because his suicide came so unexpectedly and partly because we have heard from media sources about a potential link between Prozac and suicide, I requested an autopsy and toxicology on my husband. I was, to put it frankly, extremely troubled and angered by the results. The toxicology report showed that the blood Prozac quantitation was at a level of 4100 ng. The reference range listed is a mere 91 to 302 ng. The blood norfluoxetine quantitation was 3200 ng. The reference range is at 72 to 258 ng. I am appending a copy of this toxicology report. I mentioned this Prozac level to my husband's psychiatrist. I did not anticipate his reaction. Upon hearing the level, he said, "My God, how could it get that high?"

I stated at the beginning that I did not understand how Prozac works, but I assumed that my husband's psychiatrist would know. The absence of any sign of suicidal distress from my husband was uncharacteristic and I believe that Prozac played an important role in the ultimate act.

If there is a link between suicide and Prozac, and I believe that there is, then please let us think about warning those who take Prozac and tell them about the possibility of suicide and let physicians who prescribe Prozac monitor blood levels in their patients.

DR. CASEY: Could you please conclude in the next few seconds, please? Thank you.

MS. LOVETT: If monitoring cannot be established, then I think Prozac should be taken off the market, maybe on a temporary basis, until it can be established that it can be a safe drug. It is too late for my husband, for myself, for my family: We do not have anything to gain by being here. But maybe someone else's life can be saved. Thank you for this opportunity to testify.

DR. CASEY: Thank you. James Lucas?

(No response)

Maria Malakoff?

MS. MALAKOFF: My name is Maria Malakoff. I did not prepare a speech. My husband has just committed suicide four months and 20 days ago in front of four kids and myself. My

husband was suffering a little depression.

We work with cancer patients. For the last four years we do indigents, trying to find out what causes cancer. He was a little depressed, went to a doctor that gave him Prozac. He came home and he thought it was a wonder drug. I took the job of three businesses at the same time and I was suffering anxiety. I went to a cardiologist, who asked me to go to a psychiatrist to give me something for my anxiety. I was placed on Prozac, too.

On our anniversary, February 14th, I went to Kapalua Bay, Hawaii, and cut my veins. I decided I wasn't taking this drug. My husband didn't believe me. He was a pharmacist. We came back and on April 30th he just blew his brains out in front of all of us. Nothing will bring my husband back, nothing's going to bring my kids' father back, but I believe that Eli Lilly has made other mistakes before when they got Oroflex out there that killed 28 people and it was taken off.

We're over 28. How many more have to die before somebody says, "Look, we made a mistake, we're humans, but let's look into it." I'm not blaming Eli Lilly. I'm blaming a mistake that has been made here. Please search into this.

I can't take the five minutes. I can't handle it no more.

DR. CASEY: Thank you for your comments. Margaret McCaffrey?

MS. MCCAFFREY: My name is Margaret McCaffrey and I'm from Brooklyn, New York. I raised eight children. Two of them became doctors. My daughter, Margaret, a neurologist, died a little over a year ago and I firmly believe the drug Prozac caused her to commit suicide. She was very dedicated to her profession. She was a nurse before going to medical school. She took Prozac to see her through a very stressful job situation. She believed it was safe and not addictive.

She moved here to Baltimore in July of 1990 to begin a second fellowship. She had bought a new car, had a lovely apartment, and the best of her profession lay ahead. There was no warning. She spoke to her family on Saturday and on Monday evening she was found, almost dead.

I hope and pray that Eli Lilly and the FDA will listen to me and remove this drug from the market before any more innocent lives are lost. Thank you.

DR. CASEY: Thank you. Tucker Moneymaker, please?

MR. MONEYMAKER: Thank you. On behalf of myself and thousands of other citizens in the states of North Carolina, Virginia, and West Virginia, of which I happen to the Prozac Survivor Director for these three states, I want to say thank you for allowing the public to come up here and speak and voice their opinion about this dangerous drug.

I also want to tell everybody that these are real stories, real people. This is not something wrote down on a

piece of paper, something somebody wrote up somewhere. These are real things that's happening.

My story is also real. It's just a real nightmare, something I have to live with every day. I had two sons, David Lee, age 8, and Billy, 16, a wife of 20 years, is all gone. I'll tell you why. In March of this year my wife, Sandra, had some nerve problems. She was asked to go be evaluated. The doctor put her on Prozac. He told her she was depressed because she was having nerve problems.

Now, I want you to keep this in mind, how my wife was, just a little short story. My wife was the kind of mother that always put the kids first. She would take her kids back and forth to school every day. My 8-year-old never rode a school bus. My wife was tied up in the church, tied up in Cub Scouts, room mother at school.

I heard these people talking about scientific data. I want to show them some scientific data. This is scientific data right here. I want you all to look at it. This is scientific data for those who say we don't have scientific data.

I haven't slept but about two hours since Sunday, so I want to apologize if I sound a little shaky. After being on Prozac for 21 days, my wife shot and killed both of these two boys right here. She turned the gun to herself and shot herself twice. Now she's in jail for murder.

This is the kind of lady that never took a drug, no mixed drinks, no alcohol, no reason to be depressed, just some nerve problems, like everybody has from time to time. I'm depressed. I've got legitimate reason to be depressed.

I want to ask you all, don't let this happen to nobody else. These are real people. You know, these murders and things are senseless. It's time to put a stop to it. Thank you.

DR. CASEY: Thank you. May Moseley, please?

(No response)

Betty Prentice?

(No response)

Marvin Pulliam?

MS. PRENTICE: I'm Betty Prentice.

DR. CASEY: Please go to the microphone.

MS. PRENTICE: My name is Betty Prentice.

DR. CASEY: Ms. Prentice, were you here when it was announced you would have five minutes to speak?

MS. PRENTICE: No, I was in the other room, but it won't take that long.

DR. CASEY: Thank you. Go ahead.

MS. PRENTICE: I've been off Prozac for two years and I have to deal every day with not getting a gun or taking a car and running over somebody. My kids, my son, just told me two days ago, "Mom, there're many times that I thought I

was going to have to knock you out and restrain you." My daughter told me, "You were like a zombie." I was on it four to six months.

Now my doctor, my psychiatrist, in Atlanta would not give me my records. I have finally gotten them, but too late to bring them to show you. Something has to be done and this is just not -- this is something that's real. My doctor told me it would be fatal. I moved from Atlanta to Sacramento, California. He told me it would be fatal if I went cold turkey and dropped the drug, but I went off of it and I have a pill bottle here to show you. That was my last one, September 3rd in '89.

I'm telling you right now it's taking every -- every bit of strength that I have to come here and try to tell you that something's got to be done. I'm not blaming Eli Lilly or the doctor or anybody, but you've got to look into this. Thank you.

DR. CASEY: Thank you, Ms. Prentice. Mrs. Frederick Richardson?

MS. RICHARDSON: My son, age 17, on the Prozac. His student years were happy years. He was a great source of joy to his parents. He had a thirst for life. His life is remembered as a series of vignettes. He climbed the Great Wall of China, riding camel to the pyramids of Pizzo, watching with eager fascination the animals of Serengeti. He skied

during winter months and he spent summers with his parents in south of France. It was his summer home. He was very popular and disarming. It was an irresistible love of life.

His curiosity and enthusiasm, the ease with which he made friends had always taken him off the beaten path. Once we took him with us to a Chamber of Commerce trip to the Soviet Union at a time when the stringent security measures were still in force. He went off on his own, met young people, enjoyed amenities of Russian life, all this to the amazement of nervous security people. The group heard with utter fascination as he regaled them with stories of his side adventures.

My son graduated from Wharton. He explained to us that he wanted to have more studies in humanities. As he put it to his dad, "I am too mellow in nature to climb the corporate ladder." My son spent a year in Paris. He studied everything and anything he wanted. He loved Paris and felt fulfilled.

In his letters and telephone calls he often expressed the feeling that he has been blessed with good fortune of being born to a good home with loving parents. My son came home from his year in Paris brim-full of ideas on what he wanted to do with his life. He was happy to be home, happy with his year in Paris. As always, he was bursting with energy and life.

Home one week he woke one morning feeling dreadfully sick. When his illness persisted and he was given a series of tests by his doctor, the result of each came back negative, and finally he was examined by Dr. Levy, a research scientist at U.C. Medical Center. He diagnosed his illness as called chronic fatigue syndrome, a debilitating disease, but one that is not fatal and eventually he gets well.

For the next two years my son spent time at home but he never gave up planning his future nor was he wasteful of time. He worked on a book, composed music, read a lot, played piano. He spoke of his new life and he said he wanted to marry and have a lot of children. He promised us many grandchildren.

Early in '89 his condition began to improve and he gave thought for his future. His father bought him a multi-million dollar hotel to provide his son with an opportunity to work in a surrounding that had great appeal to him while he could also pursue his artistic and creative talent. My son cherished his father. As an example of his love for his dad he once wrote, "Dad, you are a masterpiece of a father." When his father died, he was great comfort in pulling me through my sudden loss.

In August, '90, my son felt well and joined me for vacation in our usual summer place in France. He flew in, putting his Harley-Davidson on the plane with him. After an

enjoyable summer, he decided to stay a few more months and work on his recordings. He was ecstatic about a one-week engagement opportunity to sing and perform with a band his own composition in the latter part of February.

Last Christmas my son came home for a visit. At that time he saw his physician. He reported to his doctor that he had improved greatly except for some residual effects that had remained, such as headache and periodic low energy. The doctor prescribed Prozac.

Of course, my son was completely unaware that Prozac was an antidepressant. He had a fear of any form of sedatives, dreaded the toxic effect of it. After my son returned to France, excited about his upcoming performance, I read an article in The Wall Street Journal and I sent it to him. When I talked to him on the phone, I asked him if he had read the article. He said yes. He assured me that he had achieved full recovery. Indeed, he had read the article. He answered with these words, "Mom, don't worry about what depressed and crazy people do. Not only do I not feel violent, on the contrary, I have never felt happier and full of love. I love you and I love the world."

My son had contacts with home on an almost every-day basis. I did not hear from him for four days. I was apprehensive. I called a musician friend of his to check on him. They said that the cleaning woman had knocked at the

door and he was singing opera. He didn't have an operatic voice and he didn't open the door and he was talking nonsense.

This report alarmed me. I sent him a telegram to call home immediately. One additional day I called back and demanded that they break into his apartment.

DR. CASEY: Would you please conclude in the next few seconds?

MS. RICHARDSON: At 3:00 a.m. I received a telephone call that my son's body was found with another young lady in his apartment. This person he had befriended the summer before was going to the Riviera to visit him. He had told everyone how much he looked forward to her visit and how much he liked it.

While waiting for my flight in the lounge of the airport I struggled to make sense of what little information I had. The Wall Street Journal on Prozac came to mind. I placed a call to Dr. Levy and asked to call my son's doctor and have her call all her patients and have them taken off the Prozac. Dr. Levy was devastated. He had come to love my son and his gentle quality, and repeated disbelief, saying that "Your son wouldn't harm anyone, wouldn't take his life, I knew him. It must be the work of a third person."

Upon my arrival with the investigators, they were baffled by the scene. The woman had died instantly. My son had sliced himself. His hand was completely severed on the

bed. There was a knife wound on his neck, punctured his thorax, cuts all over his body, the last blow was through eye socket that had pierced his brain. He died on the floor with the kitchen knife beside him.

The investigators had searched the apartment, questioned everyone who knew him. They already had concluded that my son lived a clean life. He did not drink or smoke nor did he take drugs. They had overruled a newspaper account that it was a cult or a prowler or a crime of passion. Their findings made them more mystified.

When I mentioned The Wall Street Journal, the group revealed that, indeed, autopsy had shown Prozac in his system. They immediately accepted that the bizarre behavior must have been the side effect of the Prozac. They gave the press the finding the following day. Crime was not committed. My son and his friend were victims of an American drug prescribed by an American doctor.

A week earlier my son had excitedly reported home that his Christmas present, a red new car, finally had arrived and he had picked it up from the customs. He had dropped it to a garage for a minor adjustment. He expressed how much he looked forward to driving it. He never once drove his fancy red Christmas present sports car.

DR. CASEY: Thank you. Suzanne Robbins?

MS. ROBBINS: I am head of the Indiana Prozac

Survivors Group. For the record, this is not a religious issue. We are of all faiths. There may be Scientologists here, I do not know. I happen to belong to the Christian Church. I was a victim. Lilly, you answer me, you tell me what happened to me.

I was prescribed Prozac following surgery that had upset my exercise routine and left me feeling just like the doctor said, "a little blue." I had never taken antidepressant before, so I asked about the possible side effects. He told me the drug was so safe it should be put into the drinking water.

My first reaction came at two weeks. I remember sitting in the car and I reached over and I grabbed my husband and I said, "I feel like I'm dying." I felt like I was leaving my body. The feeling passed in about 30 seconds, so I thought no more about it.

I was sitting in a classroom two days later, when all of a sudden it happened again, only this time I'm shaking, I'm covered in hives, and my mind is racing faster and faster. You can't grab the thoughts, they won't stop. I go to the office. I call the doctor. The nurse says, "Oh, let me look in the PDR." She looked and said, "Oh, honey, that's not Prozac." I said, "Well, what's happening to me?"

Two more days passed. I was sitting in the classroom again. This time I excused myself from the

children. I said, "I must leave. I'll be back." I called the doctor's office again and was told not Prozac. I'm crying by this time. They have to send me home.

I get home and I call the doctor's office again. I said, "I have to see him, something's wrong with me." They said he couldn't see me until Saturday. I said, "You don't understand. Something's wrong with me." He finally saw me the next day, took one look at me, now covered in hives, I'm shaking, I can't think, I can't formulate a thought, and he said, "Oh, you're having a panic attack. It's not Prozac."

So I went home and I thought I'm going to die. There's something really wrong with me. Saturday I went through the day. It was a blur. I just remember feeling strange. On Sunday, I'm a Sunday school teacher, I went to Sunday school and I handed them my Sunday school papers and I said, "Something's wrong with me, I have to get out of here."

I left the church and got into my car and I'm driving the interstate, trying to hold on to the wheel. The thoughts are racing so fast and it's saying "you're going to die," and I have to hold onto the wheel to keep from going off the road. This is real people. This is real.

I finally admitted myself to a stress center. I begged them, "Lock me up because I'm going to die and I don't want to die." The internist walked in, and I remember the day so well, she took one look at me and she said, "Prozac.

You're not my first victim." She said, "The last one I saw they had doubled the dose and she was in full psychosis." I knew at that moment I would live, but I didn't understand the horrors that this drug would not leave my system right away. They had to sit by my bed and they would hold me down as I shook and they would tell me, they would say, "You're going through drug withdrawal." My God, it was horrible. I shook and I shook.

Finally, I was released after nine days. I'm fortunate. I have doctor records. It's in my record, Eli Lilly. They put it was your drug that caused this reaction. It's in my medical records.

By the way, my daughter is a mental health therapist. Guess what, people? It is a street drug. She's treating adolescents right now. They're begging for this drug on the street. We've got to get this drug off the market before it kills someone else. Thank you.

DR. CASEY: Thank you, Ms. Robbins. Dr. Carolyn Robinowitz?

DR. ROBINOWITZ: Mr. Chairman, I'm Carolyn Robinowitz, a general and child psychiatrist and senior deputy medical director of the American Psychiatric Association.

On behalf of our 37,000 members, I'm pleased to be part of this discussion and joining with the National Alliance for the Mentally Ill and the National Depressive and Manic-

Depressive Association in dealing with the allegations and concerns raised.

We believe strongly that changing the label of antidepressant medications is not warranted by the available scientific data and can have an adverse effect on patient care, decreasing access and increasing stigmatization.

As you know well, depression is a serious and grave disorder. It is a disease that has not only enormous morbidity and cost to society, but also an important and devastating mortality as well. We have certainly heard some very sad, troubling, and tragic stories and anecdotes this morning. We also know that when depression is untreated, some 15 percent of patients will kill themselves, additional tragedies, and many more suffer from untreated depression who do not suicide.

But depression is eminently treatable. Once recognized and appropriately managed with combinations of pharmacotherapies and psychotherapies, the vast majority of individuals with depression can be treated effectively and lead useful and productive lives.

But the treatment of depression, as in all other medical conditions, is not without some risk. Medications and psychotherapy can have some side effects, some of which can be serious, just as can other medications for other medical illnesses. In addition, there is the possibility that some

patients may not be responsive or may have paradoxical response to medication.

Furthermore, the key to maximum benefit and the minimization of symptoms is close, careful evaluation, and continued close monitoring of the patient's clinical situation. We also know that although suicide is not uncommon in depression and is the eighth cause of death in this country, antidepressive medication prevents rather than causes suicide.

Newer antidepressants such as fluoxetine are less toxic and are not useful for overdose, a fact that has saved many patients' lives. At times patients may be so highly depressed that they are unable to move or function. Unfortunately, treatment with medication may improve their energy level before totally clearing the depression, and such patients, at an initial phase in their treatment, may be more at risk. This requires close monitoring of the patient by the physician, and also working closely with the family to ensure patient safety.

We agree with the FDA finding that there is insufficient evidence that fluoxetine, or any other antidepressant, induces suicidal or other violent behavior. We feel that labeling must be based on sound science and not sensationalism. It is particularly important, since mental disorders in this country are subject to stigma and the

patients do not come to seek treatment or are stigmatized in their community. Yet this prevalent illness can happen to people as frequently as other major illnesses but, without the appropriate recognition, can lead to death.

I urge the FDA to consider the sound scientific, careful evidence, to recommend studies, if appropriate, to review the careful literature and the millions of patients who have been benefited by appropriate treatment for their depression. Thank you.

DR. CASEY: Thank you, Dr. Robinowitz. Herbert Rosedale?

MR. ROSEDALE: Good morning. My name is Herbert Rosedale. I want to thank the committee for the opportunity to appear before you this morning. I am the President of the American Family Foundation, which is a nationwide organization of professionals, including lawyers, physicians, health care professionals, journalists, law enforcement specialists, college and university administrators, and scientists who are dedicated to providing information to the public and professionals and concerned with preserving our institutions from the threat we perceive that exists with respect to destructive cultic groups.

I am appearing, therefore, before this group not to give personal testimony about an experience I have had with the drug. I am appearing as a lawyer who is dedicated to the

preservation of our legal and constitutional system, which I believe to be threatened by the Church of Scientology, generally, and, in particular, by the efforts of that group itself with its organization and the people whom they use who do not share our commitment to an open society.

I do not mean in any way to take away from the tragedy that people have experienced, which has been movingly described to this committee today. What I do oppose and what I do stress is the necessity for this committee to operate within our legal system and to operate with the use of objective factual analysis and not be deceived by distortions and one-sided presentations.

I am aware, for instance, that this morning you had presented to you information concerning a purported determination of the Council of Europe with respect to the drug Prozac, but nobody described what the Council of Europe was or what really happened. The Council of Europe is not a legislative body involving officials of any European nation; it is a parliamentary group of approximately 192 representatives. On September 3rd of this year six of those members submitted a written declaration to the other Council members concerning Prozac. That declaration, not surprisingly, referred to the Citizens Commission on Human Rights and other Scientology front groups that you have heard of today.

The Council of Europe's rules provide that no action would be taken on this declaration unless there were a petition submitted with at least a hundred signatories. That information was not given to this committee today.

The use of this kind of information is not unusual for the Church of Scientology. I personally dealt with a lawyer representing them who told me that it was acceptable to encourage a child to steal property from his parents' home and blackmail them unless they would make concessions to the Church of Scientology. When I asked how he could tolerate that kind of attitude and whether his client approved of that result, his response was, "You have to do whatever is necessary to achieve your goal."

With respect to the Citizens Committee on Human Rights, Dennis Clarke testifying on their behalf before you, I would like to refer to a particular instance that will illustrate the approach that should be taken with respect to their testimony and their submission of fact.

In an instance in Sturbridge, Massachusetts, Mr. Clarke's view of the recognition of human rights was to hold flash bulbs before people's faces and shoot them off about a couple of inches from their eyes. He is trying to do the same thing to this committee to prevent you from looking past the flash bulb into the light and seeing what the facts are.

Before I appeared before this committee, I had an

opportunity to talk to Dr. Edward Lottick, who is a family physician who practices in a suburban community and whose son committed suicide, he believes caused by the pressure of the Church of Scientology. He stressed to me that I should bring before this committee his strong belief that the attitude and approaches of that group should not preclude people from receiving the medication that will benefit them. He stressed that in all his years in public health he had been unaware of the actions of that group and been unable to help his son when his son needed advice most about the destructive effect of that group.

If this committee will proceed objectively, will hear all testimony, will evaluate all of the facts before it in a scientific and professional manner, it will show that an organization of zealots cannot distort the processes of this government to its own ends and for its own purposes and will do an enormous benefit to all of us. Thank you.

DR. CASEY: Thank you. Harry Samith?

(No response)

Robin Schott?

MS. SCHOTT: My name is Robin Schott. I want to know how you have decided to call this meeting and decide that it is a religious issue. We are not here today to belittle the Church of Scientology, which, I would like to add, I am not a member of. I am a Roman Catholic, thank you. We are

here today to discuss a highly lethal drug, Prozac, which, if you all would like to see my scars and my anecdote and my story, yes, we have belittled human lives here.

I thought we lived in a democracy, where we all got to live with people and we got to be people. But, instead, we want scientific evidence. Who are we testing these drugs on? Do all of you want to take this drug? Do all of you want to walk around humiliated for the rest of your lives because of something you did when you were drug-induced? Do you want to hear the lies? Do you want to get told, "Hey, maybe you'll lose a little bit of weight, maybe you'll get a couple headaches," and you try and slit your wrists? Do you want to never be able to walk back into a classroom because you have been humiliated because you tried to kill yourself at the age of 20, when you were intelligent -- you were well above intelligent, you graduated from college with honors, you were a member of Phi Beta Kappa -- you had everything to live for, and yet you wanted to die?

I entered therapy one year ago as a victim of rape. I stand before you today a victim of Prozac. It baffles my mind to think that a prescription drug I could simply compare to a felony of rape. But, yes, they can be compared, because if a drug robs you of your will to live, then it has committed a felony equal to that of rape.

I entered therapy and was pressured into taking an

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antidepressant as a quick fix to my mild depression. I am not mentally ill. There is nothing chemically wrong with my brain. I was simply depressed. My father died when I was 16. I was date-raped when I was 14. I was date-raped again when I was 18. I obviously had a lot on my mind.

So they told me Prozac was the quick fix. I had told them already I was bulimic. I was already five pounds underweight. To me, it is apparent that my psychiatrist never bothered to read the package insert. The second adverse reaction listed says underweight people should not be placed on this drug because weight loss would obviously be an undesirable effect. Well, I did lose weight, I lost 20 pounds. I shrank down to less than a human being. I was a skeleton, I was a walking skeleton with no will to live.

I became a creature of my own destruction. My adverse reactions began immediately. I have blurred vision, which continues today. When I told my psychiatrist about that, she blew it off. I took that to mean, okay, it's going to go away when I stop taking the drug or I adjust to the drug. It never went away. Today I still wear glasses.

I immediately had severe headaches, violent thought in nature, which is totally against my character -- I had never had violent thoughts before. I'm a pacifist. The whol reason I was in therapy was because of a lack of self-esteem and a lack of being able to stand up for myself. Today I am

here to stand up for myself, my right as a human being, which I feel I was robbed of.

Why am I here today? I am here to make somebody listen, to hear me, my side of the story. Yes, it's a story, it's an anecdote, it's a real live person. I had violent thoughts, I had violent natures, and I tried to kill myself seven days after being withdrawn from Prozac. It even states on the package insert that Prozac has not been systematically researched as to how long dependency would take. So I guess I get to be the living proof that, yes, there is dependency.

I would like to sum it up by saying I tried to kill myself twice. I was unsuccessful both times and I thank God I am alive today, thanks to my mother. My mother loved me enough to leave me in a hospital where I was protected.

I stand before you because I want you to be aware of what is going on in real live people.

Two weeks after I tried to kill myself, one of my friends was tragically killed. I have to live with that for the rest of my life. My mother told me, in trying to comfort me, that perhaps I was the messenger of death and I had taught all of my young friends how to deal with death head on.

I would much rather today be a messenger of life, if one of you will simply listen to what I have to say and bring life, or at least give somebody the chance, a future unsuspecting victim the chance to have a life. I thank you

and I hope that you heard what I said.

DR. CASEY: Thank you. John Smith?

MR. SMITH: My name is John Smith -- J-o-h-n S-m-i-t-h, just in case.

(Laughter)

I am Deputy Executive Director of the National Mental Health Association. I am here today representing our over 1 million members who belong to more than 500 affiliate chapters located in 43 states and the District of Columbia. The National Mental Health Association is the nation's oldest and largest voluntary citizens' organization concerned with all aspects of mental health.

Since 1909, our goals have been to change public attitudes about mental illness, to improve the services and treatments for those illnesses and, wherever possible, to prevent mental illnesses from occurring. Our 1 million members are very diverse. They are citizen volunteers, mental health professionals, former users of mental health services, and individuals, as well as their family members who suffer from serious mental illness.

Concerning the matter before the advisory committee today, I am here to state that the National Mental Health Association is opposed to any changes in the labeling of any antidepressant medication, in general, and Prozac, in particular. It is our position that the existing labeling on

these medications is adequate and describes potential side effects.

There is insufficient scientific evidence to establish a link with either suicide or violent behavior that would substantiate a label change of any kind, no matter how small, no matter how subtle.

These medications have proven to be effective for millions of patients worldwide and have saved thousands of people from committing suicide. Like all psychotropic medications, they are not effective for all patients and depressive illness will sometimes worsen. However, when taken as directed and under the supervision of a qualified physician, these medications have proven to be extremely useful therapy for an overwhelming number of patients.

While you hear tragic stories of individuals who have harmed themselves while taking these medications, it is an unfortunate fact that suicide thoughts are often part and parcel of the cost of depressive illness, whether an individual is taking a medication or not. It is estimated that 15 percent of untreated depressed patients will eventually commit suicide. On the other hand, a smaller percentage of those who are receiving treatment will also commit suicide.

The Association is particularly concerned that changing the current labeling without compelling scientific

evidence will discourage physicians from prescribing these life-saving medications. Such relabeling and the ensuing negative media coverage would also needlessly frighten potential patients from taking the medication or, even worse, encourage patients to stop taking it without consulting their physicians.

In either case, changing the labeling without scientific data would stigmatize an entire class of medications. It would also make it more difficult for patients to overcome the fear and apprehension that often accompany the process of seeking treatment for their illness.

That last thing that is needed to erect additional barriers for patients to receive care is for this stigma. Seeking medical help for this debilitating and sometimes fatal illness is hard enough for patients; imposing alarmist and unnecessary labeling on these medications would be a formidable barrier that some patients would simply choose not to cross, with unfortunate results.

Additional labeling may also result in increased skepticism about the medication among nonpsychiatric physicians. It would be very harmful if these providers failed to prescribe these medications based on reasons other than scientific evidence. To quote the September, 1991, Harvard Mental Health Letter, "It would be a tragedy if they" -- meaning the physicians -- "were to contribute to an

atmosphere in which a small number of plaintiffs and their attorneys, abetted by the Scientologists, make it impossible for seriously depressed people to use this clearly beneficial medicine."

It is our belief that this entire controversy about the safety and efficacy of antidepressants in general and Prozac in particular has been blown completely out of proportion, especially when you consider the millions of individuals who have benefited from these medications.

The FDA underscored this point recently, on August 1st, when it denied a petition to withdraw Prozac from the market. The FDA ruled that, "The data or information available at this time do not indicate that Prozac causes suicidal or violent behavior." We believe the FDA is an effective mechanism to screen, approve, and monitor prescription medications. The National Mental Health Association praised the recent FDA ruling and we continue to believe that antidepressants are extremely useful drug therapies in the treatment of depression.

One of our primary concerns is that any change in labeling will have a negative impact on access to health care which individuals with depressive illness need and deserve. Yet, again, the controversy continues. This morning you are being asked to consider these accusations once again. Mr. Chairman, I ask that you put these accusations to rest. I ask

that this advisory committee evaluate the scientific data and, once and for all, reject these claims. Thank you.

DR. CASEY: Thank you. Dr. Peter Stokes?

DR. STOKES: I am Dr. Peter Stokes. I am Professor of Medicine and Professor of Psychiatry at Cornell University Medical College. I am here today to ask the committee not to change any form of labeling on antidepressant medications, including, of course, newer medications such as Prozac.

To do this would be detrimental to the health care of individuals in this country. It would mean that individuals would, in fact, shy from the taking of prescribed medications and, in fact, many instances of this have already occurred in my own practice and I am aware of an number of letters from other individual psychiatrists and nonpsychiatrist physicians who have indicated to me that this kind of occurrence is happening in their practice.

I have been extensively involved in continuing medical education in regard to depression and other affective illnesses, and I can guarantee you that in every instance where I speak or have the opportunity to meet with physicians at meetings, these kinds of concerns come forward.

Consequently, I ask the committee not to alter labeling in any form and hence to allow treatment to be available as freely as possible, treatment with these antidepressant drugs, which are the core of approach to

depression and treatment of that terrible illness, with its high morbidity and mortality.

Just let me comment for a moment about my background and why I'm here. I've been interested for more than 25 years in psychiatric research in affective disorders. I have been practicing since board-certified in psychiatry more than 20 years ago and have taken care of, personally, some 2000 patients with affective disorder, mostly depression.

I am also board-certified in internal medicine, with a specialty in endocrinology, and board-certified in nuclear medicine. This gives me a broad aspect in terms of the approach to medical diseases, of which depression is one terrible example.

Depression, you have heard, is characterized by certain symptoms. Let me point out that depression is equivalent to suicidal ideation and behavior and potential death. This is like fever in pneumonia and can be analogous to that kind of proposition.

Let me point out to you that suicide is common in depression, it occurs in perhaps in one in 10,000 people. That is one in every small town throughout the United States -- more than one -- every year. That is a lot of people. Antidepressant medicines decrease suicidal ideation, decrease suicidal behavior.

Let us recall the recent Time magazine proposal --

or, I should say, front page -- of approximately a year ago that showed the more than 400 individuals who were killed every year in the United States by firearms. Careful reading of that data clearly documented to me that a large percentage of those persons were, in fact, depressed, showing that not only suicidal behavior and self-directed violence, but outward-directed violence, is part of depression. Let us not forget that.

Antidepressants are safe medications. They have a high therapeutic-to-toxic ratio. The newer drugs are better in that regard, including such drugs as fluoxetine, or Prozac, or Wellbutron, with the exception of one or two obvious and clearly package-marked problems. No medications that we have, antibiotics through antidepressants, are totally safe. We do not have 100-percent safe medicines; we have bad illnesses that need treatment. People need access to that kind of treatment.

A large amount of prospective data, clinical trials, observations of depression scores during those trials, and retrospective analysis of data show no increase in suicidal ideation in association with any antidepressants, including fluoxetine. Four million people have been treated with this drug throughout the world, it is estimated, without increase in suicidal ideation, without increase in suicidal behavior.

In addition, we have had some 30 years of use of

antidepressants without evidence of association of suicidal ideation or behavior. Long-term treatment with antidepressants recently, by Montgomery in England and here in this country at the University of Pittsburgh, show no increase in suicidal ideation, and that is true with my own experience with these drugs, including fluoxetine.

Let me just close by saying that 18 months after the first appearance of some anecdotal data, anecdotal material, suggesting the possible association of suicidal behavior and violence with the administration of drugs there has been no flood of further information and no scientific data to support that possible relationship.

Let me point out to you that researchers are certainly not shrinking violets. They make their opinions known. They like to look at new problems and new questions. They like to bring out the possibility that there has been a misinterpretation, an error, or, in fact, that there are things we haven't seen. None of that data has as yet been forthcoming.

In closing, I say a phrase that all of us know well as physicians: Above all, do no harm. That means don't change the labeling, don't scare patients away from treatment, don't make it difficult for nonpsychiatric physicians to use these safe, effective compounds. I ask you to consider the scientific data. Thank you for the opportunity to address the

committee.

DR. CASEY: Thank you. Shirley Surber, please?

MS. SURBER: My name is Shirley Surber. Compared to the other testimonies that you have heard today, mine will probably seem insignificant, but to my family and to myself it was really devastating. Prozac was prescribed for me for the first time on March 19, 1991. I was on a routine visit to my doctor and the nurse-practitioner asked if I had any questions or problems. I casually mentioned to her that I'm very sentimental and find myself, as a teacher, having to choke back tears on occasion while reading a story or talking to the children. She asked if I was depressed. I said no. She went through a routine questioning sort of like "Do you enjoy socializing with other people as much as you used to," et cetera. After answering all of her questions, she was satisfied that we were definitely not talking depression here.

But she said that there was a fairly new antidepressant out, called Prozac, and she wanted me to try it to see if it would help what I called the "weepies." I asked specifically about side effects and she said there were absolutely no side effects. So I said I would try it. If I had known or been forewarned of any possible side effects, I would have gladly said no.

I took Prozac for exactly 11 days, during which time I experience annoying and increasing dimness of vision,

irritability, headaches, and tension. Unaware that these were warning signs to something far greater, I attributed the problems to my new eyeglasses, which were slightly tinted.

By the night of the 11th day I was experiencing some serious shortness of breath and by the morning, Easter Sunday, I was so disoriented that I could not even dress myself for church. In fact, I couldn't organize my thoughts to do anything, so I lay in bed. I was afraid, I felt like I was losing my mind, and this was my first full-fledged anxiety attack, and it was going to get worse.

I knew that something serious was wrong, and I figured it might be the Prozac, so I stopped taking it. In retrospect, I saw the symptoms leading up to the attack starting the second day I was on the medication and building up from there. Now my body was progressively adding to my disorientation new depths of fear until I was experiencing nothing but wave after wave of pure terror and panic.

It would ease up at night, but I was afraid to sleep, because it was always more intense upon waking, and I couldn't face it. I was terrified of everything. By the 14th day I was experiencing such intensified fear that I could not stand to face life as it was for me anymore. There was, to my mind, no hope, no future. Where suicide had never been a logical solution for any reason for me, it now became my only solution, because I had nothing left with which to fight, and

I was terrified to go on living.

I thank God for his love and the love of my family. Were it not for these, I would not be alive today. My family talked me through the toughest times until my husband got me to call a doctor. The doctor's associate saw me and said he could give me a mild sedative to take the edge off, so I went in. The doctor who saw me said that my anxiety attacks were not from Prozac. He accused me of having some deep-rooted problem which I refused to disclose and he told me to go back on the Prozac, and I refused.

He referred me to psychosocial services. The therapist who interviewed me over the phone said to her it sounded like a reaction to Prozac. She asked if I was still taking it and I said no. She replied, "Good, I was going to ask you to stop."

I'm currently under my therapist's care and, unfortunately, I'm caught in the web of more medication to block the effects of the original. I now take 200 mg daily of imipramine and .5 mg one or two times daily of Klonopin. I was bedridden for four weeks before I could return to work. With the waves of fear came weakness of extremities, butterflies in the stomach, rapid heart beat, and every noise was so greatly magnified that it was like an electric shock running through me.

My therapist explained that the Prozac had severely

oversensitized my nerves and I would have to wait for them to desensitize with time. Desensitization could take days, months, or even years. In fact, they could not tell me if my nerves were permanently damaged or not.

I frequently try to wean myself off the Klonopin and so far I've had no luck. I still have waves of anxiety attacking me, but they are more subtle. I have to force myself to go out of the house or to socialize with friends, and sometimes I can't overcome the feeling, so I just sit at home.

During the attacks I keep telling myself that this will pass, I don't really feel this way. I can give myself all the logical arguments why I shouldn't be afraid. During the attacks my mind cannot process or believe what I'm saying. It's a vicious, frightening circle that's been going on for six months and could have easily been avoided altogether had there been much stricter monitoring and regulations on the use of Prozac.

Why prescribe such a powerful drug to me? As one of my friends so aptly put it, it was like using an elephant gun to shoot at a gnat. There's definitely gross misuse of this drug. Prozac may be the answer for thousands of people, but when it does cause an adverse reaction, we're not talking about a little rash here. We're talking disaster. We're talking life and death. We're talking the ability or

inability to function in society, maybe forever. Thank you.

DR. CASEY: Thank you. Sara Thomas?

(No response)

Nancy Veasey?

MS. VEASEY: I am a registered nurse and I represent the Philadelphia Prozac Survivors Support Group. I graduated from Philadelphia General in 1953, and I hope there may be one or two up there who remember "Old Blockley," and the ethical background it represents.

I am here to present facts associated with the drug Prozac. My curiosity about this drug erupted back in the late spring of 1989. I will address those circumstances in the last minute of these five minutes allotted to me today.

In September of 1990 an article appeared in The Philadelphia Enquirer. As a result of that, the Prozac Survivors Support Group in the Philadelphia area was launched. My involvement was solely to collect further data on the drug for strictly personal reasons.

Through the fall and winter of 1990 and the fall of 1991 until today I met with and talked with by phone 15 people directly and indirectly affected by the drug, not a very impressive group, but what is impressive is that out of the 15 there are five deaths recorded in my notes. These are the facts.

A 36-year-old mother of two, while on Prozac,

attempted suicide by impulsively ingesting a toxic dose of medication.

A 42-year-old man watched helplessly as his 36-year-old wife casually, with no warning, picked up a knife and cut both of her wrists while on Prozac.

A 50-year-old man with some memory impairment struggles today to express the devastating and long-lasting effect of this drug.

A 49-year-old man, while on Prozac, blacked out while driving and was involved in a car accident.

A 71-year-old man shot himself seven days after being prescribed Prozac, one week before his daughter's wedding.

A 58-year-old man, while on Prozac, developed violent behavior directed toward his sister, his primary caretaker. He was hospitalized. He has since died.

The mother of a 40-year-old female Harvard physician found her daughter dead. On the nightstand was a bottle labeled Prozac. The coroner's report showed excessive amounts of Prozac in the blood. Just three months ago, upon receiving her daughter's effects, her grief-stricken husband died. Needless to say, this is one woman who is literally immobilized by grief, as I am sure many others here today are.

In June of this year a woman found her husband dead by hanging in the basement of their home one week after Prozac

was prescribed for him. There were no signs or warning signals. He simply got up, as he did frequently at night, and went downstairs and hung himself. His son cannot go down there to this day.

There are others here. But in the last minute I wanted to say I would not be here today had my daughter not been prescribed Prozac in the spring of 1989. I would not be here had she not been near fatally injured in an auto accident on the morning of August 11, 1989, requiring air transport to the hospital of the University of Pennsylvania, remaining on life support in the trauma unit there for 12 days.

By her 29th birthday she was able to walk with only one crutch. In February, a second-stage facial peeling with bone grafts was scheduled to further reconstruct 27 facial bones that had been shattered in her face. In March, recovering from that procedure, the psychiatrist again prescribed Prozac. She was subsequently hospitalized.

I will close with words describing the effect of Prozac on all of us here today and those we love most dearly. We have suffered serious and severe permanent physical and personal injuries, mental and emotional distress, adversely affecting our ability to enjoy life fully. Thank you.

DR. CASEY: Thank you. Nedra Walnum?

MS. WALNUM: My name is Nedra Walnum. I am 32 years old, the single parent of two lovely children, ages 11 and 6.

I have been raising my children alone for six years. During the six years that I've been a single parent I've endured a tremendous amount of stress which has been directly related to being the head of a household in a single-parent home.

Despite the situation, I've been very functional in society. I've managed to obtain many goals in my career, home life, and spirituality. I've been an intake worker at the Center for Women's Studies and Services Project Safe House for two-and-a-half years. I've worked as a crisis counselor on a hot line for sexually assaulted individuals for one year. I've worked with youths through the San Diego Housing Commission. During my duration of working and raising two children alone I have completed 32 units at the local college in my community. I've been an active member of the Church of Christ for eight years.

I obtained counseling from an MFCC in 1989, feeling this was a healthy way to deal with my stress of being a single parent. The MFCC felt that I was saddened by my situation, saddened enough to need an antidepressant. She referred me to a local psychiatrist in my area strictly for medication purposes. I was prescribed Prozac, 20 mg, once a day, beginning February 13, 1990.

I appeared to be doing well on Prozac until June 25, 1990. This was the date of my first suicide attempt. Five days prior to June 25, 1990, I have little or close to no

recollection of my activities. This tells me that Prozac had already become toxic to me at that time. During these five days I did not report to my place of employment; I literally stayed in my bedroom for five days. I was not attentive to my children; in fact, I completely neglected them. My children fed themselves and care for themselves. This is totally out of line of my normal character.

On June 26, 1990, I woke up in Paradise Valley Hospital intensive care unit due to severe overdose of Xanax. I was prescribed Xanax along with Prozac due to the high level of anxiety that I was experiencing from Prozac. I then was transferred to Paradise Valley Hospital psychiatric ward, locked-down unit. There I was then prescribed 20 mg of Prozac twice a day, with Ativan, four times a day.

On July 21, 1990, I attempted suicide again. This attempt was even more severe. I took an overdose of Ativan and sleeping pills. This time I went to Paradise Valley Hospital by ambulance and was taken to the intensive care unit. I then began questioning this medication.

At this time I began refusing Prozac without the recommendation of my psychiatrist. I have been fine ever since. The bottom line is, I was never suicidal before taking Prozac. I was obsessed with suicide while taking Prozac and the obsession stopped immediately after I stopped taking Prozac.

I am outraged that the members of the medical field have spoken to this committee today insinuating that the testimonies given today can fall in the category of statistics, that 15 percent of all depressed people will commit suicide. These people that have told their testimonies here today were not psychiatric patients prior to taking Prozac. Prozac, on the other hand, has literally created psychiatric patients throughout our country.

Please hear what the people are saying to you all. We all are the results of this drug. Please immediately remove this killer drug from the market before any more people are killed and their lives destroyed, I urge all of you.

DR. CASEY: Thank you very much. Susan Williams?

MS. WILLIAMS: Susan Williams. I didn't really want to bring my daughter with me today. Unfortunately, she was so traumatized by my going out of town that I had to bring her.

Lindsay's mother began taking Prozac in August of 1988 for treatment of depression and alcoholism. She became very suicidal on the drug. She was a slight woman, she weighed 98 pounds. She was kind of hyper, to begin with, and the drug made her very, very aggravated. I looked it up in the dictionary: Aggravation is "to make worse, to annoy or to irritate." So essentially Prozac made her problems worse. She ultimately committed suicide.

One woman earlier spoke of nearly committing suicide

in front of her children; my sister did commit suicide in front of Lindsay. Another woman spoke of hollow-point bullets. That's what my sister used to do it.

Okay, the plot thickens here. A year and a half later, Lindsay's father went in for treatment for drug addiction. They began treating him with Prozac and Valium. He was a very passive man, to begin with. He became highly, highly hostile, very aggressive, ultimately committed a homicide and then a suicide while on Prozac.

I'm Lindsay's mom now. I've adopted her. And if you want to talk Prozac victim, this is a Prozac victim here, and this is not going to go away. Lindsay will tell you that her parents died of drug addiction, and when you hear that, you think she's speaking of cocaine or some other illegal drug. She's talking about Prozac. Prozac caused her parents to kill themselves.

I'm not a zealot and I'm not here with any anecdotes. This is my story and it's hard to talk about it. Life goes on and I'm a very positive person and I hope that Lindsay grows up and will be very positive with me.

I understand that Loban is being considered being approved now for weight loss. Being such a weight-conscious society that we are, think of all the young men and women who are going to want to take this drug for weight loss. You're going to have a lot more people that are becoming suicidal

and/or homicidal on this drug. I really, really think that you should consider changing the warnings on Prozac or, at the very most, removing it from the market.

Someone else spoke about the European group that was trying to decide something. Who cares what Europe is doing? This is the United States. It's not Scientology. Everyone seems to put it "us versus them," Eli Lilly or the FDA versus us, or us versus them, or the Scientologists versus everyone else. We're all in this together. There's obviously a problem with this drug and I don't understand why someone isn't doing something about it.

Yes, I believe that there are mentally ill people that probably do need to be treated with something, but there are plenty of other drugs on the market that don't seem to have had this problem. I don't see why you can't prescribe that drug to them and take Prozac off the market, even if it's temporarily, until you, the medical community, can decide what is causing this.

No one has ever really explained what Prozac does. I've heard that it taps neurons in the brain. Well, perhaps it taps certain neurons in certain people's brains that tap suicidal ideation. Who knows? No one has ever explained that. All I've heard is the Scientology issue. I'm not a Scientologist, but I don't understand why nobody has ever really addressed the technical side of how it affects the

brain and why it is causing these people to do such gross things.

My sister would have never, ever have killed herself in front of this little girl. She would have never done that. Prozac induced her to do that.

DR. CASEY: One minute, please.

MS. WILLIAMS: Oh, God, I've got another minute.

DR. CASEY: No, you are not required.

MS. WILLIAMS: I know that, but I feel, you know, that I should be here when everybody else did such a good job.

I hear people applauding pro-Prozac. I hear people applauding for the people that are against Prozac. I'm against Prozac, because I think it's dangerous, but I think there are other alternatives to Prozac. There are other drugs out there that apparently have been proven to be good drugs. Let the people that are using Prozac or having adverse reactions to it use that drug until the medical community can decide what the problem is with this drug. There is a problem.

If you choose not to do anything and then you do approve Loban, you're going to have to go through all of this again. And this little girl is going to grow up having to deal with all of that and she'll be fighting in our place where we are now. If you do consider changing the labeling of Prozac, I think it is the very least you should do for it.

Otherwise, I think you should take it off the market all together. Thank you.

DR. CASEY: Thank you. Richard Wontorski?

MR. WONTORSKI: My name is Richard Wontorski. I'm a survivor from Prozac. I wrote a five-minute speech, but listening to everybody else, I don't want to bore a lot of people in here, because a few of them look like they're bored.

The drug does cause suicidal tendencies, that's all I can tell you. It shouldn't be on the market. If it's going to be on the market, give me a choice whether it's going to label this could be suicidal. I had no choice. I went to a family doctor. I was feeling a little low. He gives me a new wonder drug, Prozac. I was told of no side effects, none at all.

If I'm going to get something -- even a pack of cigarettes tells you it could cause cancer, saccharine causes cancer, they're giving you warning on pop cans -- that's just pop, everybody drinks pop all day long. I just don't understand why you can't give a label on a medication that does have suicidal tendencies, or anything that could cause you any harm. I want to know, I want the right to know if I'm going to be harmed by a medication I'm taking.

That's why the FDA is out there, to help us, to protect us. Just like your family doctor, like myself and everybody else, we trust our family doctors. My family doctor

trusted Eli Lilly. Somebody's got to do something with this drug. I'm glad this is going about. It's taken a lot to get everybody here. I didn't want to be up here. I'm shaking in my boots now. I've never sat and talked in front of anybody before, other than a basketball group, but for these people that have stood up, my hand goes out to them, because I've been there, and the ones that didn't show and you've called their names, I think I know why they didn't want to be up here. You know, I don't want to relive any of this.

Please, Eli Lilly, take this off the market. Market things. If you're going to make another drug in lieu of this one, label the warning. I want to get -- my first prescription, I never got anything that said it was toxic or any harm to me. You take it because your doctor tells you. You take it like your religion, one in the morning, one at night.

I don't know what to tell you other than please take this drug off the market, and I thank everybody that showed up today and had the courage to come up here and talk. Thank you.

DR. CASEY: Thank you. This concludes the open public hearing session. I would like to offer everyone in the room and on the committee a three-minute stand-up-and-stretch break. Because of security reasons, I will ask all the committee members to stay here, because they cannot get out

and get back in, in time, and to let the audience know that they will have to have their I.D. badges and passes checked, so they will have a slow going out and a slow coming back.

(A brief recess was taken.)

DR. CASEY: We are moving to the next phase of the meeting. As a housekeeping matter, let everyone know that we will continue with the session -- people have ordered lunch at the table, so we will be eating out of need to sustain our energies rather than impoliteness. Please feel free to leave at any time to go to lunch, and you are welcome back. We will be here.

Before we move to the next part of the meeting, I would like to thank everyone who came to the open public session to express their personal experience, to show great courage in relating to us on the committee and to everyone else in the room about their experiences or the experiences from group members that they represent or their private or personal opinions. It has been very helpful. It was certainly worth our time, and I thank you very much, both for myself and for other committee members.

We will now move to the next session. The topic for today's advisory committee meeting is the possibility of a causal linkage between the emergence and/or intensification of suicidal thoughts and acts, suicidality, that is, and/or other violent behaviors and the use of antidepressant drugs.

Dr. Paul Leber, Director of the Division of Neuropharmacological Drug Products, will make a few opening comments.

FDA PRESENTATIONS: INTRODUCTION AND PURPOSE

DR. LEBER: Thank you, Dan. I, too, would like to add some personal comments about the demeanor and behavior of the people who are our guests this morning. I actually think it was a very instructive and useful session and we were all impressed by the sincerity and sense of conviction of the people who spoke and their interest in the problem before us.

On a more humorous note, I want to thank Dan for at least letting me know that people can leave during my presentation and, therefore, if people stay, I can take credit for the wonders of my speaking abilities.

The first observation I would make is that anybody in this room today is certainly by now aware that there are a number of individuals who believe with a sense of conviction that antidepressant drugs in general and Prozac in particular cause and/or intensify suicidal thoughts, acts, and other violent behaviors.

Now, as the federal agency that is responsible for assuring the safety and efficacy of drugs in the armamentarium, in the marketplace, the Food and Drug Administration is obliged to examine the evidence and inferences that have led those who testified to believe as

they do.

Certainly, some other sources of evidence appear, at least on the surface, to lend support to their concerns. The medical literature, for example, contains reports of cases where antidepressant drugs have been administered and appear to be followed by worsening of symptoms rather than by improvements.

It certainly is an indisputable fact that FDA's voluntary spontaneous postmarketing surveillance system has received exceedingly large numbers of reports of adverse reactions that are linked to and alleged to occur following the use of Prozac.

It is within this context of information, belief, and, I would add, some anxiety, that individuals and institutions have called upon the agency to be what I should say is more assertive in regard to our regulation of antidepressant drug products in general and, again, Prozac in particular.

However, and this is an important caveat, any consideration of the need for additional regulatory action must begin with appreciation of the fact that suicidal thoughts, acts, and other violent behaviors are common manifestations of psychiatric syndromes for which antidepressants are prescribed. Consequently, it is not ordinarily possible to determine from the facts of a

particular case history, no matter how compelling, that it involves an untoward response to an antidepressant drug, no matter how tragic the outcome of that case, whether the particular outcome is a consequence of drug treatment or simply a manifestation of the nonresponding underlying psychiatric condition. And that is a basic problem.

Furthermore, and this is also an important point to understand, a large volume of reporting to a spontaneous adverse reaction system is not in and of itself a reliable index of a drug's risk. The absolute numbers of reports received by spontaneous reporting systems, as we shall shortly hear in greater detail from a representative of the Division of Drug Epidemiology and Surveillance, is that the reporting rate is affected by the recency of the drug's introduction into the marketplace, its market share (clearly, drugs used in millions have a different absolute number of reports associated with them than drugs that have a small share of the market) and, finally, of course, publicity may grossly inflate or perhaps prevent reporting -- we do not really know.

It is for these reasons and others that assessments of the potential of drugs to cause harm are ordinarily only deemed reliable in the scientific community if they are derived from clinical sources of evidence that allow a comparison, and it is a comparison of the incidence and intensity of the events emerging in both the presence and the

absence of drug treatment.

The important point here is that an evaluation of such sources, at least to date, evaluation by FDA scientists, outside consultants, and by our physicians, have not led us to conclude that there is a differential rate of risk for Prozac related to suicidal thoughts, acts, or other violent behaviors.

However, and this is an important caveat, again, the FDA is mindful that the lack of a compelling body of evidence is not in and of itself exculpatory. Potent drugs, no matter how valuable and effective, can do harm. Indeed, they may sometimes cause the very same injury that they are intended to prevent. We all know that antiarrhythmic drugs can induce arrhythmias and anticonvulsants may lead to seizures.

Consequently, nobody in the agency dismisses the possibility that antidepressants in general and fluoxetine in particular may have -- and I emphasize "may" -- the capacity to cause untoward injurious behaviors, acts, and/or intensify them. Indeed, if you read currently marketed drug labeling of a company's drugs, you will see that the warnings -- not the warnings but the precaution section -- make clear that prescribers ought to be aware that depression is a serious illness that carries with it the risk of suicide and that in the period following the initiation of treatment great care must be taken to supervise patients and monitor them closely.

It is already in the labeling and it is the labeling of all drugs, including Prozac.

Yet I want to emphasize that the analyses of data collected from reliable sources of evidence, that is, data collected in controlled clinical trials of antidepressants, including fluoxetine, indicate that if antidepressants do cause any kind of behaviors, the incidence is too low to detect them. In short, they may be going on, but we cannot discover them, because they do not happen frequently enough.

That reassurance, for whatever it means to you, notwithstanding, the agency has been urged by several groups and individuals to take some type of more sweeping action in response to the volume and kinds of reports we are receiving about Prozac. One petitioner, as many of you know, asks that Prozac be absolutely banned, removed from the market. Another, still pending, asks that we compel Eli Lilly to modify Prozac's labeling so that it will warn prescribers and patients in a much more prominent manner than it now does of the existence of reports of suicidal induction, of violence, suicidal ideation and the like.

The agency recently determined, as was mentioned more than once, that the evidence currently available is insufficient to justify withdrawal of Prozac and, therefore, we denied the petitioner's request. In doing so, we announced, again, that it was our judgment that the evidence,

taken as a whole, continues to support the conclusion that Prozac meets the standards of drug product safety and efficacy required for marketing approval under the federal Food, Drug, and Cosmetic Act that is our national drug domestic regulatory law.

I want to emphasize again, to be fair, that this conclusion does not mean that we believe, individually or collectively, that antidepressants, or Prozac, are absolutely risk-free. Neither does this conclusion mean that the agency is going to lessen its vigilance or will cease to review and assess the significance of adverse reports it receives on Prozac now or in the future.

Reports of Prozac, like those received on all marketed drugs, are regularly monitored and evaluated. When a signal of potential concern is identified, as it has been in the case of Prozac, we take additional actions, and urge manufacturers to do so as well. In the present case, for example, the sponsor, Eli Lilly, was asked -- and, I want to mention, expeditiously complied with the request -- to examine data from previously conducted controlled investigations and was also asked to develop plans to conduct new studies, including clinical trials and epidemiological studies, studies that could provide more direct answers to the questions that have been raised in the open session earlier.

Unfortunately, it is very difficult to tell, from

where we sit, what more needs to be done at the present time. However, there is a tension in the air about this. A large number of reports continue to be received, and certainly public anxiety over the possibility that Prozac might be different in some way from other antidepressant drugs seems to persist.

It is very difficult for us to be Solomon-like in situations as complex and vexing as this. Clearly, we have to give some form of consideration to the possibility that there would be some benefit in modifying antidepressant drug labeling. We could, for example, take note of the facts that have been presented in labeling. That is an approach that one particular petitioner has urged, but we, as other people in the open session have noted, are not sure what the consequences of that act are or might be or could be (we cannot predict the future). We have to recognize that the net effect might be a reduction in the use of antidepressants in the treatment of depression, and that result might cause overall injury to the public health.

This is a point, by the way, that is not one that I alone believe in; certainly, many, many letters we receive -- which will appear in the record subsequently -- from academic psychiatrists of national and international renown have emphasized this point. Whether they are correct or not, I am not going to speak to that, but certainly it is a concern.

When you do something, there is the yin and the yang of it.

I want to emphasize, too, that our reluctance to adopt specific suggestions for modifying antidepressant drug labeling does not arise from doubts about the motives of those who are urging us to take these actions or, importantly, from the failure to appreciate the potentially positive aspects of these recommendations. It is easy enough for me to understand why someone could conclude it would be constructive and in the interest of the public health to inform individuals using the drug, and the practitioners, about the high rate of reporting, although I am not sure how that would be understood.

Similarly, it is not difficult to appreciate the arguments of those who advocate what have you got to lose? Why not at least point out that some people believe there is a special linkage between Prozac and suicidal ideation?

So I think we understand the arguments and the recommendations, but our failure to adopt them immediately is that we are really not sure how it would work out. We all have to remember that the best-intentioned of actions do not necessarily turn out well; they can cause harm.

Anyway, having given this preamble, I trust by now it should be obvious to everyone, too, why we have convened this advisory committee and why we have asked various other individuals to join us. Beyond the official questions which will eventually be read into the record, we are interested in

the collective thought and wisdom of the group that has been gathered, their counsel and advice on how best to deal with this very difficult issue.

One, importantly -- and I want to emphasize -- I do not think it affects just fluoxetine, but affects all antidepressant drugs in general, and maybe the next new drug that comes along.

Before calling on my colleague, Dr. Laughren, who is head of the Psychopharmacology Unit in the Division, who is going to provide some background information about what we actually found during the premarketing evaluation of the clinical trials that led to the approval of Prozac, I would like to take a little time to make specific mention of thanks to the committee and, also, to the guests who came, some -- or one, at least -- from far away.

I think it would be important that I introduce them individually. I will not do the committee, but I will do the guests, because I want to make clear why we found it useful to expand the membership for this discussion. They are not voting members, of course, but they will be asked to participate fully in the discussion.

They have introduced themselves, but let me state what I think are the highlights that identify them as important. If I misspeak or misrepresent you, I apologize in advance. To begin, there is Dr. Martin Teicher of McLean

Hospital and Harvard. He was the first author -- lead author -- of the paper that in many ways may have begun much of our current interest in Prozac and its link to a special type of recessional state and belief that appeared in The American Journal of Psychiatry in February of 1990. Therefore, he is in a position to speak and describe uniquely what he found that made him make the linkage between the idea of something unique in Prozac as distinct from other drugs.

Dr. Ida Hellander has been asked to join us as a representative of the Public Citizens Health Research Group. She is a co-author with Sid Wolfe of the petition that was submitted to the agency that asked us to change some of the labeling to call attention, if you will, to what are alleged to be the unique attributes of Prozac.

Dr. Stewart Montgomery is an internationally known academic psychiatrist. He is the reviewer for the Committee on Safety of Medicines, which is more or less the U.K.'s equivalent of the United States FDA. Among other things, Dr. Montgomery is a clinical trialist, a co-author of a widely used scale to assess the signs and symptoms of depression and, as he identified earlier, is also the P.I. of a major study that examined the prophylactic effects of fluoxetine versus placebo in the prevention of recurrence of major depression.

Also with us is Dr. Michael Stanley, a professor of neuroscience from the faculty of Columbia University's College

of Physicians and Surgeons. He is a former member of this committee, its former chair at one point, and is an internationally recognized expert in the mechanisms of serotonin induction of suicide and violence.

Dr. John Mann from the University of Pittsburgh is an expert on mechanisms that may underlie suicide. He is, importantly, chair of the American College of Neuropsychopharmacology's committee on the role of antidepressants in suicide and violence.

From the government we have Dr. Darrel Regier, who is Director of the Division of Clinical Research at the National Institute of Mental Health. He is, beyond a psychiatrist, an epidemiologist and one with an interest in the epidemiology of suicide.

I think I have not slighted anyone among our guests. I could say the same kinds of things about our standing committee, but I will forego that in the interest of time. Having made these introductions, I think you all should understand that this panel is ably and well suited to deal with the issues before it.

I now would like to ask Dr. Thomas Laughren, who, I mentioned, is the head of the Psychopharmacology Unit for the Division, to come to the podium. He is our resident expert on the data we have in hand on Prozac.

BACKGROUND INFORMATION

DR. LAUGHREN: Thank you, Paul. I want to begin by giving a very brief history of the NDA for Prozac and, also, what I would like to do is give you a sense of what FDA's position was on this question of suicidality prior to the approval of Prozac.

The NDA was originally submitted in September of 1983. This drug was classified as IB. Basically what that means is that we consider this to represent a modest therapeutic gain, and the reason was that it was the first drug of the fairly specific serotonin reuptake inhibitors to come in under an NDA.

We did a preliminary review and we brought Prozac to an advisory committee in October of 1985 and that committee recommended that we approve the drug. Over the next year we received a substantial amount of additional safety data, which we reviewed. In fact, the safety data base for Prozac was one of the largest we had ever seen. There were approximately 8000 patients exposed to this drug during the premarketing trials, including 6000 in the United States and 2000 from foreign sources.

In any case, we completed our review. An approvable letter for Prozac was issued in September of 1987 and a final approval letter was issued in December of that same year.

As is true of all drugs, Prozac was associated with a number of adverse events in the clinical trials. Those

adverse events were included in the approved labeling for this product, the labeling that was approved in December of 1987. It is true that there was no specific mention of a link between taking the drug and suicidal ideation and behavior, and the reason was that we found no basis for that in the premarketing data.

To be clear, we were not specifically looking for that linkage and the reason is the one that you have already heard from Dr. Leber and others, that suicidal ideation and behavior are part and parcel of depression, so it was not unexpected that we would find some reports of such behaviors in the data base. The numbers of such reports did not seem to be out of line with what might be expected. Consequently, no special analyses were done looking for that linkage prior to the approval of Prozac.

Because the issue has been raised, subsequent to marketing, of a possible linkage, we did request the sponsor to do those analyses. They have been done. We have received a report on those analyses and the material is submitted to you in the package for this meeting and you will also hear a summary of those findings a little bit later in the meeting.

I want to switch to the postmarketing phase. It is typical in the first few years of marketing of a new drug for clinicians to submit a large number of what are known as drug experience reports. Usually these are reports on adverse

events that clinicians did not expect to see in patients treated with the drug and that are not mentioned in the labeling.

As has been mentioned, we have received a large number of such reports for the drug Prozac. Dr. Stadel, from the Division of Epidemiology and Surveillance, is going to talk about those reports in much greater detail, particularly the reports that relate to the questions of suicidality and violence.

But before he does that, I want to talk very briefly about how we translate the information contained in those reports into the labeling for a new product. On the basis of the many spontaneous reports we received for Prozac, we have made a large number of changes in the labeling of Prozac. Most of these have been the addition of new adverse event terms in the labeling.

There are six sections of labeling that address adverse events: These are "Contraindications;" "Warnings;" "Precautions;" a section entitled "Adverse Reactions;" and then two special sections, one on "Drug Abuse and Dependence" and one on "Overdosage."

The question arises, where do we put new adverse event terms in labeling? There are a number of factors that determine that. One is the nature of the event, but also the seriousness, the frequency, and, very importantly, the

question of how strong the association is between the taking of a drug and the occurrence of the event; in other words, how strongly do we believe there is a causal link?

Dr. Leber mentioned that the labeling for Prozac already includes the standard "Precautions" statement. Basically, that statement cautions physicians that suicidal behavior is inherent in depressive illness. Importantly, it does not specifically suggest a linkage between the taking of the drug and the occurrence of suicidal ideation and behavior. On the basis of the very large number of reports in the spontaneous reporting system, the terms "suicidal ideation" and "violent behaviors" has been added to a subsection of adverse reactions entitled "Post-Introduction Reports."

Again, to be clear, putting those terms in that somewhat obscure section of labeling reflects our lack of confidence in a causal link between the taking of the drug and those behaviors.

Dr. Leber also mentioned the two petitions that we have received, one from the Citizens Commission on Human Rights, which has asked that we withdraw Prozac from the market on the basis of these reports of suicidality and violence. As he noted, we have rejected that petition. Our response was included in the package of materials that you received prior to this meeting.

The other petition was from Public Citizens Health

Research Group. That petition has requested that we put a box warning in the labeling for Prozac warning of the possible risk of suicidality in association with the use of Prozac. We have not yet responded to that petition, so you do have an opportunity to advise us on that petition before we respond.

We can talk later about what the options are in regard to labeling statements that fall between the extreme, on the one end, of a box warning, and, on the other end, of the mere mention of these terms in post-introduction reports.

If, after hearing all the evidence, it is your conclusion that we should make some kind of labeling change, whether for Prozac or for the antidepressant class, I would ask that you be fairly specific in giving us advice about that. It is not feasible in a meeting of this type to work out the exact language of labeling. However, it would be helpful if you could advise us about issues like content, placement in labeling, and emphasis.

I am going to stop at this point and introduce Dr. Stadel from the Division of Epidemiology and Surveillance. Thank you.

DATA FROM FDA'S SPONTANEOUS REPORTING SYSTEM

DR. STADEL: Thank you.

(Slide)

I am going to be talking about the experience of the Food and Drug Administration spontaneous reporting system for

drug experience. Briefly, the system receives about 70,000 reports per year for all drugs marketed. This is a brief reporting form: It is a one-page form that often comes to us only partly filled out (the information tends to be very brief).

Many reports go to the manufacturer from the person who observes the event and then come from the manufacturer to us, and a small fraction come directly to the agency. Those that refer to an event that is serious, a health event that is not in the drug's label, it is required for the manufacturer to submit them within 15 days of the manufacturer's receipt, and those receive hands-on review within the FDA's Division of Epidemiology and Surveillance.

There is another group of reports where an event is in the drug's label but the manufacturer receives a sudden increase in frequency of reports. They also send those within 15 days. We have been monitoring all these types of reports on a regular basis for fluoxetine for some time.

The main problem in interpreting spontaneous reports for a situation like this has been mentioned several times already, and it is what we call confounding by indication, which simply means that people who are depressed, who have the disease that antidepressants are used to treat, are at increased risk for suicidal thoughts and behavior, and so on, so that it is hard to separate out any effect that might exist

for a drug from the effect of the disease that is being treated.

There are also a lot of other issues that have to be dealt with in dealing with spontaneous reports, that is, usually only a fraction of incidence is reported. This has been studied for various outcomes, 5, 10, 15, 20 percent of incidence, perhaps, is reported under different circumstances. There can be differences in reporting behavior among different manufacturers. There has been a known secular trend -- trend over time -- towards increased reporting overall for the pharmaceutical industry and, finally, we are concerned in particular here about the impact of specific publicity events.

So all of these things have to be considered and they sum up to why data from a system like this should be viewed as a signal of something that may need further investigation and does not itself constitute evidence of causality.

(Slide)

This represents the different drugs, proportion of the market. We are talking about fluoxetine, trazodone, amitriptyline, desipramine, and maprotiline, because these were drugs that for various reasons were thought worth looking at all reports in the suicide-attempt category and other categories that I will be showing you, so it is to get some idea of what the experience across antidepressants has been,

although my main comments will be specific to reporting for fluoxetine.

This simply shows you the large and consistent market share that amitriptyline has held over the years and the rapid increase in market share for fluoxetine, with the relatively smaller shares for the other drugs.

(Slide)

I will now go on to the terms that we use in the analysis. COSTART is a dictionary of terms that are used to code adverse experience reports as they come in to the FDA. There have been changes in the terms over time, so that the term "suicide attempt" was introduced to the system in January of 1989. Prior to that, all suicide attempts had been coded under psychotic depression or overdose. Likewise, the term "intentional injury" was introduced in July of 1989 and would have similar consequences for trends over time in reporting for different drugs.

(Slide)

This gives you the overall numbers I will be talking about and shows, of course, the very large number of reports that have been received for fluoxetine. Those numbers add up to a very large number. They, in fact, represent a total of 880 unduplicated reports, that is, more than one term can appear in a report, so you can have something listed under suicide attempt that is also counted under overdose, because

of the nature of the counting process.

The comments, I think, that bear here, in particular, have to do with year of marketing, which has a big impact on reporting, 1988 for fluoxetine, 1982 for trazodone, 1961 for amitriptyline, 1971 for desipramine, and 1981 for maprotiline. Actually, trazodone and maprotiline are included in our considerations partly because they were marketed closer in time to fluoxetine, so if we did try to make any sort of comparisons, they would be somewhat better. I think the comparisons are, nonetheless, quite difficult and quite limited among the drugs, as we will see.

(Slide)

This gives the same data for the other two outcomes, hostility and intentional injury, showing you the number of reports received for the time period from the beginning of marketing of trazodone in 1982 through July of 1991, which was chosen as the cutoff time.

(Slide)

This gives data in an effort to at least achieve the first level of control that one would like to see, and that is control for the total reporting. That is, there has been a very high rate of reporting for fluoxetine. Part of this is probably corporate behavior. We know that there are differences of this type among the companies. So it is useful here to put the categories as a percent of total reports, and

what you see is that for overdose, in the middle, it is actually not that different for fluoxetine and other antidepressants, the differences in the categories called suicide attempt and psychotic depression.

There are also differences in the categories of hostility and intentional injury.

(Slide)

The next part of this is to begin talking about fluoxetine specifically and what has happened over time in reporting for fluoxetine. This curve is the number of all reports received for all types of COSTART terms or events divided by the number of prescriptions per year for the drug. It shows a pattern, except for that big zig-zag, which I think is an artifact of a lot of reports that would have been coded earlier getting coded a little bit later. If you even cut out that part of the curve as a reporting artifact, the curve itself is characteristic of many drugs, that is, there is an upswing of reporting in the initial year or two of marketing, followed by a kind of wave crest and the invarying rates of decline over time after that. So the overall reporting pattern for fluoxetine is not, in shape, unusual; however, the numbers are larger than we ordinarily see from those drugs.

(Slide)

This gives you the reporting rates for the three categories under which suicidal thinking, suicidal ideation,

and suicide attempts would have been coded. The line categories, I think, are pretty self-explanatory. Remember that the term "suicide attempt" was introduced in January of 1989 when you are looking at the graph.

The W and the T are to indicate the Westbecker incident in September of 1989 and the report published by Dr. Teicher in the first part of 1990 so as to give you some feel for the potential impact of publicity related to these events and similar events on the reporting, because, remember, we are talking about reporting, which has to do with the incidence of the disease, the use of a drug, and whatever the reporter perceives about that and decides to do about observations. So reporting behavior is not incidence behavior and has to be evaluated in the context of the possibility of changing perceptions and intentions on the part of reporters over time.

Here we see a very large increase following Dr. Teicher's article and I think the implications there are pretty self-evident. It does, certainly, time-wise, appear that the publication of the article may have stimulated more reporting, regardless of what that reporting itself means.

(Slide)

This is the same curve for hostility and intentional injury. It shows the same pattern, that the reporting rate increased greatly here. Remember that July of 1989 was the time for introduction of the term "intentional injury."

(Slide)

I am going to talk just a little more about an effort to compare reporting for fluoxetine and trazodone because of trazodone being the most closely marketed in time, with its year of marketing in 1982 versus fluoxetine. The reason year of marketing is so important is that the other drugs in the comparison, especially amitriptyline and desipramine, were marketed enough earlier that the whole dynamics of reporting were different, and I really would not even attempt to compare reporting for drugs marketed much farther back than this because of the powerful effect of changes in reporting and in the reporting system in earlier times.

This gives you the denominator data to show you the pattern of marketing for trazodone, the number of prescriptions in millions by year, and for fluoxetine.

(Slide)

This shows you the reporting behavior for suicide attempt, overdose, and psychotic depression. I should mention that in choosing trazodone as a comparison, we did also look at the National Disease and Therapeutic Index and other sources to try to compare the populations that are taking trazodone to the population that is taking fluoxetine.

In broad terms, they were not greatly different in terms of age, sex, the specialty -- that is, percent

psychiatrists that were prescribing the drug -- the diagnostic categories, whether it was a first visit or follow-up, whether it was a new prescription or a refill, and whether the desired drug action was depression or otherwise. These were broadly similar between the two drugs, although there were some differences in the various categories I have just referred to.

(Slide)

This shows you the difference in reporting. Now, you will note that in the first year of marketing for trazodone there was a reporting rate for the combination of suicide attempt, overdose, and psychotic depression which is similar in magnitude to the first year of marketing for fluoxetine and, in fact, would represent somewhat greater than first year because of the overall trend over time towards increased reporting.

Over these years, 1982 to 1988, there was about a two-and-a-half-fold increase in overall reporting for all drugs combined. It is hard to determine how that fragments out in terms of the net change in reporting for different drug categories, so I will just refer to it as an overall trend of increased reporting. It would mean, if anything, that the first year for trazodone would be higher than the first year for fluoxetine.

On the other part of it, however, the trazodone reports there are all in the category of overdose, while the

1988 category for fluoxetine includes a small proportion, a little under a third, that are in the category of psychotic depression (I will discuss that more a little later). The overall picture, as you see, is, if anything, higher first-year reporting for trazodone, a very abrupt drop -- more abrupt than we usually see for most drugs from the first to second years -- whereas in fluoxetine you have the first year being similar, or smaller, and then the increase especially taking off in 1990, which I previously related to the events in publicity.

(Slide)

This shows the same data for hostility and intentional injury. There is higher reporting for these in the first year of marketing for fluoxetine but, of course, the major take-off, as with the other categories, is following the events that occurred in publicity.

That ends the slides. The last part of the work that we did was a preliminary effort to do a hands-on look at case reports that were received for fluoxetine and the other drugs. A group of people reviewed these to try to do, very roughly -- I want to emphasize that the reports are really sometimes quite incomplete. Not only is the form brief, but often large portions of the information are not provided, so they are very difficult to interpret. Many times all you can do is interpret that there is not enough information in the

report to know much more than what drug they were on and the general category of what the report is about.

Nonetheless, we did do a hands-on review of a sample of the reports in the suicide attempt, overdose, and psychotic depression categories and in the hostility and intentional injury categories. We did a sample of the fluoxetine reports and we did all of the reports for the other drugs, because the numbers were so much smaller.

This was an effort to look, in a preliminary way, at the patient's prior history, the time course of drug and event, whether there was any kind of dechallenge information or rechallenge information, so that what one is able to say is what the reporter thought he was seeing. This was looked at whether what the reporter described seemed at all plausible in linking drug to outcome.

I think the plausibility was considered to be possible in a little under a quarter of the reports, whereas for the remainder -- of these numbers up here, for about three-quarters of the reports, the conclusion was that there was just too little information, really, to make much of anything of it one way or the other. Or if the information was there, people felt that the other potential explanations were fairly strong.

That is where we are at. My conclusions, in looking at this, are that I think, first, one has to realize that a

reporting system like this, for the reasons I have described, can be suggestive of things that require further study, but it is very, very difficult to achieve causality from these types of data, a judgment of causality. There are, in this instance, simply too many other possibilities. There are, sometimes, with other drugs, rare instances in which a spate of reports can be so striking as to lead to action. But here there are many potential sources of confounding in the data.

Likewise, I think we have to be careful in interpreting the quantitative number of reports. The relation of reports to disease incidence is not at all straightforward and can be profoundly affected by the reporters' perceptions of whether it seems like they ought to report. Publicity events and self-fulfilling prophecy events, and so on, can be rather difficult to untangle with these types of data.

On the other hand, spontaneous reports can sometimes signal events which would be of low enough overall frequency to be difficult to quantify in most clinical trials, so that they can be useful for identifying issues which may be appropriate for focusing new studies, whether clinical trial or rechallenge or other types of studies. They may be helpful in focusing the direction of some further studies.

Thank you.

DR. CASEY: Thank you, Dr. Stadel. Does the committee have any questions that they would like to ask of

Dr. Stadel, Dr. Laughren, or Dr. Leber?

DR. REGIER: I would like to know if there is duplication in these reports, so that a person who reports a suicide attempt or a report of a suicide attempt could also be reporting multiple events, including an overdose, a psychotic depression or hostility, and so forth?

DR. STADEL: I actually pointed that out at the time. In that slide that shows the three categories, where the total number is about 1200 or 1300, if you add up the numbers for fluoxetine under the headings of suicide attempt, overdose, and psychotic depression. Those three represent, in fact, 880 unduplicated reports. There is overlap in the terms, yes. If it was coded as suicide attempt and overdose by the person coding it, it would go into the computer under both COSTART terms. We did check the number of unduplicated reports in that category so as to be able to tell you that. It is 880 in that overall category.

DR. HAMER: If there were two suicide attempts by the same person, does that go in twice or once?

DR. STADEL: Two separate attempts by the same person ought to go in twice, I think. A follow-up to one attempt by an individual would, hopefully, get coded as a follow-up report, that is, we would attach follow-up information on an individual. But an individual who engages in two separate events would properly be considered two

separate events.

DR. LIN: I was wondering whether you also have information comparing Prozac with the other two recently released antidepressants, clomipramine and buproprion?

DR. STADEL: I do not have any information.

DR. TEICHER: Two things -- (that was very interesting): First, I am glad that you introduced those new terms. Prior to our publication we contacted the FDA to look into whether there was something that had come up in the spontaneous reporting and when we discussed what we observed, we were told they would only go under the COSTART term "worsening of depression," to have people develop obsessional suicidal ideation, and then it seemed like a massive amount of data to try to plough through to find out whether it had been spontaneously reported.

I think you also need an additional term for suicidal ideation in there, although it might be conflicting.

The other thing is, did you look at the Valium data? There was an article in JAMA, I guess in about 1976, that was very similar to what The American Journal of Psychiatry reported, that looked at development of suicidal ideation in individuals taking Valium to see if after that report there was a widespread change in the amount of spontaneous reports of any kind of adverse response.

DR. STADEL: I have not done an analysis for this

purpose at the present time, no.

DR. LEBER: Actually, there is another point, too, that in 1976 adverse drug reporting rates overall were extremely low. I think that somebody like Dr. Anello, who may have a longer overview of the system, might be able to -- what fraction, Dr. Anello, do you think of reporting of today's rates was going on in 1976 or 1975?

DR. ANELLO: The FDA was receiving about 10,000 reports a year from the period 1968 through about 1983. From that time it has been increasing and we are now receiving about 80,000 reports a year.

DR. CASEY: May I make a technical comment for the record that clomipramine in America is not listed as an antidepressant, though in other countries it is.

DR. STANLEY: Could I ask, is there a possibility of having the same case reported twice?

DR. STADEL: Yes. We try to deduplicate, yes. We make considerable effort at deduplication. It can happen.

DR. STANLEY: I was wondering, because you mentioned the poor condition some of the forms are received in, you might get a physician reporting a case --

DR. STADEL: You can get something from a physician and a separate report from a consumer.

What you saw up here were what we call domestic spontaneous reports, that is, they came to us either from the

manufacturer or directly from health professionals, mainly from manufacturers, who themselves received them from health professionals.

I did look at what fraction of those coming to us from the manufacturer came initially from consumers. I also looked separately at how many consumer reports came directly to the agency. The overall patterns that I described to you are not changed by those considerations and I doubt that double-reporting of individual cases would much change this. We do try to deduplicate but those occasionally will get missed, but I do not think it would make a major difference.

DR. STANLEY: Do you know what percentage? Is there any way to estimate the --

DR. STADEL: I do not have a percentage for it. As I say, I am confident, in this analysis, where a good deal of hands-on review was done, that it would represent quite a small fraction.

DR. DUNNER: If I understood your presentation correctly, the data-collection system is not adequate to let this committee come to conclusions about this important issue based on your sense of reliability of the data?

DR. STADEL: I feel that my primary purpose is to try to present the data and let you decide how you should interpret it. I will say that what I am trying to point out is that there are lots of sources of potential error in here,

so if you do decide to interpret this one way or another, I would urge doing so very carefully, walk carefully on this path, the cliff is steep.

DR. DUNNER: If that is a valid assumption, and I think you indicated it is -- you seem to agree with me -- then is there a system that the FDA should put in place that would answer this question more reliably without increasing the federal budget to the extent --

DR. STADEL: That last part is a little difficult.

(Laughter)

We are trying to use other resources which are more quantitative and there are a variety of these. However, we are dealing here with an event which, if there is any causal event, is clearly of low enough frequency that I do not have any quantitative prospective data source or other mechanism for measuring it at that level.

You cannot get below an incidence rate of, say, somewhere between -- on a log scale -- 1 in 1000, 1 in 10,000. You get down to a rate where we do not have mechanisms for quantitative determination. Of course, if you have a drug that is widely enough used, if there were a very small subgroup, it would result in a comparatively large number of people over a period of time, so it becomes a very difficult thing, where, on the one hand, spontaneous reports might be the first place that you would pick something up

and, on the other hand, you have to be very careful of the noise-to-signal ratio in these types of data. There are lots of sources of potential error. I cannot help much more than that.

DR. TEMPLE: I wanted to say -- and Bruce can defend it himself -- I do not think it is a question primarily of the reliability of the data. Even if every report to us were perfect and well documented and just as good as what you might see in a journal, the problems with these data are that they are not easy to interpret, because there is not any control group and the events in question are part of the underlying disease. That is the single most difficult circumstance in which to review uncontrolled data.

It is difficult enough to do that even when the event is something weird, like agranulocytosis, because you are never quite sure what the spontaneous rate is. When the event itself is part of the disease, it is the most difficult possible circumstance to try to make use of a spontaneous report. You have to resort to looking at the details of the case and reach some kind of judgment, but it is very difficult to be sure.

It is not that the data are of poor quality; it is that this kind of system does not necessarily do very well in teasing out a drug-induced reaction from a reaction that is part of the disease itself. It would be like trying to decide

whether an antianginal drug caused angina; it is very difficult to do that.

DR. STADEL: I think what these kinds of data may help to do is to help one decide whether one feels some scientifically rigorous methodology is warranted, the investment in doing a study, like a clinical trial, and perhaps some details of cases, if one does a detailed case study, might help to identify what component of the patient population one might try to focus such a study on. If it looked like some cofactor were an important risk factor, then one would say, well, maybe if I am going to do a clinical trial or a rechallenge study, I should try to selectively recruit people who might have some factor that would give them a differential susceptibility.

If it can be, I think, a guide to further work, it is useful. It is very difficult when you have it alone to go beyond that, I think.

DR. LEBER: I think one of the points that has to be made about the quality of the system that is important is that the breadth, depth, and detail provided in the 1639 report is rarely enough to allow you to decide whether or not the phenomenology exhibited by patients compares or does not compare to, say, a unique form of -- it is not like growing feathers on your arm, as Feinstein described, where there is no question about the event being related causally.

Take something we want to discuss in today's committee, the issue of is there something unique about the phenomenology described by Dr. Teicher. You could never get that from the quality of reports, unless you were very lucky, and even if somebody went out to search our 1639's that had been reported to determine, on the basis of no standard case definition that those reports met, is exceedingly difficult.

The system's quality is also weak as well as the inability to use the system to estimate risk on and off drug. It has flaws, but it is a useful signal to make you do scientific experiments.

DR. MANN: My question relates to the data that were presented, trying to draw some comparison between the different types of antidepressants in terms of reports of, say, suicide attempts. First, it was not clear to me how you derived the denominator, the exposure of the patients to drugs. You implied that there were a number of indices that you could have alternatively employed, new prescription rates, total prescriptions, et cetera. I was not clear how you determined your denominator, as it were, which represented relative exposure of patients to the different types of antidepressants.

Then, when it comes to the numerator, you did describe one initial procedure to control for differential reporting rates by correcting for global or total numbers of

reportings within each individual type of drug. But perhaps it would be helpful to elaborate upon other options in terms of the numerator. In other words, what were the rates of unduplicated suicide attempts among the different types of drugs? How do these data, for example, compare to the data derived from the poison centers consortium, or from the DAWN system?

The data that you gather from the adverse drug reports represent what proportion, do you think, of the national numbers of suicide attempts for each drug in question and how do those estimates, once you make them, result in a comparison of your data with other sources of numerators for suicide attempts?

DR. STADEL: There are quite a few questions in there, so I will try to skip and jump.

The only rate comparison I presented was a comparison of fluoxetine and trazodone, and in those slides the numerator is the number of reports that received the COSTART term, regardless of whether it received other terms, only I showed it for the aggregate of the three terms. The denominator is IMS America data on the number of new and refilled prescriptions dispensed during that year, total prescriptions. It is merely an effort to control the number reporting for the volume of prescribing; that is all the rate is.

Comparison of DAWN and the others, I am not an expert on poison control systems and poison reporting systems, and I have not made any attempt to do that. There are a lot of differences, including intent, that is, the intent of reporting of poison is different from the intent involved in reporting a drug overdose. Our intention here was to try to give you a picture of what the agency has received, and I have made no comparison to systems like DAWN, and we would be reluctant to do so, because they are intended for very different purposes.

I have done it in some other circumstances, and the comparison is not very helpful much of the time.

As to percent of incidence that these data represent, one of the things I said is that I do not know. Underreporting for almost everything associated with drugs, when it has been studied, in those instances where it has been studied, is very high. That is, if the coincidence of taking a drug A and having disease B is at some rate, only a small fraction of that, in general, will be reported as an association between drug A and disease B. That is just generally true, like underreporting is on the order of 85 to 90 percent in those areas where it has been studied.

Even, for example, the one I personally know best was that in the United Kingdom there was a study of the extent of reporting of pulmonary embolism in women receiving oral

contraceptives. At the height of the publicity no more than 15 percent of the associated cases were reported to the Committee on Safety of Medicines, and that was at the peak of the publicity thing.

So you are working in an area where small changes in the reporting fraction would have more impact on the reporting rate than the relationship between the drug and the disease itself. That is one of the reasons I am trying to tell you that these are difficult data to deal with. We cannot ignore them, they sometimes signal important things, but they have to be viewed in that context.

You had a number of components. I hope that helped.

DR. CASPER: I also have a clarifying question about reporting, especially in relation to overdosage and suicide. When you report those two categories for the tricyclic antidepressants, how do you report overdosage on your reporting form? If it is reported as an overdose and not as a suicide attempt, do you categorize this as overdosage but not a suicide attempt? If it is reported as a suicide attempt and overdosage, would this be reported --

DR. STADEL: As both. You look at a sample of these reports, and the best way I can give you is actually looking at a sample. What you see in the overdose is all straight overdose. The patient took 20 pills, was taken to the emergency room and had his stomach pumped out. That may have

been coded as a suicide attempt. Some overdose reports are considered accidental and are not coded as suicide reports. But that is what they tended to look like.

This is a point, actually, I wanted to mention, so I am glad you bring it up. For fluoxetine and for the other drugs, pretty much all of the things that wound up coded under overdose were simple overdose reports. That is, they did not talk about suicidal ideation, they did not talk about hostile behavior, they just said the patient took a lot of pills, and either it was considered a suicide attempt or it was not.

The reports where you do see that language occur either under suicide attempt or, most of them -- actually the highest proportion occur in the category that was coded psychotic depression. I do not know why that is, that is just how they happened to code the stuff. But what it says, in part, is that a big chunk of the graph that shows the suicide attempt, overdose, and psychotic depression, the part in the overdose, a large chunk of that is not dissimilar in fluoxetine and the other drugs. That part kind of drops out if you start to try to ask about the plausibility of the report in terms of whether there was ideation or behavior that one might think was unusual.

DR. CASPER: I have a further question, because if you report overdosage with antidepressants, I think we have to assume that a large proportion of those overdosages are

suicide attempts.

DR. STADEL: And they are coded as that.

DR. CASPER: Are they coded this way if they are not reported this way?

DR. STADEL: A large proportion of them are, and they are both reported that way and coded that way.

DR. CASPER: But if they are only reported as overdosages, which might be true for the past, especially the early years, someone might not have called an overdosage a suicide attempt. They would be called and coded as an overdose.

DR. STADEL: I tell you, I cannot bring to mind clearly an image of what fraction of the ones coded as overdose that I went through also had the code suicide attempt. A substantial number of them did, but right off the top of my head I cannot give you a sample.

Of course, under suicide attempt there are lots of things that are not overdoses, because they used another mechanism. I do not know the answer to the exact overlap in that group, I am sorry. I would have to go back and look it up.

DR. HELLANDER: What criteria did you use to decide if a report was plausible or not? You said three-quarters were not plausible and one-quarter were.

DR. STADEL: Six people looked at the reports that

were taken. A sample was taken, about a 10-percent sample was taken from the suicide attempt, overdose, and psychotic depression cells for fluoxetine, and a 20-percent sample was taken for the other drugs in the overdose category, and then all of the ones that were just one integer in the cell, all of those reports were taken.

Six people looked at them and it was really a judgment by the individual. This was a very preliminary kind of thing. We talked, in the first part of looking at it, about trying to establish criteria, and in the time frame that was available for preparing this presentation, it was not feasible. So I had the six people look at these, and they looked at them as to whether -- now, the types of things people discussed, of course, were did the person have a past history of suicidal behavior, what was the time course between initiating the drug and the event as it was described, was there dechallenge information, that is, the patient stopped taking the drug and the problem seemed to go away, was there rechallenge (there is, in a few reports)? Those are the kinds of considerations, but there was no formal structure. This was done in a very preliminary way simply to try to sort those into two big piles. Those were what the reporter described.

If you took the description of the reporter at face value, it was at least, let us say, not implausible -- it was reasonable as a potential -- whereas there were many of them

where we simply say we were not given enough information to do anything.

DR. LEBER: I think this is a point that came up in internal discussions. We would like to point out something. Presumably anybody making a report to the spontaneous adverse reporting system believes that there is a plausible relationship between the administration of the drug and the appearance of the event. So when a team of people, no matter what their qualifications are, look over a series of reports, what they are really looking at is not the plausibility issue, but how well the reporter conveys and makes or writes the scenario of the causal relationship.

What I think this team found was that in many cases, even though there is probably a good basis for the reporting in terms of the logical sequence, that is, the event occurred after the administration of the drug, the circumstances were such that promoted the reporting that in most instances the individual making the report did not provide enough information to substantiate the case in a compelling way. And in instances when they did, everyone said, yes, that is a plausible case, because they provided it.

It is really more of an index of how well people write than whether or not they are correct in terms of their causal assumption.

DR. STADEL: That is generally true and, I think, a

good clarification. The only additional comment is there are some where it is fairly extensively described and you do not think it is very plausible. That is, there are some like that, where there is so much else, the patient was on six different drugs and he tried to kill himself five times in the last eight years, there were so many things involved that even if the time sequence was all right, and so on, you were reluctant to do much.

DR. LIEBERMAN: As a follow-up to Dr. Teicher's question about spontaneous reporting system behavior, although Valium may have been too far away to be comparable in terms of an increase following publicity, if I recall correctly from the Halcion meeting following publication of articles in the lay press, there was an increase in report of the adverse incidence that occurred.

DR. STADEL: That was possible to do over a longer period of time; however, before some of the publications and there were other aspects of the analysis which were easier to conduct. I would have to go back to the exact time frame. The first year of marketing for the two drugs compared there, triazolam and clonazepam, were much closer together, which is generally better in terms of those kinds of comparisons, and the first part of that was before a lot of the publicity events.

In the latter part, in fact, you can see some

changes in the reporting rates in that, in the bottom part of the tables, which are consistent with an impact of publicity on reporting. The early part of the comparisons was before so much of that, so we had a little more confidence in it. Here the large increase in reporting comes one quarter after publication of Dr. Teicher's article.

I want to say that does not mean that the increase in reporting could not be -- that does not tell you whether those cases were or were not related to the drug causally; it simply tells you that the number reported went way up. It does tell you that there appears to have been a publicity dynamic involved and you have got to think about that in interpreting.

DR. REGIER: To compare the reports from this system with other potential systems where we can look at rates of suicidal behavior, it is obviously helpful to have a clear numerator and a clear denominator. In order to do that, if we assume that the three behaviors, the suicide attempt, the O.D., and the psychotic depression all could potentially cover the range of suicidal activities, we would be talking about 800 events.

The question is, over what time period can we place these events? Can we place them, for example, say, 500 of the 800, over a single 12-month time period, so that we would be able to then estimate the number of people on Prozac during

that same 12-month time period and be able to get some kind of rate against which we could compare ratesin clinical studies or epidemiological studies?

DR. STADEL: That is a very useful observation. In fact, we have used that approach in some other areas, basically trying to compare the number of reports observed to some expected value computed out of other data resources. Here I can tell you that the 880 unduplicated events occurred for fluoxetine between the initial marketing and July of 1991. That is when they occurred, that is when the analysis is confined to.

However, if you look at the curve for those three events, you find that most of them occurred later than that, that they occurred between the second quarter of 1990 and July of 1991. That is where the bulk of those three events occurred, because that was the large increase in the rate of reporting. So both the rate of reporting went up and the denominator of usage was going up, so that means the absolute N was way off on the right of the curve, so they are clustered there.

The problem with doing what you are suggesting here is that you see the number of reports received and you call that your observed value. You compute an expected value and then you have to decide what you consider to be the plausible underreporting fraction. And when you have all these dynamics

going on with publicity, that gets hard, because, you see, you have got to compare the observed number to the number expected after correcting the number of expected for the expected frequency at which incidence would be reported, the reporting fraction.

That reporting fraction, under these highly volatile reporting circumstances, is very difficult to estimate.

DR. REGIER: I understand the difficulties with the system and that it is really an early warning system that has its own unique place, it is not a well-sampled population, and there are all those limitations. But in order to get the maximum value out of it, I think it would be useful to have even the last 12 months' experience instead of just a cumulative experience. If we had exactly what the best estimate would be for the maximum number of reports that could be suicide in a 12-month period of time, then we can ask Eli Lilly how many patients were on the drug in that period of time, or we could ask the prescription source how many patients, on average, are there per prescription, so we had some denominator that was useful for comparing, for example, with clinical trials, where they are now asking specifically, following Dr. Teicher's publication, how many have suicidal ideation out of that population, and we also have epidemiological data on the number of people in the general population who report suicidal ideation and suicide attempts.

DR. STADEL: I agree with you that the approach is a valuable one. I wanted to mention all the disclaimers, but I agree with you and, in fact, I think we should do some of our future work along those lines.

DR. CASEY: Dr. Stadel, may I ask you a question? You have listed a lot of limitations of the information. You told us it is a signal system. Is there a signal here?

DR. STADEL: The computer system is called Oracle.

(Laughter)

I would have to say that is a matter of personal opinion. I see my primary job here today as trying to report the information to the people you are soliciting opinions from. I can give you mine, but with those caveats as to what I view my role here as, as I am trying to put in the hands of the advisory committee information so they can decide whether they think there is a signal, so I have a certain reluctance to discuss my personal view of it, unless you make it irresistible.

(Laughter)

DR. TEMPLE: Sure, it is a signal. There are a lot of reports and some of them look like they are not implausible. The question is, what next?

DR. CASEY: But would you stay around for the next few hours, so that if any other questions come up from the committee members, you will be available to us?

DR. STADEL: Surely, I will.

DR. LEBER: I think it is important to recognize that it was recognized as a signal early on. This all was recognized as a signal early on and was one of the factors that led us to ask the sponsor to initiate a number of comparisons, which they are going to be presenting today, because those comparisons allow us to look at depressed patients coming from the same pools or samples exposed to fluoxetine, exposed to placebo, and exposed to comparative drugs.

DR. CASEY: I thank the members of the FDA for their thoughtful and concise presentations. They will obviously be available for further input as we discuss later on.

We will now move to some outside-the-agency presentations. The next one will be by Dr. William Potter, who is Chief of the Section of Clinical Pharmacology, and will speak on behalf of ADAMHA-NIMH.

NIMH PRESENTATION: STATEMENT ON BEHALF OF ADAMHA-NIMH

DR. POTTER: It is a pleasure to be invited here and thanks to our colleagues at the FDA. Dr. Goodwin, the administrator of ADAMHA, asked me to briefly address a few major policy issues, which is the broad question of whether or not there is sufficient evidence that certain antidepressant drugs increase suicidal behavior -- might have in terms of an impact on our broader mission goals, specifically that of the

National Institute of Mental Health, which falls under ADAMHA.

(Slide)

From the ADAMHA point of view, what we are confronted with is an enormously important public health problem, we are dealing with an extremely highly prevalent illness which now is estimated to affect 11.6 million adult Americans, 5.8 percent of the population. This illness has a very high morbidity, in some estimates, as I will show you, next to that of cardiovascular disease in this country.

This illness is highly lethal in untreated patients. Comparing on the subgroup of patients, it can vary from maybe 10 percent up to more than 20 percent in bipolar disorder, and we know -- and certainly one of the major tasks of ADAMHA over the last 20 years has been to fund much of the research -- that there are highly effective treatments available.

But when we look at our epidemiologic data, and Dr. Regier, who is here on the committee, can address this more specifically, we see an exceedingly low proportion of depressed patients actually seek treatment.

I just want to briefly highlight each of these points, to put what you are hearing today in the context of the overall national picture of a public health need.

(Slide)

First of all, from the Rand study, only heart disease is associated with more bed days than depression. So

here we have an estimate, a factor of two bed days per month for heart disease. The next is depression, with chronic lung disease and things like diabetes following much lower. So this is a very serious disease in terms of morbidity. There are other ways of estimating cost and loss of man hours of work and so on, but this is a very dramatic way just to see on a very clear, simple level what a serious illness we are dealing with.

(Slide)

In terms of affective disorders, it has to do with the proportion of people making suicide attempts with these three diagnoses that fall under the depressive category: major depression, dysthymia, and the mania bipolar disorder. As you can see, the rates per 100 for suicide attempts of one form or another are enormously greater in major depression, dysthymia, and bipolar disorder. In the red you see the rates in control populations, matched for age, sex, and so on.

It is quite clear that a diagnosis in the affective or depressive disorder spectrum enormously increases the rate of suicide, particularly if untreated.

(Slide)

If you look at completed suicides, these are data gathered from a number of studies, what you will see is that the disorder in terms of diagnosis which is most associated with suicide is, not surprisingly, affective disorder. Here

are some others: alcoholism, schizophrenia, and so on. The point is, again, we have a core disorder and the natural course of the illness, untreated, is to progress in an alarming proportion of the population to suicide.

(Slide)

You have heard some already of the discussion, and you will probably hear more, about whether or not, in this one case, this drug fluoxetine is causing suicidal behavior. As a Public Health Service agency, we have had to ask ourselves the question, is there a sufficient signal here for us to be alarmed? Obviously, if we are advocating pharmacologic treatments of depression and one of our treatments is actually causing an adverse event as serious as suicide, we would have to change our whole view.

What we did is, before this meeting and over the preceding months, we tried this last week to pull together the information that was available on what the odds or the probability that this drug might be really causing suicide is. This is the way we looked at it, because we felt we had to look at the question.

These are the data provided by Lilly. There were about 3 million people over the last three years, perhaps, in this country on fluoxetine. We have taken an estimate that two-thirds of them might have met diagnosis for depression. The data are not broken down that way, but that seems a

reasonable assumption.

Using the ECA data, which, again, Dr. Regier could address more specifically, that we have from the National Institute of Mental Health, we find a 3.65-percent likelihood of prevalence per year of people attempting suicide. If you take the multiplier, then, out of these 2 million with depression treated with the drug, you would expect about 73,000 to make a suicide attempt.

Again, you just heard some discussion about where these numbers come from, but we took an estimate from the reporting data from the FDA, that maybe for a one-year period you would get about 500 reports. So these 500 reports, as a percentage of the expected occurrences, is only 0.7 percent -- it is less than 1 percent. Obviously, there must be underreporting and we do not take these data to say that fluoxetine, or any other antidepressant drug, is that effective.

(Slide)

But the evidence is way in the direction -- I will summarize this in a pie chart -- way in the direction of the drug being preventive for suicidal behavior, not inducing it, on a population basis. As a Public Health Service agency, we are interested in treating the population.

If you want to look at this, again, take this whole pie as being around 3 million people, with a couple of million

(in blue) being those treated for depression, maybe with fluoxetine, we would have expected (in the yellow) this many suicide attempts. This little tiny red line is a sliver of the so-far reported suicide attempts on this drug.

So from the ADAMHA point of view, we have not been presented with evidence to cause alarm that this antidepressant, or any other antidepressant, is contributing that much to suicidal behavior. To the contrary, the past and the present data go in the opposite direction.

(Slide)

We have another major concern, and that is that although there are effective treatments for depression, taking antidepressants is very unpopular among patients who have the illness. This is simply a sort of self-preference-of-the-public graph. The way to read this is, here, below the line, you ask people, "Would you rather take the drug, take a pill, for your condition?" The blue line means, "I'd rather live with it until it passes." Above the line, "I'd rather take medication."

Headache? Most people would prefer to take medication. For colds, upset stomach, and by the time to backaches, people will say, "Well, maybe I shouldn't take a medicine, maybe I should just wait until it passes." But look at depression over here, only 12 percent of people, when asked, "If you had depression, would you rather try to take a

medication for it or would you rather live with the illness until it passes?" So this is the current public attitude, that people do not think they should take medicines. They think it is sort of immoral, or something like that, so they are not getting the treatment that they need.

This is the consequence of the stigmatization of mental illness, in this particular instance of depression.

(Slide)

A recent quote from the author William Styron, I think, is particularly relevant at this point. He says, "Most people survive depression, which may be its only blessing, but to the tragic legion who are compelled to destroy themselves, there should be no more reproof attached than to the victims of terminal cancer." And yet we blame people in our society for having depression, we criticize suicidal behavior, and so on, when what we should be doing is finding ways to encourage people to seek the effective treatments that are out there.

(Slide)

In summary, to make the core point, from our point of view, from the ADAMHA-NIMH point of view, the current state of the union is that we have an extremely prevalent illness affecting over 10 million people which has very high morbidity (next to cardiovascular disease), which is highly lethal, untreated, and for which there are highly effective treatments available, and only a low proportion of depressed patients are

seeking treatment, and in that context we feel that until there is far, far more substantial evidence that antidepressant drugs are causing suicidal behavior and are making our patients worse, we take the position that instead of trying to withhold these drugs, there should be much more aggressive effort to make them even more widely available and given to the appropriate patients.

Thank you for your time.

DR. CASEY: Thank you very much, Bill. I will have the committee ask you a few questions that are related to clarifying your presentation but not yet to go into the large number of theoretical or scientific issues, because we have so many other people to present.

DR. HAMER: Back on the slide you had in which you showed approximately 2 million prescriptions and approximately 73,000 expected attempted suicides and approximately 500 reported, if that population had been a nondiagnosed, normal population of 2 million people, what would the expected number of suicides in that population be?

DR. POTTER: It was on the earlier slide -- I would have to double-check the actual number. Maybe Dr. Regier knows it off the top of his head.

DR. REGIER: It is less than 1 percent.

DR. POTTER: About the same, actually.

DR. REGIER: No, it is considerably less.

DR. POTTER: It was 0.7 percent we estimated here.

DR. REGIER: No, that was 0.7 percent of the 3.65 percent.

DR. HAMER: Out of 2 million randomly selected people in the United States, what percentage of them can we expect to commit suicide or attempt suicide in a year?

DR. REGIER: The lifetime prevalence reported in the ECA was 1 percent of the entire population would have a lifetime suicide attempt report. The one-year report is a fraction of that.

DR. TEICHER: The analysis that you did hinges very critically on that 3.65 percent number, which in my review of all the other literature on incidence of suicide supports nowhere near a 3.65 percent number. All the other studies have data that are in the 3 per 1000, not 3 per 100.

DR. POTTER: No, no, these are people diagnosed with depression.

DR. TEICHER: For people diagnosed with depression it is 3 per 1000, not 3 per 100.

DR. POTTER: That is suicide attempts, not completed suicides.

DR. TEICHER: This is attempts?

DR. POTTER: That is correct.

DR. TEICHER: The data are 3 per 1000, not 3 per 100, in a massive amount of other literature. I do not think

that number is correct. It does not jibe even with the 15-percent lifetime for untreated depression if you are having 3.65 percent per year. I do not think that is an accurate number.

DR. POTTER: Dr. Teicher, that is, I think, one reason why Dr. Regier is here on the committee.

DR. TEICHER: We can start citing studies, if you want to go over each one that has different numbers, but that is a very important point that really needs to be looked at very carefully.

DR. POTTER: Again, my role is not really to discuss the content of these specific epidemiologic studies. Dr. Regier is on the committee and will be here all afternoon. He was the director of those studies.

However, just from the logic of it, I would point out to you, even if you want to multiply by 10, the reported incidence is still less than 10 percent, even if you wanted to take that number. Our point is that on the current data available, however you juggle the numbers -- and I understand there is going to be considerable debate over the best way to come up with estimates here -- however you juggle the numbers, the signal is extraordinarily small compared to the other signal of morbidity and mortality that we observe.

DR. LEBER: I want to ask a clarifying question. Dr. Teicher, you said there were many studies. What kind?

Are they epidemiologic studies, I presume, that you must be referring to?

DR. TEICHER: They range from a variety of studies. If you look at -- first, look at the data, say, for the large-scale epidemiological study where mianserin was used, where amitriptyline was used, you have instances where you have 11 per 1000, 15 per 1000 for suicide attempts. If you look at the maprotiline data --

DR. LEBER: I am a little confused. An epidemiologic study would not ordinarily be using a drug. Perhaps you are talking to large-scale multicenter trials that you conducted over short intervals of time.

DR. TEICHER: No, these are studies where they have looked at physician use in the general population. They are not large-scale trials.

DR. LEBER: So they are actually sampling what? See, I think part of the argument here is that people derive estimates from different sources and it is consistent that you would have very widely varying estimators, because you are not specifying what the source precisely is. The rates of 3.65 percent of suicide attempt per year come from what?

DR. REGIER: That comes from the epidemiologic catchment area, which is a sample of 20,000 representatives, adult, both institutionalized and community residents, and it is standardized, then, to the age-sex-race characteristics of

the U.S. adult population.

DR. TEICHER: What about Dr. Fawcett's data? Is he here?

DR. CASEY: Could we save part of this discussion for later on? We will come back to it, because it is an important topic. I want to give everyone a chance to ask Dr. Potter questions.

DR. HELLANDER: I just wanted to note that those was very interesting data you just presented on the undertreatment of depression, but perhaps the quote by Styron was not so well chosen, considering that he has considered his suicidality to have been induced by Halcion and wrote about it in Darkness Visible and was rechallenged with Halcion after back surgery and became suicidal again. He now writes and speaks about the dangers of Halcion, and in one recent editorial concluded that he avoids Halcion as if it is cyanide. Anyway, I just wanted to say that that maybe was not the best choice.

DR. POTTER: I thank you for the comment, because if one is interested in packaging the best sales pitch, I agree with you, one would like to line up testimonials from witnesses and all, but the point that Styron makes -- and Styron is not an expert on pharmacology, so do not ask Mr. Styron to be an expert on pharmacology -- he is, however, someone who expressed very well the question of stigma and has become a major spokesperson for that. And that is a very

important issue.

We do not ask our depressed patients, we do not ask our cancer patients, we do not ask our heart disease patients to be the critics of the drugs they take and their best treatments per se, but we do ask them to speak to the major issues, and Mr. Styron has done that.

DR. CASPER: I was intrigued by your slide about the public's interest to take medication or not to take medication. I am wondering how you derived the data for your column on depression, because most everyone has had a headache, but very few people know what a depression is like, what we could call, currently, diagnostically, a major depressive disorder is like.

Therefore, I think it would be very difficult to make a judgment about their willingness to take medication for it. I think we should be very careful about asking whether patients who might feel depressed would be willing to take medication, and I think we should be very careful to advocate taking medication for feelings of depression. I do not believe you wanted to transmit that message -- I hope.

DR. POTTER: No. Thank you very much. I think the clarification is extraordinarily well taken. Obviously, when you do a survey like this, people who have had experience of headache will know what we are talking about. A lot of people will never experience a severe syndromal depression or

melancholic depression and really will not know what you are asking about, so your point is well taken.

Again, though, these graphs are to dramatize the problem with which we have been confronted, that the people who really do have severe syndromal depression are not seeking treatment at the level which one would expect, given the efficacy of known treatments.

DR. CASEY: Bill, you commented from the data that there are 500 reports of attempted suicide over an estimated --

DR. POTTER: On an annual basis there were 800-and-something cases. You have just been having this discussion, actually, a few minutes ago, and it goes back and forth with how you do those numbers.

DR. CASEY: Given those numbers, is it possible to detect a signal from that information one way or the other about whether fluoxetine, or any other drug, is having an effect, since we are getting less than 1 percent of the information? You said perhaps the drugs are having an intended anti-suicidal effect, and I wonder if the information is clear enough there, or strong enough, to allow us to say one way or another what they mean?

DR. POTTER: I have heard only a little of the discussion this morning, but the analysis is not at the level of scientific data that would allow us to draw a scientific

conclusion of a preventive or protective effect. But it certainly is not of the scientific level that would suggest to us that there is a problem in the other direction. Really, what we were looking at the data to ascertain was should we be worried, and what we are trying to say is, the signal here for us to worry that we have a new dangerous problem on our hands is not there.

DR. TEMPLE: Bill, if I understand you, you took 2 million people as a sort of estimate of patient years of therapy, is that right?

DR. POTTER: No, the data available to us from Eli Lilly was that about 3 million people in the United States had been on fluoxetine. We guessed that maybe two-thirds of them would have had depression, and this is over a three-year period, so this is the cumulative three-year exposure of everybody who has had a prescription written, whether they actually took it or not, whether they had it for one day, one week, or a year. That is what that is.

DR. TEMPLE: I guess I would think that to make an estimate of how many expected suicides there would be, you would need some kind of estimate of patient years of therapy to apply your rate per year to.

DR. POTTER: That is quite correct.

DR. TEMPLE: Mind you, I think that would be difficult.

DR. POTTER: Exactly, and we have had hours of these debates internally already. You are obviously going to have hours more. Again, if someone wishes to do an elaborate mathematical model about what the various potential estimates would be, that would be fine. But, again, in any way that anybody has looked at these data that we know, and we have asked many people, many experts who are statistical and epidemiologic experts, there is not a sufficient signal. That is what we are saying.

We agree the data are not great quality data.

DR. TEMPLE: We have ways, and people here might talk to you about it, of estimating the average duration of therapy associated with prescriptions.

DR. POTTER: Actually, I think Dr. Regier made some attempts to gather this information. Apparently, it was not available on short notice.

DR. TEMPLE: It "ain't" great, either, but it is something.

As a comment on what Dr. Casey was saying, if I hear the thrust of this, what you are, in part, responding to is what we have been told by a lot of people, which is, look at how many there are. Five hundred people. Doesn't that make any difference to you? What you are saying is that in the ordinary course of people's lives who have severe depression, a much larger number of suicide attempts can be anticipated.

The number that has been reported is a very small fraction of that.

I must say, whatever way you slice the numbers and however you correct it, that figure still seems to be true.

DR. POTTER: Thank you, Dr. Temple. Actually, I will do something that the other speaker was not willing to do. I will personalize this a little bit, and I think most of the clinicians around the table who treat a lot of depressed patients might do that, too. Out of the few hundred depressed patients that I have known well enough to be aware of their treatment in my lifetime, I would say five or six have committed suicide, so a higher percentage than the report. Those are aggressively treated patients, being treated at research centers by expert clinicians and everything else. People do commit suicide on this, so it is not surprising to me, as a clinician -- not as a government representative, but as a clinician -- that there are this many suicide attempts or suicides.

DR. SCHOOLER: I wanted to raise one other caveat with your pie chart. That is that I do not believe that the system that was described allows the discrimination of diagnosis.

DR. POTTER: You are correct.

DR. SCHOOLER: So that, essentially, dividing into the smaller number that represents the diagnosis is not

precisely fair.

DR. POTTER: That is quite correct. It would be very useful -- the agency would like it very much if the pharmaceutical industry would take on the burden of somehow tracking the actual diagnoses for which people prescribe drugs, but my guess is that would be a very expensive process.

DR. MONTGOMERY: A small point. I found that presentation very interesting and take the point that you make that there is no signal in a worrying direction, which I think is very similar to the statement that was made by the previous speakers. I just wanted to say that it really would seem, in this circumstance, better to turn to the controlled studies with placebo and compare the data to get that full message across.

DR. POTTER: Absolutely. Precisely. Actually, since Dr. Montgomery raised something about what should alert us -- you did not quite do this, but I will take the license to move one step further -- without going into the science of it, there is, in fact, a substantial body of highly replicated data suggesting that a low amount of a serotonin metabolite in this drug fluoxetine affects a neurotransmitter called serotonin, the low amount of that is supposed to be associated with more impulsivity, aggressivity, suicidality, and so on, so, if anything, this class of drugs, if you wanted to work from a theoretical perspective, if anything, this class of

drugs should be better anti-suicidal agents, given where our biological science is today.

That is another factor, which is very complex to explain, but I will mention it, too, that enters into our thinking.

DR. CASEY: Thank you very much. We appreciate your time.

Next we will move to the phase where we offer the opportunity to the pharmaceutical industry to make presentations, and members of the Eli Lilly Company came forward, so we will hear from them. The first speaker will be Dr. Robert Zerby.

PHARMACEUTICAL COMPANY PRESENTATIONS

ELI LILLY AND COMPANY: INTRODUCTION

DR. ZERBY: Dr. Casey, Dr. Temple, Dr. Leber, Dr. Laughren, and members and guests of the committee: Eli Lilly and Company appreciates the opportunity to present our data today for thorough scientific review and analysis of the facts surrounding the topic of suicidality and depression.

This advisory committee is an appropriate forum for such a discussion. Had the well-intended anecdotal reports been allowed to undergo the usual scrutiny in the scientific community without the attendant lay publicity, a clear consensus would have emerged, without creating unwarranted fear in the minds of depressed patients and their families.

Consistent with this view that scientific questions should be addressed by scientists, we have submitted our data for publication in peer-reviewed journals. The first of these papers, that describing a meta-analysis of our large U.S. clinical trial data base, just appeared in The British Medical Journal. Others will follow soon.

In addition, we are continuing to study the problem of suicidality and depression. In collaboration with the FDA and outside consultants, we have just initiated a study which will better characterize patients in whom suicidal ideation emerges during various forms of treatment.

Our presentation today will be made by three speakers. First, Dr. Jan Fawcett, Professor and Chair, Department of Psychiatry, Rush Presbyterian Saint Luke's Medical Center, is one of the world's experts in the area of suicide and violence. Dr. Fawcett will review the association of suicide and depression.

Next, Dr. Charles Nemeroff, Professor and Chair, Department of Psychiatry, Emory University, will review the available literature on the emergence of suicidality during treatment of depression. Dr. Nemeroff has published extensively in the area of affective disorders.

Last, Dr. Gary Tollefson, Executive Director, Lilly Research Laboratories, will review the Lilly data.

We will make the following points in this series of

presentations: One, suicidality is part of the disease of depression and the greatest risk of suicidality occurs when the disease is undertreated.

Two, there is no consistent pattern among anecdotal reports and postmarketing adverse event reporting of suicide and violence. Furthermore, these are not unique to any specific product. They do not provide adequate scientific evidence of a causal association between suicide or violence and any specific form of antidepressant therapy.

Three, fluoxetine is especially valuable in the treatment of suicidal patients because of its safety record in overdose.

Four, epidemiologic data and controlled clinical trials have not demonstrated induction of suicidality due to treatment. To the contrary: Antidepressants are shown to be effective in lowering suicidal ideation.

Five, the labeling of antidepressants already accurately represents the state of knowledge and appropriately warns of the risk of suicide in depression.

Finally, speculative labeling changes based solely on anecdotal data will be distorted by special interest groups and create unnecessary barriers to treatment.

Dr. Fawcett?

THE RELATIONSHIP BETWEEN DEPRESSION, SUICIDALITY, AND TREATMENT

DR. FAWCETT: Thank you, Dr. Zerby.

(Slide)

I am happy to be here to contribute to today's discussion and because I am bringing you coals to Newcastle, as it were, delivering a message to you that has been delivered repeatedly by previous speakers, I will try to do it rapidly.

I am here to bring you four major points. The first is one that has been echoed and re-echoed, and that is suicide, a very tragic and preventable occurrence, is inherent to the disease of depression.

Secondly, the treatment of depression, especially the primary affective disorders, can prevent suicide.

Thirdly, the failure to have access to treatment, to proper diagnosis, or effective treatment can increase suicide rates in depression.

Lastly, even with today's antidepressant treatments that we have developed and even with the progress that we have made, there are substantial numbers of patients who will still, unfortunately, suicide and not respond to treatment, and may suicide with treatment.

(Slide)

The prevalence of depression in the U.S. population and its morbidity have already been discussed by Dr. Potter -- with much nicer slides, I might add -- showing the tremendous effects on productivity compared to other medical

illnesses, as in the Rand study.

(Slide)

The fact that depression leads to suicide in the Guze and Robins review of over 15 studies leads to a 15-percent lifetime suicide rate has also been discussed. What has not been mentioned so far with regard to this is the fact that in the first two to three years of follow-up the percent of death from suicide in these studies, in the 11 studies that were published before the introduction of any antidepressant drugs, before 1960, showed 60 to 70 percent of all deaths were related to suicide in the first two to three years, falling to about 50 percent in three to eight years of follow-up, with a planing out of the asymptote of that curve, out to 20 years, at around 15 percent of deaths.

I think that if you contrast that with our collaborative study, data from the NIMH collaborative study, where we have a 10-year follow-up, our 10-year rate of suicide compared to, let us say, Loker's study, which showed rates of 7 or 8 percent (we are not talking about percent of deaths now, we are talking about percent of the sample) committing suicide, we have a 3.5 percent rate of suicide at 10 years follow-up so far.

The representation of depression in suicides, as has already been attested to, is very highly associated with depression.

(Slide)

We have also reviewed the data on the epidemiologic catchment area data base, it has been thoroughly discussed. We know that there is a certain lifetime prevalence of suicide attempts in an untreated community population and that psychiatric diagnoses are the strongest risk factor, especially depression.

(Slide)

Suicidal ideation and acts or behaviors, of course, are symptoms of depression. This is one of the reasons we see suicide during antidepressant treatment, of course, and this has been repeated over and over, again, today. I will not push it any further.

(Slide)

The current status of antidepressant therapy is an important point here. Inadequate care resulting from a lack of understanding or misunderstanding of depression is expensive and many of these people are undertreated or have no access to treatment. I would like to mention two fresh data sets, one from a study of adolescent suicide, by Dr. David Clarke, an NIMH-funded study in Chicago, in the three-county area around Chicagoland, where he has followed up and interviewed the families and friends of 86 adolescent suicides. Thus far, the antidepressant medication treatment rate in those 86 suicides is 7 percent. Thirty-three percent

of the suicides had been in mental health treatment at the time of their suicide, and only 7 percent were receiving any antidepressant drugs. About 10 percent were receiving any psychoactive drugs at the time of their suicide.

In another study in our suicide prevention research center by Dr. Clarke in geriatric suicide, in 56 geriatric suicides (over 65), only 5 percent of these patients were receiving antidepressant treatment. Only 13 percent had ever had psychiatric treatment, even though 40 percent of these people had seen a doctor within one week of suicide.

We have a tragically low incidence of treatment with antidepressant medications, not an indication that the treatment is causing the suicide; quite the reverse, that undertreatment is obviously causing suicide.

(Slide)

In our controlled study, the collaborative study, another NIMH-funded study which gave us a prospective follow-up of 954 patients with major affective disorder collected in five university centers, we saw 25 suicides in the first four to five years and 34 suicides by the time of our 10-year follow-up, for a final rate that I gave you.

Thirty-two percent of those suicides occurred in the six months after study entrance and 52 percent after the first year of study entrance. Clinical predictors of suicide, comparing the suicides with all the nonsuicides, include high

hopelessness scores, loss of pleasure and interest scores, cycling within an episode in those patients with bipolar illness, and also double abuse, abuse of alcohol plus one other drug, increased the rate of suicide long term by 10 times in this sample, and not having a child under 18 also biased toward suicide, even though sometimes I think having children under 18 may bias toward suicide -- or homicide.

(Laughter)

(Slide)

Other risk factors associated with suicidality have been reported in the literature. I will let you read these. They include severity, length of episode, previous suicide attempts, concomitant psychotic ideation (which also turned up in our collaborative study, I did not mention it), and hopelessness. Beck has also done prospective studies, of which not enough have been done, and has found hopelessness a high predictor of suicide.

(Slide)

Another risk factor associated with suicidality is the so-called roll-back phenomenon, which, I think, is very important and known to clinicians. This is the notion that often when patients are treated for depression they show an increase in energy and their capacity to make decisions before their hopelessness lifts, and the risk of suicide is great at that time. Anyone treating depressed patients should know

this and should take this into account. This is a question of physician education in terms of the treatment of depression.

(Slide)

Other factors that you have seen related to suicide are history of violent behavior, emergence of bipolarity or, as we call it, mood cycling. Alcohol abuse we saw just prior to suicide as a short-term predictor. Anxiety we saw in our prospective study as not only a predictor, but a modifiable predictor that was a short-term predictor, within the first year. Recent studies by Dr. Katie Bush in our department of patients who suicide inpatient, inpatient suicides, have shown very high levels of anxiety, reflected in staff nursing notes prior to suicide in our inpatient suicide sample.

(Slide)

Is suicide predictable? That is the major problem we have in preventing suicide, is that it is very difficult to predict. Our recent prospective study allowed us to look at time-related predictors and, at least in our data, the 954 cases with the 34 suicides, we found that anxiety, panic attacks, poor concentration, and insomnia formed a cluster which predicted suicide within a year of the patient's interview as opposed to the predictors that we have all been taught to look for, such as hopelessness, prior suicide attempts, and suicidal ideation communicated to a clinician, which only predicted long-term suicide in our study and not

short-term suicide.

So we may need to refocus our predictors to be more effective at predicting suicide and preventing it as clinicians.

(Slide)

What are the reasons for suicide during antidepressant treatment? We see, first of all, depression waxes and wanes in severity and frequently we are not affecting the natural history of depression with our treatment, especially early on, and the depression may get better spontaneously -- that is why we do controlled studies -- and it may get much worse after we introduce treatment, having nothing to do with the treatment or nontreatment.

(Slide)

Patient noncompliance is another major barrier to treatment and it does not do any good, of course, if patients are frightened of the drugs they are being treated with. I know anecdotally of two patients who stopped their Prozac, because of such fears conveyed to them by well-meaning friends and relatives, who committed suicide weeks later, having recurrences of their depression.

(Slide)

I am going to go through these slides in the interests of the committee's time and get to the last one, listing all the reasons for treatment failure. There are many

reasons for the failure of antidepressant treatment. I mentioned patient noncompliance. I should say something about inadequate dosing. It has been shown recently by the studies of Thrace and Cupfer that patients maintained at too low a dose for maintenance treatment (and this was shown in earlier studies as well) often will relapse and have recurrences of depression when they are inadequately treated. This raises the risk of recurrence and suicide.

Refractory depression is still a significant problem. We estimate that up to 20 percent of patients respond to no antidepressant treatments, pushing us to look for other ways of combining drugs to get better responses in these patients. My reading of the pharmacologic literature, which uses improvement, not recovery, as a criterion, frequently, is that another 3 percent of patients who show improvement are still not well, they are not back to their normal sense.

A person with a Hamilton score of 10 is not a patient who is recovered; he is a patient who still has symptoms. There is evidence that these patients are more likely to recur who have partial responses.

Intercurrent life events is self-explanatory, because depressed patients, of course, are more sensitive to any stress and unable to cope with it and frequently will show exacerbations of both depression and suicidal ideation in the

face of negative life events which are unpredictable -- especially real estate developers in this current economic atmosphere, since the tax law of 1986.

(Laughter)

Concomitant drug abuse is probably one of our greatest problems. In his recent testimony before the NIMH meeting on severe mental illness and homelessness in Chicago, actor Rod Stieger testified about his eight-year depression following open-heart surgery and how he did not respond -- it took him four years to get diagnosed (not a person who did not have access to the health care system, certainly) and another four years to get a response -- he told me this personally. It took him four years to have someone convince him or identify and convince him to stop drinking before his antidepressants worked, and he did respond, he told me, to desipramine and he considers himself well now.

Concomitant drug abuse or alcohol abuse is certainly another factor. Many of these factors, of course, defeat treatment and make treatment seem not so great in some patients and not such a tremendous outcome, and yet if we can overcome some of these comorbid and other aspects and have better treatments, we should be able to save more lives with treatment.

(Slide)

Our conclusions are, of course, that depressive

disorders are very common. Suicide is a clear symptom of depression and is difficult to dissociate from it, except with adequate care and treatment. The increased risk of suicide in patients with depression goes up to 30-fold in certain studies. Patients will manifest suicidal acts or ideations as part of the natural history of the disease, even under the treatment. We still have a long way to go in being effective at even predicting suicide, even the so-called experts. We have a lot more to do and we should not be hindered any more than we absolutely have to be by restrictions and things that are going to frighten people from accepting treatment.

Thank you very much.

DR. CASEY: Thank you. The next presentation will be by Dr. Charles Nemeroff, Emory University.

A REVIEW OF LITERATURE OF SUICIDAL IDEATION OR ACTIONS DURING TREATMENT OF DEPRESSION

DR. NEMEROFF: Thank you, Dr. Casey.

(Slide)

I hope you find this quote a bit more to your liking. This is a quote by Dr. Kraepelin, the father of the current Western psychiatric nosology, who describes suicidality in his patients with depression. This severe type of suicidal ideation has been known for centuries. It is not new. Dr. Kraepelin stated: "The patients, therefore, often try to starve themselves, to hang themselves, to cut their

arteries. They beg that they may be buried alive, driven out into the woods and there allowed to die. One of my patients struck his neck so often on the edge of a chisel fixed that on the ground that all the soft parts were cut through to the vertebrae."

This is the behavior that we see as clinicians in our depressed patients, in our untreated depressed patients.

(Slide)

What I will attempt to do in the next very few minutes is to review the literature that is currently available on the emergence of suicidality or the attenuation of suicidality during active treatment for depression.

(Slide)

I would like to start off with a few brief points, if I could. First, anecdotal reports fail to establish cause and effect, and I think this is the cornerstone of what the panel must come to grips with today, because essentially the COSTART system is uncontrolled data. It is data, but it is difficult to interpret.

The real issue is how can we, scientifically, as a profession, come to grips with this difficult issue? Clearly, what we need are double-blind placebo-controlled trials. I would like to read a quote from David Kessler, Commissioner of the FDA. In his recent article in the New England Journal of Medicine, he said, "Scientific rigor requires that data

presented during an activity be reliable, that is, capable of forming an appropriate basis for medical decision making. Scientifically rigorous data are developed through study designs that minimize bias. Anecdotal evidence and unsupported opinion should play no part in a scientifically rigorous program."

So the issue, then, is what, on the one hand, can we learn from case reports and anecdotal data, and I think it can give us a signal for prospective studies. I remind all of you that the history of medicine is replete with examples of medical decision making based on anecdotal case reports, to wit, the use of widespread tonsillectomies in all of our children -- at least not our children, but there are very few people in this room who have tonsils. We have now discovered that that was unnecessary surgery, and how did we discover it? By prospective controlled trials.

Indeed, we have to determine what the current evidence is, and I shall quickly review this for you.

(Slide)

Dr. Montgomery, one of the invited panelists today, said in an article in 1987, "The only evidence that would be acceptable is the demonstration in a prospective double-blind trial that a difference in suicide rates was consistently seen with a specific therapeutic agent."

(Slide)

Let me now quickly review these data. There are 16 published reports of suicidal ideation occurring in patients receiving fluoxetine. Please take that in the background of 4 million patients having taken this drug worldwide and the data that Dr. Potter and Dr. Fawcett presented about the fact that suicidality is part and parcel of this illness.

(Slide)

I would like to take this opportunity to briefly review the Teicher report, which essentially has launched a maelstrom of activity in the lay press and controversy about this drug. There were six patients reported. These patients had multiple complicating factors. Let me speak to a few of these issues.

They were, by and large, treatment-resistant. They are not your run-of-the-mill patient with simple major depression treated by a family practitioner or by a private practice psychiatrist. They were patients referred to a tertiary medical center for treatment resistance. They had a number of complicating factors, including comorbidity, other diagnoses, multiple personality disorders, other personality disorders known to be associated with suicidality, alcohol abuse, temporal lobe epilepsy.

A recent letter in The American Journal of Psychiatry by Downes, et al., raised the question of whether these patients did not have frank brain disease by virtue of

abnormal EEGs and limbic dysfunction. In this reply, Teicher stated that, yes, indeed, many did have abnormal EEGs and that they likely did have limbic brain dysfunction.

Shall we draw conclusions about the efficacy of an antidepressant on the basis of six extremely unusual, complicated, treatment-resistant cases? Three of the six patients had previous suicidal gestures. They were impulsive and they were on a bewilderingly large number of concomitant medications, including antipsychotic drugs and benzodiazepines, themselves implicated in some untoward side effects.

Of course, the greatest criticism, that Dr. Teicher himself acknowledges, is that this was retrospective and uncontrolled.

(Slide)

Are there other pieces of evidence in the literature? There are two cases reported by Masand. One was a treatment-resistant patient to imipramine, another a patient who received concomitant treatment with alprazolam, and a case by Dasgupta.

(Slide)

There was a case originally reported by Hoover, but since that time Hoover has retracted the suggestion that the suicidal ideation originally reported in this patient was secondary to fluoxetine. Hoover says, "It is unlikely that

fluoxetine has any relationship to the development of suicidal ideation."

What else in the literature might support this notion that fluoxetine is associated with suicidality?

(Slide)

There are six cases by King in six adolescents with obsessive-compulsive disorder but a number of other complicating organic factors were identified and the authors themselves acknowledge that the association might well have been coincidental. Then there is a single case by Koizumi.

(Slide)

What about other antidepressants, stepping away from fluoxetine for the moment? There is the often-quoted Damluji and Ferguson report published in The Journal of Clinical Psychopharmacology, four patients who became suicidal during treatment, a phenomenon not unknown to any clinician in this room. Two of these patients, surprisingly enough, after being removed from desipramine, responded quite well to fluoxetine and, in fact, their suicidality was associated, as we would expect, with depression and not with a particular pharmacological agent.

(Slide)

What about other agents? There is a single report of amitriptyline in a double-blind study. Fifteen refractory borderline patients receiving amitriptyline showed an increase

in suicidal threats, paranoid ideation, and the like, compared to 14 nonresponding patients.

Taken all together, with these anecdotal data one has to raise the obvious question. It seems likely that what we have here is a situation that we are taught in medical school. Things can be true, true and unrelated. Patients can be suicidal, patients can be being treated with an antidepressant, yet there is no cause-and-effect relationship. At best, these are anecdotal reports.

Let us now look to see the other side of the coin, what I think to be considerable evidence that active, aggressive antidepressant treatment, as Dr. Potter described it, is associated with an amelioration of suicidality.

(Slide)

In a study reported by Helmut Beckman and Christine Schmouse, two well-respected European investigators, amitriptyline was compared with promethazine in 50 severely depressed inpatients over a one-month treatment period. Not only was imipramine clinically superior but, in fact, it was superior not only in overall global ratings for major depression but for suicidal ideation as well.

(Slide)

Nomofensin, an antidepressant drug unrelated to the serotonin uptake blockers, 757 patients were classified into four different subgroups and nomofensin was a superior agent

over placebo, yet, surprisingly, perhaps, in view of this overall controversy, suicidal depressions, the most severe subtype, were the best predictors of response to nomofensin.

(Slide)

Recently Dr. Tollefson has analyzed a double-blind placebo-controlled series of antidepressants, 226 patients randomized to placebo or an active antidepressant for seven weeks.

(Slide)

The results were rather clear. There was an increase in suicidal ideation in the placebo group compared to the controls. No other class of antidepressant studied was associated with suicidality.

(Slide)

Even more importantly, not a single case of this ego-dystonic suicidal preoccupation that Dr. Teicher reported was observed in any of those studies.

I might add, on a personal note, that of the several hundred patients whom I have treated with fluoxetine and other related antidepressants, I have not observed this type of ego-syntonic suicidal behavior, either.

(Slide)

There is, of course, active investigation of other antidepressants. Another serotonin uptake blocker is the drug pyroxitine [phonetic], the SmithKline-Beecham drug, clearly,

in Europe, an efficacious antidepressant. In a study published by Dunbar and Mewett of almost 3000 patients who received pyroxitine, 554 with placebo, and almost 1200 with other antidepressants, in patients with no or mild suicidal thoughts, pyroxitine did not cause a worsening of suicidal ideation.

(Slide)

In fact, suicidality as an adverse event was no more frequent in pyroxitine-treated patients than those treated with placebo or active control. Thus, there was no evidence from these very large N's studied that serotonin uptake blockade per se is associated with increased suicidality.

(Slide)

Fluvoxamine, a drug currently under investigation by Solvay and Upjohn, has been studied by a number of investigators, including Dr. Montgomery. Fluvoxamine is significantly more effective, at least in these two studies, than imipramine in reducing suicidal ideation.

(Slide)

Similarly, sertraline, the Pfizer drug, the Psychopharmacologic Drugs Advisory Committee at its 33rd meeting stated the emergence of substantial suicidal ideation was low in all treatment groups and placebo rates exceeded the rates for active agents.

(Slide)

Although Dr. Tollefson will review the Lilly data per se, I did want to include some published fluoxetine data. In the study by Mueijen in 1988, suicidal feelings, as estimated by the HAMD-3 item, was significantly reduced among 14 fluoxetine-treated patients compared to 16 or 14 placebo or mianserin-treated patients two weeks after therapy.

(Slide)

One can use anecdotal data in any way one wishes. I simply want to show you how one can do that. This is a report published in The American Journal of Psychiatry by Cornelius, which suggested that five patients with borderline personality disorder and recurrent self-injurious behavior could be treated successfully with fluoxetine. They suggested that fluoxetine should be the treatment of choice for patients with depressive and impulsive symptoms in the context of a diagnosis of borderline personality disorder.

I would suggest to you that I have as little confidence in these anecdotal reports as I do in the anecdotal report of Teicher, and that, in fact, there is no substitute for controlled prospective double-blind clinical trials.

(Slide)

The last fluoxetine report to review is Sacchetti's of 62 patients receiving a range of 20 to 60 mg and, in fact, the patients who responded best were the patients who had a history of suicide attempt. Again, this would argue against

the notion that serotonin uptake blockers in general and fluoxetine in particular would be associated with an increase in suicidality.

(Slide)

In conclusion, there is simply no scientific evidence whatsoever, no placebo-controlled double-blind study that has established a cause-and-effect relationship between antidepressant pharmacotherapy of any class and suicidal acts or ideation.

As Drs. Potter and Fawcett have suggested, limiting the availability of antidepressants could have a very profound adverse effect in terms of increasing the morbidity and, in fact, mortality associated with untreated or undertreated depression.

Thanks very much.

DR. CASEY: Thank you, Dr. Nemeroff. There may be some questions, but I will ask the committee to hold their questions until all the representatives from Lilly have presented, so that the Lilly Company can have the benefit of the cohesiveness of their presentation.

Next will be Dr. Gary Tollefson from Lilly Research laboratories.

A REVIEW OF THE LILLY DATA BASE REGARDING FLUOXETINE

DR. TOLLEFSON: Thank you. I would like to thank the FDA for the opportunity to present data from our

controlled clinical trials of fluoxetine.

(Slide)

During our presentation of our Lilly controlled blinded studies we will overview four topics: an analysis of suicidality during depression; an analysis of suicidality in non-mood disorder trials; an evaluation of our clinical data base for evidence of paradoxical or clinical worsening; and a similar evaluation looking for any evidence of violence or aggressive behavior associated with pharmacotherapy.

(Slide)

In approaching evaluation of these potential associations of suicidal acts, ideas, of violent behavior during the pharmacologic treatment of depression, we have evaluated multiple data sources.

(Slide)

These include spontaneous adverse event monitoring, prospective suicide studies as a possibility, epidemiological data bases, and controlled clinical trials.

(Slide)

We have carefully evaluated spontaneous adverse event data and share the conclusions that there are significant limitations in this type of reporting system. We will be reviewing adverse events in the controlled blinded trials with fluoxetine later in the presentation.

(Slide)

Spontaneous adverse event data, as you have heard, suffer from having no reliable denominator. At best, only a gross estimate can be made based on sales or prescriptions provided. Events also are reported regardless of causality. On careful review, as you have heard, the majority of Prozac-related adverse events appear unrelated or noncausal to the drug itself. Spontaneous adverse event data also do not put events into context with other suitable comparative drugs. Thus we lose a sense of relativity.

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In addition, reporting, as you have heard, is highly influenced by a variety of variables. Webber has already published that peak reporting occurs approximately two years after a product's launch and thereafter decreases. Reporting is also influenced highly by the volume of product used. Thus the more popular a product is, the greater the number of absolute adverse events that are likely to be reported. Also, a variety of examples illustrate that the number and the nature of adverse events are substantially influenced by publicity. This has been well demonstrated several months following the publication of Teicher, et al.

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We view data that are generated from spontaneous event reporting and case reports to be hypothesis-generating. We have chosen to test these hypotheses based upon the

remaining three methods of study that I have cited.

(Slide)

These alternatives include prospective suicide-specific trials, epidemiological data bases, and detailed studies drawn from controlled double-blind clinical trials. In consultation with the Food and Drug Administration and noted external experts in the fields of depression and suicidality, we have already generated a series of protocols to better characterize patients who experience an increase in suicidal ideation during pharmacotherapy or other forms of treatment.

The first of these protocols has already been initiated.

(Slide)

We have also evaluated a variety of leading epidemiological data bases. These data bases have the caveat that they are not always well equipped to detect or capture mental health- or mental illness-related events such as suicidal ideation.

(Slide)

The first of these epidemiological data bases that I would share is the Drug Safety Research Unit's Prescription Event Monitoring System, or PEMS. This is a system under the direction of Dr. William Inman in the United Kingdom. This group has analyzed over 12,731 patients prescribed fluoxetine

and concluded that there was no evidence of fluoxetine-induced suicide attempts.

The second data base that I would like to attend to is the Drug Abuse Warning Network, or DAWN. DAWN collects information on emergency room and medical examiner mentions in association with drug use, either illicit or prescription. The number of emergency room mentions with regard to fluoxetine are not disproportionate when adjusted for the number of prescriptions written.

Regarding the number of medical examiner mentions with fluoxetine, again, relative to the number of prescriptions written, DAWN has concluded that the fluoxetine experience is substantially lower than that with other antidepressant agents.

A third data set comes from the National Center for Health Care Statistics. This has indicated that there has been a consistent, albeit modest, decline in the absolute number of suicide deaths and the rates of completed suicide per 100,000 individuals since the introduction of fluoxetine in January of 1988.

(Slide)

The focus of today's presentation, however, is on the large and comprehensive controlled clinical trials and data from Eli Lilly and Company. We approached these controlled clinical trials with three specific questions in

mind: Is pharmacotherapy associated with an increase in the rate of suicidal acts; is pharmacotherapy associated with an increase in the emergence of substantial suicidal ideation; and, thirdly, is pharmacotherapy associated with an actual reduction in suicidal ideation amongst depressed patients?

(Slide)

The initial analysis that I will present to you is from our mood disorders trials. In these clinical investigations of depressive disorders we had the luxury of two different clinical data bases. Together, as you can see, the N is quite impressive; over 5600 patients were studied in the clinical trials.

These two data sets differ in some very important clinical aspects, which we will be discussing momentarily. Data set number one is drawn from the U.S. IND for fluoxetine and data set number two is studies done outside of the United States, referred to as international trials. You can see these include placebo-controlled, comparative-controlled, and three-armed studies with both compared and placebo controls.

(Slide)

We are looking at three principal outcome measures here in these studies. The first one is a suicide act. The definition here is that we have defined a suicide act as behavior judged to be purposefully undertaken to produce an outcome of self-harm. The second outcome measure, to attempt

to capture what has been described in the literature as a clinical phenomenon by Teicher, et al., we have called the emergence of substantial suicidal ideation. This is defined as individuals who, at base line in clinical trials, had an item 3 score from the Hamilton Depression Rating Scale score of 0 or 1 that increased at any time during clinical trials to a 3 or 4 (that is during the double-blind component of those trials).

Just for a moment I would like to review what item 3 is. From the Hamilton Depression Rating Scale item 3 is a five-point scale ranging from a score of 0 -- as you can see, the absence of suicidal symptoms -- to a maximum score of 4, which is indicative of a suicide attempt. The third outcome measure was improvement. We defined improvements of suicidal ideation as a decrease in the Hamilton item 3 score from base line to patient's last clinical visit.

The first statistical method that was applied in the analysis of the U.S. IND depression data base was the Pearson chi-square test. This was performed to compare all treatment groups that you saw in the earlier slide. Again, we will focus initially on just the U.S. IND clinical characteristics, and I would point out that the patient characteristics at base line in the U.S. IND trials were comparable with respect to patient age, patient gender, total depression severity at base line, and item 3, suicidality.

(Slide)

On this slide you see the incidences of suicidal acts from the pooled U.S. IND trials. The first point that I would make is that the rate of suicidal acts in controlled clinical trials was low. There, as you can see, was no statistically significant difference between any form of therapy. I would also point out that in an analysis of fixed-dose trials with fluoxetine there was absolutely no difference in the rate of suicidal acts that did occur in that particular cohort relative to the dosage of the drug administered.

Presentation of these post-randomization data does not include one additional important observation. That is, there were three individuals who had suicide acts, one of which was fatal, that occurred during the placebo lead-in component of these trials.

(Slide)

I now move on to the emergence of substantial suicidal ideation. This is based on the same clinical data set, with one exception. You can see the denominator has changed here. That is based upon the fact that we are examining patients who, at base line, had an item 3 score of 0 or 1 in order to meet the criteria of the emergence of substantial suicidal ideation.

I would like to emphasize in this analysis, consistent with the observation of suicidality as a symptom of

depression, that approximately one-third of the total U.S. IND data base had item 3 scores of 2 or greater at base-line randomization. This, of course, underscores the presence of some degree of suicidal ideation that was in existence prior to drug therapy as part of the disease course.

As you can see here, significantly -- statistically significantly -- fewer patients had the emergence of substantial suicidal ideation with fluoxetine than either placebo or comparative tricyclic antidepressants in the U.S. IND trials.

(Slide)

This slide reflects the third outcome measure, and that is improvement from base line to last study visit. These data demonstrate convincingly that approximately two-thirds of patients improved when receiving active pharmacologic treatment for depression, either fluoxetine or tricyclic antidepressants.

I would also like to emphasize that fluoxetine is statistically and significantly associated with more improvement in item 3 scores than was placebo.

(Slide)

In summary, in the U.S. IND studies on Prozac, there were no statistically significant differences among fluoxetine (or Prozac), placebo, or comparative tricyclic antidepressants in the rate of suicidal acts.

Secondly, fluoxetine was actually associated with significantly fewer cases of the emergence of substantial suicidal ideation than either placebo or comparative tricyclic antidepressants.

Thirdly, an important point to clinicians and to public health in general, active pharmacologic treatment with either fluoxetine or tricyclics was associated with significantly better performance than placebo regarding improvement in suicidal ideation as measured by item 3.

(Slide)

Now I am going to move on to our international controlled trials in depression.

(Slide)

You have seen this slide previously. I would point out that, as one might expect, the international trials in depression were more heterogeneous from site to site and they obviously reflected the cultural and the scientific diversity that one would see in a multinational study.

(Slide)

Again, patient characteristics were completely comparable in the analyses by these same four parameters.

(Slide)

The statistical methodology, recognizing these significant heterogeneity and international trials of depression, led us to investigate the consistency of results,

investigator to investigator, by using the Mantel-Haenzel incidence difference test. This method allowed us to analyze treatments with respect to select variables after stratifying by protocol.

(Slide)

In our worldwide trials, we have, then, two head-to-head comparisons to share with you: fluoxetine versus placebo and fluoxetine versus tricyclic antidepressant medications.

(Slide)

This first slide looks at the incidence of suicidal acts by Mantel-Haenzel, providing, from your left to your right, the data analysis in the U.S. IND trials, the international trials of fluoxetine in depression and, thirdly, a pooled, worldwide experience in over 5000 patients.

(Slide)

As you can see here, this method was used and provided evidence that there was no statistically significant difference regarding the emergence of suicidal acts between fluoxetine and placebo in the U.S., international, or worldwide studies.

You can see that the percentages are slightly higher in the international data base and that, in fact, reflects that in the international trials we had a greater number of inpatients, we had a higher rate of base-line suicidality at study randomization, and patients generally, in the European

experience, tended to be continued in trials despite having suicidal ideation longer than their counterparts in the U.S. might normally practice.

One other important observation is that in the international trials more than 40 percent of the individuals randomized had base-line suicidal ideation present.

(Slide)

Now we look at the emergence of substantial suicidal ideation. You will note that the U.S. data and the international data appear similar regarding the rates of ESSI, or emergence of substantial suicidal ideation. The rate is numerically lower with fluoxetine when contrasted with placebo, and that achieved, statistically, a trend within the U.S. IND data. When all of the data are pooled between the United States and the international trials, you can see that statistical significance at 0.03 was achieved, whereby more emergence of substantial suicidal ideation during clinical double-blind trials was associated with placebo than with active drug therapy.

(Slide)

Once again, we also visit the third outcome measure of improvement in item 3 scores. As you can see, fluoxetine was significantly statistically better than placebo in these trials, both within the U.S. experience and the pooled U.S. and international or worldwide data. Once again, more than

two-thirds, approaching three-fourths, of all patients experienced an improvement in their item 3 scores, base line to last visit, while receiving active treatment.

(Slide)

We will now focus on an evaluation, as you remember from the Mantel-Haenzel, of a comparison between fluoxetine and other standard tricylic antidepressants. Again, overall, we observed a very low incidence of suicidal acts. You can see there was no statistically significant difference between fluoxetine or tricyclic antidepressants in the U.S., the international, or the pooled worldwide data bases.

Regarding the emergence of substantial suicidal ideation, the absolute prevalence, fluoxetine appeared somewhat better than the tricyclic antidepressants in the U.S. and the worldwide data bases. However, overall, the results demonstrated no statistically significant differences in the two different treatment assignments.

(Slide)

Regarding improvement in item 3, item 3 improvement was comparable between fluoxetine and TCAs within the U.S. IND data base. However, in the international data base, tricyclic antidepressants appeared to have significantly more improvements than did fluoxetine. I would remind you, though, that fluoxetine had statistically and significantly greater improvement in ideation than had placebo. A caveat in

interpreting this particular individual analysis is that there was statistical evidence of significant heterogeneity trial by trial. Thus the pooling of these particular data in this analysis might be in some question. We show it, nonetheless, to give you that comparison.

(Slide)

In summary, the international data replicated our U.S. IND experience. It demonstrated no statistically significant difference between fluoxetine or tricyclics in the occurrence of suicidal acts and no difference from the base-line rate with placebo. Fluoxetine was superior to placebo in the prevention of emergence of substantial suicidal ideation and there was no difference in substantial suicidal ideation emergence between fluoxetine and tricyclic antidepressants. Fluoxetine was superior to placebo in the improvement of item 3 suicide ideation scores.

(Slide)

Returning to our original three questions regarding the pharmacotherapy of depression, is there evidence that pharmacotherapy increased suicidal acts based on this over 5000-patient-sample data base? The answer was no.

Is there any evidence that there was an increase in the emergence of substantial suicidal ideation with the introduction of pharmacologic treatment? Again, from this data base you can see the answer was no.

The third and a very important question, was active pharmacologic therapy associated with a reduction in the majority of patients with suicidal ideation? The answer was a resounding yes.

(Slide)

I would now like to turn your attention to the trials that were done on non-mood disorders, nondepressive disorders.

(Slide)

As you can see here, the hypothesis of why we did this data analysis was that if antidepressant medication carried the inherent risk of promoting suicide or hostile and aggressive events -- and that was apart from the natural history of the disease that it was being prescribed for, i.e., depression -- then one would expect that drug-induced effect to emerge in other disorders where it is prescribed.

(Slide)

What we did was, we looked at our U.S. IND data bases for three clinical disorders: bulimia nervosa; obesity; and obsessive-compulsive disorders. These three trials represent over 5000 patients who were investigated.

(Slide)

Once again, in these non-mood disorders, patients were comparable across the assignment to either fluoxetine or placebo.

(Slide)

Here we, first, look at the incidence of suicidal acts. As you can see, there is no statistically significant difference between fluoxetine and placebo regarding the incidence of suicidal acts with bulimia, obesity, or obsessive-compulsive disorder: In fact, there were no acts in trials of OCD.

(Slide)

In review of the data for emergence of suicidal ideation during pharmacotherapy, as you can see here, there, again, was no statistically significant differentiation between placebo and fluoxetine with regard to suicidal ideation in any of the three non-mood-disorder trials.

(Slide)

In summary, there was no evidence of an increase in suicidal acts in non-mood-disorder patients receiving fluoxetine. There was no evidence of an increase in suicidal ideation during administration of fluoxetine to non-mood-disordered patients.

(Slide)

Thus we would summarize that there is no suggestion that fluoxetine induced suicidal acts or clinically significant ideation in a non-mood-disordered cohort.

(Slide)

There has also been some discussion in the

literature about a hypothetical clinical worsening amongst a very small number of patients receiving antidepressant medications. This has been labeled a so-called paradoxical reaction. The next few slides examine that hypothesis.

(Slide)

We used the following definitions to examine that hypothesis in our mood- and non-mood-disordered trials in the U.S. IND. These definitions, in fact, for the most part, reflect the mirror image, or the opposite, of what are typical response definitions.

First of all, in depression, a 50-percent-or-greater increase in the 17-item Hamilton Depression Score from base line to any point during study; in bulimia nervosa trials, at least a 50-percent increase in bingeing or vomiting at any point during clinical trials; in trials with obesity, based upon outliers beyond the 99th percent of weight gain in placebo recipients, a greater than 12-pound or equal-to-12-pound weight gain during eight to 12 weeks of drug therapy and; lastly, in obsessive-compulsive disorder, a 25-percent-or-greater increase in the Yale-Brown Obsessive-Compulsive Scale, again, at any time during clinical trials.

(Slide)

As you can see, in the analysis for possible paradoxical worsening, in fluoxetine versus placebo and fluoxetine versus tricyclics, there was no statistically

significant differentiation between either placebo and fluoxetine or fluoxetine and tricyclic antidepressants, suggesting there is no evidence of worsening with either active drug that differentiated them from placebo.

(Slide)

We now move on to the bulimia trials. The first outcome measure, an increase in vomiting, you can see there was statistical significance and, of note, that statistical significance was such that there were fewer paradoxical worsenings amongst bulimic patients receiving active drug treatment with fluoxetine than with placebo.

(Slide)

The same statistical significance held true in looking for binge eating. There were fewer paradoxical worsenings with active drug therapy than with placebo.

(Slide)

The same statistical significance held true in obesity trials. There were fewer paradoxical or unanticipated and unexpected weight gains in patients receiving fluoxetine than in placebo recipients.

(Slide)

Last, but not least, in the assessment of paradoxical worsenings in obsessive-compulsive disorders, there was no statistically significant differentiation of fluoxetine or placebo regarding unexpected worsenings.

(Slide)

In conclusion, looking at these U.S. IND depression and non-mood-disorder trials, we saw no evidence of paradoxical worsening in fluoxetine-treated patients.

(Slide)

I said I would briefly share with you studies looking at discontinuation rates during the controlled clinical trials. As you can see here, and as one often would expect with the use of any active pharmacologic agent, adverse event experience is more common with active treatments than with placebo. I would point out, though, that fluoxetine was statistically and significantly associated with fewer side effects leading to discontinuation of treatment than comparator tricyclic antidepressant agents.

(Slide)

I will show you a perhaps equal or of greater importance slide, and that is retention in study. These are discontinuation rates for any reason, looking at fluoxetine versus placebo and fluoxetine versus tricyclic antidepressants. As you can see here, there was a statistically significantly greater number of patients, over half, who received fluoxetine and were able -- I am sorry, let me restate that. There were a statistically significant number of patients who failed to discontinue, or, in other words, stayed in the studies, receiving fluoxetine and, when

compared with tricyclic antidepressants, once again, there were significantly fewer patients who discontinued clinical studies.

One can conclude that, compared to placebo, active therapy was associated with longer study retention. Specifically, head to head, fluoxetine performed significantly better than placebo or tricyclic antidepressants.

(Slide)

In summary, there were no significant relationships that were seen. We took that one step further, though. As we have heard, there are possible hypotheses that have been generated considering that there may be a certain association in rare patients between an adverse event experienced and an increase in suicidal ideation.

Accordingly, we analyzed this entire data base of over 500 patients with depression for their adverse event experiences. For the sake of time, I will only comment on one adverse event experience. That was looking at activation, including the experience of akathisia. In comparison versus placebo or compared to tricyclic antidepressant there was absolutely no statistical association between suicidality and activation relative to drug assignment or placebo assignments.

(Slide)

I am going to move on to another question that has been posed to this committee. It is the final question; that

is, whether or not fluoxetine precipitates aggression or hostility.

(Slide)

We used the following method to address this question. We evaluated the spontaneous adverse event data for violence or terms that would identify violent, hostile, or aggressive behaviors. We then applied these terms, the so-called aggression cluster events, to our double-blind placebo-controlled trials across all indications, depression and nondepressive disorders.

From that we identified 13 individuals of some 10,000 who experienced an event cluster of aggression.

(Slide)

Let me emphasize that in those clinical case report analyses of those 13 individuals there was no evidence that in any of these cases the aggression led to serious bodily harm to others. From a clinical perspective, the acts were of limited significance. But as you can see from the data analysis, fluoxetine was statistically significantly less likely to have resulted or to have been associated with an event from an aggression cluster than placebo. The absolute numbers: nine events with placebo, only four events in fluoxetine; the percentages, 0.65 placebo, only 0.15 with fluoxetine (significant at a 0.008 level).

(Slide)

Thus, in the placebo-controlled double-blind clinical trials, fluoxetine was significantly less likely than placebo to be associated with aggression. In fact, the evidence suggested that aggression was less likely to have occurred in patients medicated with an active antidepressant agent.

(Slide)

In conclusion, we have reviewed the various data bases or possible hypothesis-generating methods to look at these interesting questions posed to the committee. We have already heard that spontaneous event reporting suffers from numerous caveats. There are advantages to prospective, suicide-specific, double-blind controlled studies and, as you have already heard, these clinical studies looking at suicidality and depression have already been commenced.

There are epidemiological data bases that can be reviewed and, as you have heard, there is absolutely no evidence from those data bases of an increase in suicide rate since the launch of Prozac, nor any evidence in the DAWN data base looking at coroner or medical examiner mentions of an unexpected increase in fluoxetine events; in fact, on the contrary, there were fewer fluoxetine mentions than expected for the number of prescriptions rendered compared to tricyclic agents.

(Slide)

Thus, the overall conclusions that we would leave you with are, based upon a comprehensive analysis of our data:

. suicidality is part of the natural history of the disease of depression;

. compared to placebo, fluoxetine was not associated with an increase in the rate of suicidal acts and mood disorders;

. fluoxetine was associated with fewer cases of the emergence of substantial suicidal ideation than were seen with placebo;

. fluoxetine was more effective than placebo in reducing base-line to last-visit item 3 scores (in other words, improvement in suicidal ideation); --

(Slide)

-- there also was no evidence of suicidal acts or ideation in the non-mood disorders, bulimia nervosa, obesity, and obsessive-compulsive disorders;

. there was no evidence of a paradoxical or clinical decompensation with regard to the treatment of fluoxetine in mood and non-mood disorders compared to the placebo rate that would be seen, in part, as reflective of the diversity of the clinical presentation of these disorders; and

. aggression or violence was less likely to occur with fluoxetine than with placebo.

It is our feeling that the major public health

concern relative to suicidality and depression is the current stigma, underrecognition, or undertreatment of a very serious disease and, secondarily, in those patients who do experience suicidality as a part of the disease, the concern about pharmacologic treatment is specifically the risk of drug overdosage.

With that, I would like to thank you for your time and return to Dr. Zerby.

DR. ZERBY: Thank you, Dr. Tollefson.

Let me very briefly summarize our data in reference to the questions posed to the committee. First, the only scientifically valid approach to the evaluation and treatment of emergent suicidality in depression is through an analysis of appropriately controlled data. Neither anecdotes or spontaneous reporting allow distinction between fluctuation of the severity of the underlying disease and the treatment-induced worsening.

No blinded controlled clinical trials have demonstrated an excess of either suicidality or violence during antidepressant therapy. To the contrary, antidepressants have been shown to improve suicidal thinking. Thus, credible scientific data demonstrating a causal association between antidepressants and suicidality do not exist.

Second, the rare anecdotal reports of suspected

antidepressant-induced suicidality are not unique in either occurrence or characteristics to any specific agent.

In response to the final question, neither the number of spontaneous events nor the nature of the specific events justify unsupported changes in labeling. The number of events observed with fluoxetine is entirely compatible with the age of the product, the extensive clinical use of the product, Lilly's vigorous reporting policy, and unprecedented publicity.

The anecdotal reports of suicidal ideation have no features which can reliably be identified as a unique syndrome beyond the spectrum of depressive illness. While additional studies, such as those which we have initiated, are appropriate, speculative labeling changes based on anecdotal data would benefit no one, while needlessly alarming and potentially hurting many seriously ill patients.

We will be glad to entertain additional questions.

DR. CASEY: Thank you, Dr. Zerby. I will ask the committee to now use a few minutes to address specific questions to the Lilly Company related only to their presentations, and if there are more general questions about the issues, we will have the Lilly people available as resources.

DR. DUNNER: It is my understanding that there was a difference in the reporting system by the company and,

therefore, to the FDA for this compound versus other compounds. That has been alluded to, that the reporting of adverse events has been more complete since the introduction of fluoxetine than with other compounds?

DR. ZERBY: The reporting system that Lilly has is applied to all Lilly compounds. There are no unique features of reporting for fluoxetine. I would hasten to emphasize some very critical points. We report everything, regardless of causality. That is all very compatible with FDA standards, but that point needs to be reemphasized. The conclusion that because a report exists in the data base the physician or we conclude that it is causally related is simply not true. Many of the cases that are in the data base, in fact, specifically indicate that the physician felt that the event was not related to fluoxetine, but we report that anyway.

The other thing to point out is that in the reporting we do not -- the patient need not be on the drug at the time that the event occurred. In other words, we report events if there has been some exposure to fluoxetine.

DR. DUNNER: Therefore, some of the reports that go into the FDA data base are reports that are coming from the clinician to the company to the FDA?

DR. ZERBY: That is right. In fact, that represents the majority of reports. Of the reports at the FDA, we think about 95 percent -- by FOI information -- come from Lilly. I

would add that 80 percent of those events are, by FDA standards, nonserious.

DR. DUNNER: So in order to understand this 500 to 800 events that we are talking about today in some context, they could represent a maximal number of events that actually occurred in the U.S. and they also could represent some portion of the maximal number, dependent on the thoroughness of that reporting system on the part of Lilly?

DR. ZERBY: Everything we receive is reported to the FDA in compliance with their standards. I think the issue is how much information actually gets to us.

DR. LIEBERMAN: Dr. Tollefson, you presented some very thorough and clear analyses, which I presume were based predominantly on acute treatment studies, controlled acute treatment studies. Is that right?

DR. TOLLEFSON: The data from the depression trials, the acute double-blind component of the depression trials, ranged anywhere from four to 13 weeks. I would point out the reason for looking in the double-blind trial, obviously, is to try to control for other variables -- that was an advantage.

However, we have experience, in the non-mood disorders, with patients treated anywhere from six to 60 weeks, and then in compassionate use protocols with fluoxetine, or other protocols that have been used outside of double-blind, there are experiences with well over one year of

exposure to the drug.

DR. LIEBERMAN: That is essentially what I was going to ask. If one looked at the controlled trial data solely, they might not extend through a hypothetical period of risk, and do you have data for longer periods of time, either maintenance treatment or --

DR. TOLLEFSON: I think that is an excellent question. What we decided to do is to take what we thought might be the worst-case scenario, and those were patients, a very large number, that were put on compassionate use. As you know, by definition, compassionate use patients are patients who have not responded to any other vigorous efforts at treatment and might be considered a high-risk group for suicide.

Looking at those patients, followed a mean of six months -- but, as I said earlier, the range being out over one year -- their rate of suicidal acts actually was less than that that has been reported by Winneker or as Jan Fawcett had cited, so even in that worst-case scenario the rates were less than what has been reported in the data as a whole by, again, Fawcett and Winneker.

DR. LIEBERMAN: Can you estimate the number of patients that may have been followed in that context?

DR. TOLLEFSON: It is approximately 800 patients in compassionate use trials.

DR. LEBER: Jeff, you were going somewhere with that question, and I wonder if you would like to explain where you were going? I think I know, but --

DR. LIEBERMAN: Why don't you say?

(Laughter)

DR. LEBER: I am presuming that you are trying to make the point that if the hazard, that is, the risk of having an adverse event, is nonuniform across the time of exposure, that events that have a hazard that rises late may not be captured, because relatively few people are placed at risk late, and that these relatively short-term studies lasting perhaps eight weeks, at most, in the domestic studies, up to maybe 12 or 13 weeks in nondomestic studies, have not looked enough at the chronic course of treatment, since episodes of depression are now treated six months to a year, to rule out the possibility that there is an emergence of something in the long run.

DR. TOLLEFSON: May I make one other comment on that, Dr. Leber?

DR. LEBER: I think Jeff was going there, and he is the one who has to tell me that he was.

DR. LIEBERMAN: That is exactly right.

DR. TOLLEFSON: I was going to say that we did also analyze the data based upon patient exposure to drug; that was the entire data base. There was no relationship between

suicidal acts and length of exposure.

DR. CASPER: I was wondering whether you could enlighten us whether the patients, I think in the U.S., in the four- to six-week treatment trials, were seen on a regular basis, probably evaluated weekly, were probably also in some other form of treatment, perhaps psychotherapy or family therapy or some other form of treatment, at least regular contact? That is, these patients did not take Prozac and did not see either their general practitioner or a psychiatrist for a prolonged period of time. They were under supervision. That is question number one.

The second question relates to plasma-level monitoring. Have you ever considered plasma-level monitoring or have you done that with fluoxetine?

DR. TOLLEFSON: Your first question had to do with the protocol design, and I would say yes and no. The patients, obviously, as a standard for this type of clinical investigation, were followed regularly, and most often that meant a weekly visit. On the other token, they were not benefiting by other modes of therapy, nondrug therapy, such as psychotherapy, again, to protect the integrity of the clinical study of drug versus placebo.

Are they different from the patients that might be encountered in primary care practice as far as the level of follow-up? Possibly, yes. On the other token, they probably

represent a more severely depressed patient population with a lot more risk factors for suicide than one would see in a standard primary care office practice.

Regarding the second question, we have looked at fluoxetine and its desmethylated metabolite. There is a lack of any substantial correlation between those drug concentrations and either therapeutic response or, particularly, the issue of suicidal acts.

DR. ESCOBAR: This may relate to Dr. Lieberman's question. In the preamble, I believe it was Dr. Nemeroff who reviewed the evidence for the relationship between suicide ideation and the use of other antidepressants in the controlled trials. It occurred to me that he did not review the very few long-term maintenance studies, such as the one by Dr. Pryan. I would be interested in knowing, since Dr. Pryan is here, whether there was any relationship.

DR. CASEY: Could we save that to committee discussion and keep our questions specifically directed at this time to the Lilly people? Bob, will you be available to avoid or answer that question later on?

DR. PRYAN: Yes, I will be available.

DR. CASEY: Thank you.

DR. HAMER: This also is related to Dr. Lieberman's question. I believe, in reading the material, that several of the studies had open-label extensions and you did not analyze

-- or at least you did present -- the data from those. Did you analyze those data and, if so, how long were the open-label extensions and what kinds of results did you see?

DR. ZERBY: We have had patients treated in open-label extensions and compassionate use for up to eight-and-a-half years. In fact, there are about 2000 patients who have been treated for more than six months in some monitored way. The problem with the interpretation and the way that we did the controlled clinical trials is there is not a suitable comparator group. The way that we analyzed them is the way that Dr. Tollefson mentioned, looking at the rates of occurrence, and then compared that to an epidemiologic data base. In reality, the numbers were actually lower than one would have expected from, for example, Dr. Fawcett's work.

DR. REGIER: I wanted to speak about Dr. Fawcett's presentation. As I understand the presentation, he mentioned that there were 954 individuals who were entered into that study and that of those 954 there were 13 who actually committed suicide within the first year of entry into the study, which, in relation to Dr. Teicher's question about base rates, would amount to a completed suicide rate of 1.4 percent. That is completed suicide as opposed to even suicide attempts.

I wonder if Dr. Fawcett could comment on those rates and if he has any information on rates of suicide attempts

with this population.

DR. FAWCETT: The suicide completion rate was lower than we had anticipated, based on other studies, although the percent of deaths was just as high. In other words, if you take the early studies that were quoted by Guze, we had, in our first year, 70 percent of the deaths reported were from suicide. Other studies just with one- or two-year follow-ups had reports that high, but the actual percent of the sample seemed quite low for the first year after hospitalization, although it represented 50 percent of the suicides that we had.

That is the face of our feeling, following treatment, which we could not match -- it was not controlled or randomly assigned -- but we felt treatment was not that intense as we expected in five university centers. So even with moderate treatment, we saw, I think, a not-too-high suicide rate. These were 85 percent inpatients that we were following.

They were equivalent to the rates reported way back by Lowcher in his ECT group, where he compared ECT against nothing and for 10 years he got a 1.5-percent rate of suicide in the ECT group versus 7 percent in the no-treatment group, so they were comparable to his ECT group for the first year.

As far as suicide attempts go, I know that about 260 of those patients have made suicide attempts, and I cannot do

it by year, but I think in the first five years there were about 260 attempts, which averages out to about 5 percent a year, which is very similar to the Avery finding of non-ECT patients -- I think it was 5 to 7 percent of suicide attempts in the Avery-Winneker study, as I remember it.

Does that answer your question?

DR. REGIER: Yes. I think it is very important to deal with the issue, because Dr. Teicher had asked for your data base, and that speaks directly to the issue of what is the expected base rate in either a community population or in a clinical population.

DR. CLAGHORN: I would like to talk for a moment about the selection-bias issues. We have got a large sample of individuals but we have excluded from them people who are physically ill. We have excluded from them people who have significant suicidal thinking. We have really taken the lower end of that, sampled off the bottom end of that part of the range. We have made some selections on the basis of age. We have excluded a wide variety of other diagnoses.

I think the question emerges in the Committee's mind at this point, are we seeing something in our naturalistic reporting system that reflects a different selection of individuals than we see in the controlled clinical trials and, therefore, there may be an incompatibility between those two lines of information?

Is there any way you could address the issue of how the broad population might differ from this selected population?

DR. ZERBY: That obviously is always a problem when you are dealing with experimental compounds and using placebo arms and trying to investigate the safety of a drug. One has to balance the ethics of putting seriously ill patients, for example, into the trial.

I would have to say, first of all, with regard to the suicidality, to reemphasize the point that Dr. Tollefson made, that really the only exclusion for suicidality was in the view of the investigator that that patient was at high suicidal risk at the time. Many of the patients, however, by looking at HAMD item 3 had significant suicidal ideation but were still enrolled.

The other thing that I would emphasize is that not all trials excluded patients even at high suicidal risk. About 50 percent of the trials outside the U.S. had no such exclusion and a few within the U.S. had no exclusion. So not all trials were that restrictive.

The other thing, as everyone is doing, we are trying to open up more widely age limits and so forth. We have an ongoing geriatric study. We will have a much better idea about those kinds of populations when that study is finally broken.

DR. CLAGHORN: One follow-up: Have you actually broken out the studies that did not use that exclusion and analyze them separately to confirm that they come to the same conclusion as the trials generally?

DR. TOLLEFSON: We looked at protocols that either included or excluded patients who had suicidal ideation or high suicide risk, and the data are really indistinguishable in the two different subcohorts.

DR. SCHOOLER: I wanted to follow the line of questioning that Dr. Claghorn was addressing in another way. One of the general problems with clinical trials is exclusions and who gets into them. From the data base that you have, which is a very elegant one, I think, approximately what number of cases would you estimate had been screened in order to get that number of patients into the studies, given the kinds of criteria that were set up in each one? Just roughly. Are you talking about 50 percent? 30?

DR. TOLLEFSON: I cannot give you an exact number. I think, in general, what you are talking about is probably about one out of two to one out of four patients who would be included. I do not know if anyone in our group would have that specific information right now.

LILLY REPRESENTATIVE: (Not at microphone). It varies from protocol to protocol --

DR. TOLLEFSON: The bottom line is there is

variation, depending on the protocol.

DR. ZERBY: One other thing perhaps worth noting is in that screening, some patients were screened out not because they are too ill but because they are not ill enough.

DR. SCHOOLER: I would say that still would affect the generalizability in both directions.

DR. TOLLEFSON: Outside of the controlled data base that we presented, I mentioned that we had compassionate use. There are also studies that have been done in mild depression, or dysthymia, for example, so we have looked at a variety of different mood disorders, without any deviation from the basic concluding points that were made.

DR. MONTGOMERY: I have a comment which may help to answer Dr. Claghorn's very interesting point, and this is, we looked at a group -- the data were presented in the recent Florence meeting -- of 107 patients with a history of repeated suicide attempts, without major depression (they were largely personality disorders). We followed them up for six months or until they attempted suicide and we achieved a suicide attempt rate of 18 attempts in each group, representing a 35-percent attempt rate in this population. Clearly, people were dropping out as they went along, but the life table analysis that we did showed absolutely no difference in the attempt rate or in the speed of the attempt on drug or placebo, and that very largely backs up data in the nonmajor-depression

population which you have seen presented today.

DR. CASPER: I was amazed by Dr. Montgomery's comment that the attempt rate under drug was not less than under placebo conditions. Actually, from the data we have seen here today, you would expect a lower attempt rate in patients taking an effective antidepressant medication.

DR. MONTGOMERY: These patients were not depressed. They were not suffering from major depression and so, therefore, it is testing whether the drug was effective in those groups who maybe ought not to have received the antidepressant, and the answer for us was that there was no provocation of suicide. Neither was there induction of suicide attempts in that group.

DR. CASPER: Did they have any change in any other symptoms? Or did fluoxetine at the time have no effects on this population?

DR. MONTGOMERY: As far as we could tell, the difference between the drug and placebo was minimal. They followed exactly the same course in both groups.

DR. CASPER: I have, really, another question, and that concerns the group of patients who did not complete the studies. You said that the patients, actually, proportionately were less in number than those in tricyclic drug studies. Did you analyze the reasons why patients discontinued medication, dropped out of the study? I mean,

there are obviously many reasons why patients do not continue a particular drug study, but did you look at this population, because this might be a population which might be of interest to our discussion today, since they might have developed some symptoms or adverse reactions which, indeed, might be side effects of drugs done in only a very small population.

DR. TOLLEFSON: The question, if I understood, was on the slide that had to do with discontinuation for any reason or discontinuation due to an adverse event? I was not sure which one you were referring to.

DR. CASPER: Either one.

DR. TOLLEFSON: As you remember, the basic conclusions there were that patients compared to placebo on either tricyclic or fluoxetine were more likely to experience an adverse event, which would make sense. Fluoxetine rates, though, were significantly fewer than were seen with tricyclics. Then we moved on to a discussion of any discontinuation from study for any reason and, in fact, there were far fewer, statistically significantly fewer, discontinuations with drug therapy with fluoxetine than either with placebo or tricyclics, meaning more patients were retained in the study.

Now, had, from any of those three assignments, fluoxetine, placebo, or tricyclic, the patient experienced an increase in ideation potentially, theoretically, as an adverse

event, for example, in the placebo cell, it would have been captured in the analysis as a clinical worsening or, if the emergence were substantial, it would have been caught in that ESSI, or emergence of substantial suicidal ideation.

Those individuals, remember, as we said in the definition of the data analysis, we were looking at a difference from base-line randomization to their last visit or, for that matter, any visit during the clinical study. So if they experienced that adverse event at a termination point of the study, they would have been included in the data analysis.

DR. CASPER: My question also concerned the analysis of adverse events, in general, not just suicidal ideation, but agitation, restlessness, or other symptoms. Did you look at those? Did you do an analysis in this population who discontinued the control trial?

DR. TOLLEFSON: For example, at the closure of the U.S. IND base at the end of 1989, suicidal acts or ideation as a side effect, if you would map it as such, under active treatment with fluoxetine was not in the top 20 events. The most common things were the ones that people would encounter in clinical practice, such as nausea, headache, or restlessness. We do have that. In fact, we could show you the rank ordering, if you are interested.

DR. MANN: One of the concerns that was expressed on

a placard outside the building was that Prozac kills. One of the problems with the limitations of the data set generally being presented and discussed here from the controlled clinical trials and from the various kinds of continuation data that you have is that there are not any data on deaths through overdose.

I wonder, first, whether you could tell us a little bit about what in the analysis you might have done, using the DAWN data set, on actual fatalities due to suicide attempts or overdoses related to Prozac and, secondly, whether you have tapped the same data set in order to determine whether there are any differences between fluoxetine and other antidepressants in terms of presentations to emergency rooms, for example, with an overdose.

DR. TOLLEFSON: I would refer back to our review that we did do of the epidemiological data bases with this group. First of all, as you recall, when we looked at the PEM system, the Inman group that looked at over 12,700 fluoxetine recipients observed no evidence of fluoxetine induction of suicidality or suicidal deaths.

We then moved on to the DAWN data and there are two components that one can analyze within that Drug Abuse Warning Network. The first one was just general emergency room mentions. As I commented, in light of the volume or the popularity of the medication as a denominator, the DAWN data

base concluded there was no disproportionate increase in mentions of suicide at emergency rooms relative to fluoxetine.

Then we moved to discuss, within the DAWN data, the other subset, which were medical examiner mentions of deaths and, in fact -- and we can show you those comparisons -- the fluoxetine experience, when considering, again, popularity by prescription, was substantially lower in medical examiner mentions than tricyclic antidepressants. That, I think, definitely reflects the differential therapeutic indices between conventional tricyclics and some of the more novel serotonin-selective uptake inhibitors.

Last but not least, is the general point from the National Center for Health Care Statistics that absolute numbers of suicides -- lethal, death -- have gone down somewhat since the launch of the product.

DR. ESCOBAR: Going back to the selection of the samples, I am particularly interested in having a general idea of the criteria to select particularly the nondepressive samples, because I have a hunch that in the real world fluoxetine is being used for a large number of nondepressed patients. Do you have any idea of what proportion of the individuals who entered those trials were real patients, users of services, and what percentage or proportion of them were symptomatic volunteers recruited through newspaper advertisements and, if so, does your company have a specific

policy on those advertisements?

DR. TOLLEFSON: That is a very difficult question to address with regard to the percent of patients, say, derived from newspaper ads versus normal patient care. I would think that there would be more patients recruited in that way in the obesity trials than in the depression trials, the mental illness trials, and I think, for the most part, those are centers that are very highly skilled in those areas and have very selected populations and not generally seeking those from newspaper ads.

DR. ESCOBAR: Some of the companies have policies on the advertisements that are placed by the P.I.'s. Do you have any such policy?

DR. TOLLEFSON: Let me, just for one second, refer back to your earlier question. If you were speaking on the non-mood-disorder trials, obesity, OCD, and bulimia, those are patients in clinical studies using DSM-III-compatible criteria for OCD and for bulimia nervosa and defined criteria that are medically acceptable for obesity; those were not just random clinical observations.

DR. ESCOBAR: It is the way they are recruited, how they came to the attention of the investigators.

DR. TOLLEFSON: Now, again, that would not be a corporate issue. The corporation does not recruit patients. There are academic investigators who recruit patients. Some

academic centers, as you know, may use print advertising. That print advertising is subject to that institution's institutional review board policy and it would have to approve whatever advertisement was used.

DR. CASEY: Dr. Lin, please. Again, I ask people to have just specific comments to Lilly, so we can proceed with our committee discussion.

DR. LIN: I also have a question about the patient selection and potential bias. I think it is a very important question and I do not know whether there is an easy answer. In the case report literature, I think many authors suggested that patients with atypical depression, however it is defined, may be more susceptible to this kind of side effect. I wonder whether you have data to address that or whether there is any plan to look into that issue?

DR. TOLLEFSON: There clearly are published trials, not necessarily sponsored by Eli Lilly and Company, looking at selective serotonin-reuptake inhibitors such as fluoxetine in atypical depression. The data suggest, as I am sure you know, that the selective serotonin-reuptake inhibitors appear as efficacious as monoamine oxidase inhibitors and better tolerated and appear superior to tricyclic antidepressants in atypical disease. One would expect that with the classical features, with hyperphasia, hypersomnia, et cetera. They would seem to be a reasonable option.

That is not necessarily based on our Lilly data base we heard today, but published academic literature.

DR. MONTGOMERY: One way of answering Dr. Escobar's interesting question is to comment on the difference between the international studies and those conducted in the U.S.A., because my understanding is that the international studies did not have the ability to do recruitment by advertisement; it is not a technique for raising patients for studies in Europe.

I wonder whether you would confirm that, because that would help Dr. Escobar to answer that question.

DR. TOLLEFSON: Yes, that is true. Thank you.

DR. HELLANDER: I have a question about the doses of fluoxetine that were used. I am assuming that it was 20 to 80 mg in all the studies, but could you tell us, perhaps, what percentage of the patients were on the lower end, 20, and what percentage were on the higher end, 80? Could you also try to do the same with estimating the percentage of the patients who were in the shorter trials, the four- to five-week trials and those who were in the longer ones, toward the 24-week end?

DR. ZERBY: I am only able to give you a gross estimate -- some of my colleagues may be able to clarify it. There are a large number of patients at the high doses of fluoxetine in these trials. Many of the early trials with fluoxetine were done at higher doses than subsequent trials, when we looked at fixed doses. My

estimate would be that roughly 40 percent were 40 to 60 mg and probably 20 to 30 percent were at 20 mg.

DR. TOLLEFSON: I would like to reiterate the comment, though, that we did, in the fixed-dose studies, which ranged from 5 mg to 60 mg, an analysis to see if there was any association between suicidal acts or ideation and dosage and there was none.

DR. TEICHER: A couple of questions. In terms of the coroners' data, where you showed the extraordinarily low frequency of adverse reports with fluoxetine, did this require that the coroners pick them up on assay and were they all prepared to do assays on it, or required that it be documented in some way in terms of medical history? How did they know that they were on fluoxetine?

DR. ZERBY: They did not require assay confirmation. In fact, it could be as little as some evidence that they were on the drug would be sufficient as a coroner's mention or medical examiner's mention.

DR. TEICHER: I am interested in the converse. In some cases, say, with tricyclics, did they say that the patient was on tricyclic because they had toxicology data, and were those toxicology data in some instances not available for fluoxetine?

DR. ZERBY: I do not know exactly how one can answer that. I know assays for fluoxetine now are not uncommon and

people can assay for that. I do not think there is any limitation in the ability to measure it. I guess I would be almost more concerned, with all the publicity, with even the coroners being influenced by the recognition, by saying this patient may have been on Prozac, when, in fact, the patient was not on Prozac.

I think there are issues, too, that emerge with medical examiner mentions.

DR. TEICHER: I think, also, it should be noted in terms of the trend of the mortality or number of suicides going down over time, one important fact to filter into that, that I am sure you are aware of, is that it has always been reported in epidemiological studies that one thing that influences the overall rate of suicides is whether the country is at war or not, and there was a conflagration.

The other thing is that in terms of our case report, our first patient was in a Lilly-sponsored trial that we reported. The interesting thing was, her Hamilton Depression Score, item 3, was completely insensitive to the change. She started out with a 3, because she had some very, very mild suicidal thought. She basically thought for about three seconds that she wanted to take all her pills, said it was foolish, and went no further.

Then, during the course of treatment, it became obsessive and unrelenting, but it still scored a 3 -- it did

not go to a 4 -- and an earlier one was lower than that. If we looked at most of our cases, that would have been the way they went. So the Hamilton item itself is not a great fine screen for suicide; it is a very coarse instrument. That may be a problem in really interpreting those data.

DR. TOLLEFSON: I would just open it up. This committee has greater expertise than I, but I think if someone only had a mild, transient thought of suicide, many investigators would not have scored that a 3.

DR. TEICHER: But it was.

DR. TOLLEFSON: There is a continuum on the Hamilton in the absence of suicidality to, on the far end, an act, and what we tried to capture in the definition of emergence of substantial suicidal ideation was what I thought your patients had had, and that is the absence or relative absence of ideation, going to a very strong, intense ideation, with or without an act.

I would just add, we did look at other indices. In the international trials we had Dr. Montgomery's scale available. We also used a patient report, the Hopkins Symptom Checklist, item 15, subjective patient report, on the intensity of ideation or on hurting one's self, or thoughts of death. None of those three outcome measures, the MADRAS [phonetic], the Hopkins Symptom Checklist, or the Hamilton, showed any deviant results. They were all entirely

consistent.

DR. LEBER: I have a clarification. I may have missed this, because I was out taking care of some administrative business, but when you were presenting the DAWN mentions from the medical examiners, is there a breakout between those which are overdose completed suicides and those which are violent completed suicides? Obviously, there is an interaction there. The patients are selected for the overdose suicides by virtue of the other type of antidepressant they are using, whereas within the, say, violent type, hanging, shooting, et cetera, that is the group I presume we would want to look at if we were doing any kind of case control methodology.

DR. ZERBY: To my knowledge, that has not been broken out, by violent or overdose. It is just the implication that the drug was involved in some way, but not necessarily overdose.

DR. TOLLEFSON: Although I think one could say that if the patient -- we are looking at patients in that study, Dr. Leber, that, given the safety profile of the drug, they would probably, if they were really truly suicidal and wanted to end their lives, they would have to find a method other than fluoxetine.

DR. LEBER: That was precisely my point, because if I wanted to look at the cause prevalence, if you will (and you

have to adjust it for market share and the time in the calendar year), in the group that committed suicide by a violent means (not the group that overdosed, because that will not give you a sample of fluoxetine exposures), you want to look back among those who completed suicide, correcting for use of drug in that particular epoch in which they committed the suicide, to find out whether there is anything. I do not think that has been done yet. I know that other people have probably thought of the same thing, but I wondered if you had done it.

DR. TOLLEFSON: The DAWN data, as far as the emergency room mentions, of course, focus on suicidality, but the medical examiner mentions are on fatalities and then linkages with antidepressants, so it is not unique to just have drug overdosing as a method of death.

DR. CASEY: Thank you very much. We appreciate your time and your presentations. We now move to the phase of the meeting where the committee will address the questions put forward by the FDA. We are also able to discuss other issues which we bring to the table which we think will be relevant.

COMMITTEE DISCUSSION/RECOMMENDATION(S)

The four questions are:

. "i. Is there credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent

behaviors?

. "ii. If so, does the evidence indicate that a particular drug or drug class pose a greater risk than others?

. "iii. If the whole class or a particular drug cause emergence and/or intensification of suicidality, what actions, if any, should the Agency take?

. "iv. Even in the absence of sufficient evidence to establish causation, do the large volume of reports and/or the type of reports received justify some Agency action, e.g., a modification of labeling for some or all antidepressants?"

I would like to go to the first question, initially: "Is there credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors?" I open the question for discussion by the committee.

DR. HAMER: Like everyone else on the committee, I read all the material very carefully before I came here. I paid attention carefully to the presentations. These data have been analyzed very thoroughly, I think. A statistician, I do not remember exactly who it was -- it may have been John Tookey -- once said, "If you torture the data, they'll confess."

I think these data have been tortured thoroughly, and they still have not confessed. I mean, there have been so

many P values and so few significant ones and so fewer that showed any indication that antidepressants seemed to play a role in attempts or emergent suicidal ideation, I would find a hard time answering "yes" to question i.

DR. CASEY: How about answering "no?"

(Laughter)

DR. HAMER: To answer "no," you are asking me to accept the null hypothesis. Of course, as a statistician, I can never accept the null hypothesis. But I am surely coming close.

DR. MONTGOMERY: There is one important study which has not been discussed today, and that is the study of maprotiline in long-term treatment, a one-year study looking at two different doses of maprotiline against placebo. That study, with 1100 patients in it over a one-year period, has sufficient power to test for the presence of suicidal acts and it reported that maprotiline was associated with a significant increase in suicidal acts compared with placebo.

It is a one-off [phonetic] study. It is the only one I can find in the literature with sufficient power to be able to test it and it goes to some way, along with the report of Soloff, who reported, in a very much smaller number of patients in an acute study, as Dr. Fawcett has said, that amitriptyline may be associated with an increase.

I would take both of these studies as warnings that

the phenomenon may exist for some antidepressants. But I am not in the habit of accepting data on a single study and I would commend this committee to watch this situation relatively closely in the meantime.

The other area of concern is that the benzodiazepines have a labeling for the provocation of suicidal acts in some places in Europe. That is based very largely on anecdotal data but there is a study, again, by Calgary and Gardner, with alprazolam provoking suicide attempts. I would put the benzodiazepines, possibly, in a category which you would need to watch a little bit more closely.

The question you ask, for the data that have been presented today, I must say that I agree absolutely that the data are neutral to positive, that there seem to be less effects than placebo, rather similar to other antidepressants.

DR. CASEY: The maprotiline data, that was a two-dose study against placebo?

DR. MONTGOMERY: Yes.

DR. CASEY: Are the results dose-related?

DR. MONTGOMERY: No, very interestingly, the doses that they chose were very low, 37.5 mg versus 75 mg of maprotiline versus placebo in three equal groups, and the attempt rates were equal in very low-dose and in the 75-mg dose groups, so there appears to be no dose relationship

there. This is an important study, because it found that both doses of maprotiline were better than placebo in reducing subsequent depressive episodes in this long-term efficacy trial. So, therefore, it indicates that suicide and suicidal attempts may be dissociated from the recrudescence of depression. So that is something that is a warning to us that we should carry on looking at these data very carefully.

DR. CASEY: Was concomitant medication allowed in patients in that study?

DR. MONTGOMERY: I am afraid that all I have of the trial is a French publication and it needs to be examined in far greater detail.

DR. LEBER: I wanted to bring out something that Dr. Montgomery just mentioned that I think that we would want to emphasize. The evidence presented today includes not only the evidence from controlled comparisons, but all the other evidence that we heard, some of which is anecdotal, and that is not always inappropriate, because it is possible to conceive of some anecdotal reports as an N of one experiment in which sequences of events are so improbable in the absence of treatment that you conclude that the drug might have done it.

I think we are trying to get a broad answer to this question. We understand that the rates, if they exist (we came to that conclusion almost unaided), are probably quite

low, but does the possibility still exist in your minds as a reasonable one? Do you think there is any evidence on the basis of the reports and anecdotes that you have had and heard about that it does? For example, Dr. Teicher is here for a reason. He was convinced. He is a reasonable man, an academic psychiatrist. Why? What persuaded some of you and not others?

So when you answer this question, I hope you will focus not only on the controlled trial data, which I think Dr. Lieberman pointed out is covering a small proportion of the total time-duration of the average treatment course, and look at all the evidence and see where it is weak and where it is strong. So with that charge added to it --

DR. MANN: In relation to Dr. Leber's comment, what we can learn from the data that have been presented is that patients who are on antidepressants are not entirely free from the problem of suicidal ideation, attempts, or completions. We are dealing here with probabilities and, from a statistical standpoint, the drugs basically seem to be ranging between, as Dr. Montgomery mentioned, neutral and favorable -- some may say highly favorable.

But that still does not mean that there are no patients in whom one finds suicide attempts, suicide completions, and perhaps the development of severe distressing suicidal thoughts. The nature of things being what it is, it

there is an additional need to be careful about monitoring patients who are on these medications and, for that matter, for those who are not on these medications.

DR. CASEY: In relation to that, Dr. Leber has given me an excerpted translation of the French study that Dr. Montgomery referred to. In relation to my inquiry about concomitant medication, it says, "The only possible therapeutic associations" -- meaning those also allowed -- "were benzodiazepine-type tranquilizers, Clobazam, lorazepam, and flunitrazepam." So, once again, we have the complication that the benzodiazepines in that setting make it more difficult to understand the maprotiline data.

DR. SCHOOLER: To come back to question i., I have some concerns about a response to that question, and that is that it is not clear to me that data have been evaluated with respect to these questions for the wide range of antidepressants with the kind of attention that the fluoxetine data have received. Indeed, it is very clear that within the FDA's own reporting system terms dealing with suicide have only been there since 1989. That is one point.

The second is, I found myself enormously touched and responsive to a number of the stories that we heard this morning and, in particular, to the point Dr. Temple raised, I think, that many of these seem to be unprovoked in the sense of having lengthy histories. I guess I would say that the

data from the trials that were presented here, I think, are very convincing as far as they go, but I am not completely convinced that those are all the data that we need in order to be able to say, no, there is no credible evidence to support a conclusion that antidepressants _____ -- you know, complete the sentence.

I guess the question that I would raise in turn would be what would additional data be that we might want to see that would make it possible for me to say the data -- and by that I would mean a wide range of data, not just the clinical trial data -- have been tortured and they have indeed not confessed.

DR. CASEY: I agree, and I think you will probably have a large number of committee members agree. Given the information that we do have, do you feel that -- that is related to question i., and I know you want the caveat that "I don't feel I have all the data," but, on the other hand, we have to live with what we have and we have to make some decisions and give some guidance.

Your last point is really issue number iv., which I think we can have a creative discussion about: How shall we go about addressing issues that are now missing from our information base?

But given the information base we have now, do you feel that there is evidence to conclude that antidepressant

drugs cause the emergence and/or intensification of suicidality?

DR. SCHOOLER: I will go a step further, then, which is that we had a certain amount of data presented here this morning and this afternoon. Then, just a few minutes ago Dr. Montgomery mentioned a maprotiline trial which was certainly not familiar to me -- this is not an area of expertise for me -- but it was my sense that it was not familiar to a large number of people around the table. My question is, is it that we are restricted to the data that have been turned up here today or are we looking more broadly at what evidence there is available?

DR. CASEY: We are not restricted. If you would like to sit on the fence, it is quite fine.

DR. SCHOOLER: For the moment.

DR. LEBER: A technical point: Obviously, data are accumulating. I believe I first heard of this paper this summer when I was a guest of Dr. Montgomery in July. A paper appearing this week in The British Journal of Medicine is going to report on a meta-analysis of fluoxetine and it will cite this particular paper. So this particular paper is not widely known now; it will be shortly. It is available in French.

Are you holding up the BMJ? There we have an illustration of it and you are welcome to take a look. This

is the meta-analysis that does reference the French paper.

The point I was trying to make is that obviously data keep coming in and we keep looking at them and you will iterate toward what you believe is the correct position.

The one thing I would ask about that one single case, though, is you have one thing I guess we would call the experiment-wise error rate. Clearly, we are doing hundreds and hundreds of controlled comparisons. Surely once in a while some will turn out to show a difference that incriminates the drug. I think Stu was making the point that he does not like one occasion of anything: It is not one swallow that makes the summer.

How does everyone else feel about that? Are these types of studies going to be persuasive?

DR. LIEBERMAN: Let me make a couple of comments by way of responding to question i. I think if anything has been driven home today, it is that many more people suffer and die from not receiving medication for depression than are harmed or die from receiving treatment with antidepressant medications.

The question then becomes at what cost is this in terms of adverse effects potential? In terms of the data that we have heard about today and are aware of from the literature, there are controlled data, which is the preferred mode of data, and then there is the spontaneous reporting

system, or anecdotal data. Both have their various limitations.

The controlled data have limitations, maybe, in terms of generalizability and in terms of not extending entirely through the period of risk. Spontaneous reporting system data and the anecdotal or case report data have inherent limitations in them, but reflect the mass of information that is known to date.

Based on both sets, it is hard to say that there appears to be any credible evidence indicating an increased risk for antidepressants inducing suicidal behavior. The most compelling evidence clearly was the very dramatic and tragic testimonials by individuals this morning which have impacted terribly on their lives, and that is hard to ignore. Placing that against the objective evidence that is normally evaluated scientifically, it still seems that there is not a credible basis on which to determine that there is an increased risk of antidepressant drugs, unless the methodology that has been used heretofore to evaluate that -- and it may be that clinical trial methodology is less sensitive to indices of suicidal behavior -- but unless the methodology was greatly flawed, it does not seem to have turned up in a very conspicuous way.

DR. STANLEY: To actually continue on with Jeff's point about the methodology, it has been suggested that

perhaps the assessments of suicidal ideation or acts may not be as sensitive as we would like in some of the controlled trials. As someone who works in this field, we grapple with this all the time in trying to come up with adequate measures.

I see it as a difficulty in general for the field. We are right now struggling with trying to come up with measures for impulsiveness and this poses great difficulty. I think it would not be a bad idea to consider in the future, as part of clinical trials where this issue is pertinent, that some more elaborate forms of assessment, either of suicidal ideation or acts, maybe possibly expanding to acts of aggression of violence, be included.

DR. CASEY: Given that, what is your sense of an answer for question i?

DR. STANLEY: Again, like, I think, everyone here, I was greatly moved by the personal comments of the individuals who have experienced hard times, suicidal behavior and aggression and violence. I try to look at that experience that is reported individually and then go to the clinical trials, which, despite their drawbacks and whatever limitations there are, provide for me, as a scientist, the frame of reference that I feel most comfortable with in judging whether something is real or not above a certain probability.

Even within that context, as far as I could see,

there was no support to say that there is credible evidence of a causal link. In trying to put in context the anecdotal remarks, I look -- because as has been mentioned by a number of people here, they are, in some instances, very complicated cases -- so I try to look at their experience in light of the controlled trials that are in the nondepression sector. For the bulimia, the OCD, and for the obesity, again, I do not see any kind of induction of suicidal behavior, so I do not see that there is a causal link.

DR. LIN: I want to first say that I am generally in agreement with what has been said, especially what Dr. Lieberman mentioned earlier. I think the kind of information that we have been receiving and talking about belong to two areas. One belongs more in the area of hypothesis generation and the other area is more hypothesis testing. Both are important, but in making decisions, we have to rely more on the resource of hypothesis testing that has to come from the placebo-controlled double-blind studies. The evidence that we have looked at so far very clearly indicates that there is no evidence in terms of association between the drug and suicide risk.

However, the case reports are still valuable in the sense that even though they do not point to an increased suicidal risk in the population of more typically depressed patients tested in the studies that have been reported, maybe

the case reports and the results from the surveillance data can be looked at to see whether they point to any more specific hypotheses that could be tested in the future, such as maybe subgroups that may be at high risk that we do not know about.

DR. TAMMINGA: I would continue along the vein that Drs. Lieberman, Stanley, and Lin have been talking. I will try to articulate a "no" answer to question number i., in that Dr. Leber has actually called together a committee of science advisers, and unless you call for our resignation, as was suggested this morning, in fact, I think that the kind of advice you get from a group like us needs to be based on the numbers that have been presented. Clearly, from the data that have been presented, it would be hard to answer anything but "no" to question number i.

But, also, in listening to the personal reports that were given this morning, one would have to think of those personal reports as being either entirely coincidental to the drug treatment or perhaps some rare idiosyncratic reaction to the drug. As I was listening to the stories that were presented, it was hard to understand some commonality of response that would have made me think of a possible mechanism for a rare idiosyncratic response, because there were such differences in the stories that were presented.

It would seem to me that if some rare idiosyncratic

response to fluoxetine or to the other antidepressants is occurring, it would really take a much bigger data base than what we have to make a conclusion on that. So I would give a "no" answer to question number i.

DR. CASEY: Are there other committee members who want to address this? If you do not volunteer, I will ask you about question i.

DR. CASPER: I would want to join the committee members who have spoken by considering the data which have been presented and the data we have available right now on the populations which have been studied, on populations of depressed patients which have been studied. I do not think one could answer the first question but with a "no."

But I want to qualify my answer, because reviewing the literature and the reports we have received and listening to the heart-rending reports we have heard this morning, there are, I think, some common factors which might present themselves as risk factors.

In Dr. Teicher's report, what emerges is that patients were treated despite the fact that their depression did not improve. They continued treatment with fluoxetine. In some of the other reports we have received in the literature, the same has happened.

Now, this is not common in clinical practice and, I would venture, was very uncommon when tricyclic

antidepressants were introduced into psychiatric treatment. We were actually quite careful, and one would, knowing what we have heard again and again repeated today, knowing that depression is frequently and not uncommonly associated with suicidal thoughts, fantasies, ideas, which can emerge, which can disappear, which can reemerge, and cause sometimes suicidal acts -- if one knows this and one treats anyone with an antidepressant, one of course monitors the response. I have been concerned about the therapeutic optimism in trying to continue to treat patients who have not responded with a particular antidepressant.

So I would want to qualify my response in that under proper conditions of psychiatric treatment, and I would also want to mention this again in response to the reports that we have heard this morning, most of the men or women who were placed on fluoxetine I do not believe were really seen in treatment or monitored on a regular basis.

I think under those conditions an antidepressant might be associated with increasing suicidal ideation. I do not think we could at this point say whether it is causative, but we cannot rule out that the agent might not be involved in suicidal ideation, because the depression goes untreated.

DR. CASEY: Dr. Hellander?

DR. HELLANDER: I did not think I was going to get to comment, since I am not a voting member.

I am as hesitant to reach a conclusion on the basis of such preliminary evidence as anyone, and so I will not. I think the Lilly data are obviously very reassuring, although I am very concerned about the issues that we raised about the possibility of selection bias, that what they observed is not really what is happening. I think it is also true that it could be a rare side effect that would not be picked up in their clinical trials.

Also, I guess I am very disappointed today that we have not heard from the three people who have perhaps reported the most cases. We have not heard much from Teicher today, we have not heard from Worshing in Los Angeles about the association of akathisia with desperate thoughts, we have not heard from King and the association of treatment of OCD in children with fluoxetine, possibly with the emergence of some suicidal behavior.

I remain concerned that a small subgroup of people might respond badly to Prozac and other antidepressants and that we are perhaps missing them in looking only at the aggregate effect. Perhaps at this point it is so preliminary -- it has only been a year, I guess, or so since this effect has been suggested. The large data bases we have looked at have been, obviously, from the drug company itself. I guess I would like to see other data that would support that.

DR. TAMMINGA: I think that the committee would

appreciate, Dr. Hellander, your making some of the arguments of those people whom you just mentioned in lieu of their being here.

DR. HELLANDER: Well, Teicher is here, and I would actually really appreciate it if he would have a few moments to talk, because I am very interested in his views and fully expected them to be more elucidated.

But the known side effects of Prozac are very different from the tricyclics. They are anxiety, insomnia, and agitation, some restlessness. In particular, Dr. Worshing in Los Angeles believes that in some patients, he has seen five patients with movement disorders -- he is actually a disorder movement specialist -- who develop akathisia on Prozac and, associated with this restlessness and terrible feeling that they had because of that, can develop some desperate thoughts. It was not like out of the blue they wanted to kill themselves; it was that they were so uncomfortable from the akathisia that they then became sort of desperate and became suicidal. With treatment of the underlying problem of akathisia, for example, with either dosage reduction of fluoxetine until the akathisia disappeared, or treatment with a beta-blocker, they did better. Or else taking them off of Prozac altogether their suicidal ideation disappeared.

That was his hypothesis. Not everybody agrees with

this. I have talked to other psychiatrists who treat a lot of schizophrenics who say they see neuroleptic-induced akathisia all the time and it is not particularly associated with desperate suicidal thoughts. So it is only a hypothesis and by no means confirmed. But that is what one person has observed and it is quite convinced of.

DR. CASEY: Could we save some of these for question ii, because I think we are expanding beyond --

DR. LEBER: Dr. Temple points out that we cannot get to question ii until we answer question i.

DR. CASEY: Watch me get to question ii.

(Laughter)

DR. ESCOBAR: My answer to question i. is clearly "no." But I believe there is a signal. A signal of what, I am not sure. It is not only the very moving testimonials we heard this morning but also the European data that Dr. Montgomery referred to, but also the concern I have about the lack of long-term controlled data we have in this country.

With that qualifying statement, I need to answer "no" to question i.

DR. LIEBERMAN: I was going to comment that although it seems that we are reaching a consensus in terms of general antidepressants and nonevidence to indicate increased risk for suicidal behavior in response to question i., there are lingering issues regarding fluoxetine that are being raised.

I think one of them has to do with not just the issue of suicidal behavior or self-aggressive behavior, but whether its side effects are different.

Clearly, it has a different side-effect profile, but in many respects that is a favorable aspect of the drug in terms of its utility. There may be, also, and this is something in relation to question ii. that might be considered, there may be some unfavorable aspects of its side-effect profile that relate to the major issue before us of aggressive and suicidal behavior, but it sounds like we are sort of moving off the general antidepressants and focusing more on the general clinical effects of fluoxetine.

DR. CASEY: I agree. Dr. Teicher?

DR. TEICHER: I would like to give a different tack on the issue and a different response. The question itself asks if there is credible evidence to support a conclusion that antidepressants cause the emergence. What we focused on, largely, is the scientific numerical data, which asks not does it cause it but is the incidence greater than the incidence on placebo? It is a different question.

I think that the data are reassuring that we have a situation where it is not worse than placebo in terms of the outcome measures that they have looked at and, in some instances -- in many instances -- it is better than placebo. But as Carol pointed out, it does not exclude the possibility

of rare idiosyncratic side effects, particularly in patients who would not have met their inclusion criteria for their clinical trials. That has certainly been my clinical experience, at least my observations suggest that some patients get much worse on the drug.

Now, if we are dealing with rare idiosyncratic responses, these are very hard to pick up in double-blind placebo-controlled studied, especially if we are dealing with incidence. It is hard enough to pick up, in double-blind placebo-controlled trials, efficacy of an antidepressant compared to placebo. Many trials fail to find it. When we are dealing with something which is vanishingly low and comparing it to a spontaneous rate, you are not necessarily going to find it. That does not exclude that possibility.

My way of thinking about it is to think about it in terms of what do antidepressants do and what do we know about suicide? I think there are a lot of different pieces of information that we need to consider. The first, the roll-back phenomenon has been mentioned, or the fact that some antidepressants have a very prominent energizing effect, and that if you have a patient who is suicidal but psychomotor retarded and inhibited in action and you give him this stimulating antidepressant, you may produce an uneven resolution of his depressive symptoms, and he may have, then, the energy to act on his suicidal thoughts.

So in those instances antidepressants can facilitate suicidal behavior, or enhance it. Again, they may be much more beneficial than harmful, but you have one clinical situation in which that can occur.

Secondly, you have the possibility that some antidepressants can produce a paradoxical worsening of depression, the phenomenon reported by Demlugi, where some patients on the medications simply become worse. They become much worse than you have ever seen them in the course of their treatment. You take them off the medication and they get better. That is the dechallenge aspect of it, which lends some credence to its being drug-induced.

If you then have a rechallenge and they get worse, again, you start to add some data that this is a real phenomenon. With the Prozac data, we have data on two patients with rechallenge who developed the phenomenon again. Overall, worldwide, I am aware of eight cases of rechallenge where they have had this effect a second time. Unfortunately, they are not blind rechallenge and blind rechallenge would be much more compelling than open rechallenge. But that is something to be looked at.

So I think that some small percentage of patients can have a paradoxical worsening. I am not sure that defining it as a 50-percent increase in their Hamilton is the way to go, but I appreciate the fact that Lilly looked at it, and

their data, again, are quite reassuring.

Another mechanism that one has to think about that has not been brought up is the antidepressant-induced akathisia. If we look at the neuroleptic literature, a lot of associations have been made in the neuroleptic literature between the emergence of akathisia and suicide attempts or aggressive behavior. Most clinicians believe that, though I do not think it has been looked at carefully in double-blind placebo-controlled studies, but it is clinical lore. Akathisia is a dangerous state and patients in a state of akathisia act in ways that are destructive and dangerous and they have to be really carefully monitored. It is a really dangerous side effect.

We know now that tricyclic antidepressants and selective serotonin uptake inhibitors can produce some degree of akathisia. Conceivably, that is a mechanism wherein at least some patients may be propelled into a state of suicidal behavior or aggressive behavior that they would not have been propelled into just given their natural illness. Again, it is not going to picked up in these comparisons.

Another factor is that some elegant work over the last few years has really pointed to the importance of anxiety in suicidal behavior, the risks of panic and long-term outcome in suicide and short-term suicide risk, or just generalized anxiety. We know that some of these drugs can produce a

worsening or an exacerbation in anxiety, at least initially, and sometimes they can induce panic attacks. You add a panic attack to a patient who is already depressed and that may be the straw that broke the camel's back, so that in those cases you may have patients who go out and commit suicide who would not have committed suicide otherwise. That is another factor.

An additional factor that is important is drug-induced stage shifts. This is a controversial area in psychiatry, where they have looked for years as to whether drugs can precipitate episodes of mania, mixed mania and depression, or produce rapid cycling. The vast bulk of the literature suggests that antidepressant drugs as a class do this, that a substantial percentage of bipolar depressed patients will get switched into a mania or a mixed state or will cycle more rapidly.

We know that the mixed state, in particular, carries a high risk for suicide. It is one of the most dangerous states that a person can be in. Taking a bipolar depressed patient who may be psychomotor retarded, lethargic, not even thinking and concentrating and not particularly suicidal and putting him into a mixed manic and depressive state may markedly enhance his risk for committing suicide. That is another mechanism by which they may do this.

An additional mechanism: The early studies of suicide have pointed out that perhaps the most important

single symptom immediately associated with suicide is insomnia. Many patients take drug overdoses or make suicide attempts because they cannot get to sleep. The original report said do not underestimate the consequence of insomnia. The antidepressant drugs differ markedly in their effects on sleep. Some antidepressant drugs are sleep-promoting; other antidepressant drugs may produce insomnia as a side effect. If you take a depressed patient who is pretty close to the edge and you add to his symptom list insomnia, you may push him over the edge. So that is another way in which antidepressants can render a patient more suicidal.

Let me talk about what we have discussed. We have discussed suicidal obsessions. The reason why I believed, in our complicated cases, that we were dealing with a drug-emergent effect was not simply coincidence, not that they went on the drug and they developed suicidal ideation. By and large these were patients who were well known to us. We had been following them for about six years, on average. They had gone through innumerable other medication trials. We were very familiar with their illness and its manifestation, and the symptomatology that they developed during the time they were on fluoxetine was unlike anything they had experienced prior to or then following fluoxetine.

DR. CASEY: You are expanding onto item ii. more and more, and I would like to be sure that we stay focused to

question i., and I am soon going to ask for a vote of the committee. Do you have some more --

DR. TEICHER: I am trying not to discuss specific agents. I am trying to basically talk about --

DR. CASEY: I hear a lot about Prozac in your comments.

DR. TEICHER: Okay, but that is something I have been looking at. Basically, many of these things did not have to do with Prozac. It is essentially enumerating mechanisms through which antidepressants can produce suicidal ideation. I think we need to hear these mechanisms, to think about them, in order to really give this question fair consideration.

DR. LEBER: I have a point of information, because I think there is a fundamental difference between collecting information and demonstrating in a comparison between two groups under controlled conditions that the incidence of events is different. You, then, on the basis of how much variation, reach the conclusion that one does not seem to be as frequent as the other and, on the basis of some calculations, assume that it is not tenable under the assumption that they are both equivalent. That is how we do establish causality.

You suggest there is another road to the truth. I am not sure quite how you would do it, but it does not involve making comparisons. Instead, you have been raising issues of

mechanism. If I can conceive of a mechanism, you seem to be saying, and that mechanism might -- you often slip and use the word "can" -- produce an event, therefore, it is plausible and possible, and I agree with you, it is.

But we are engaged in a public discussion where evidence is what is persuasive, and I ask, do you have the evidence that akathisia, one, induces suicidality, that sleep deprivation induces suicidality? You talk about not being able to test these phenomena in controlled trials, and yet your original report specified very clearly that 3.5 percent of the patients treated in your institution with fluoxetine experienced this phenomenon. Three-and-a-half percent, I might say, is an exceedingly high rate, which in controlled trials of the patients of the sort that would be at McLean would be easily detected.

I am trying to draw out the difference between speculation, which is good for hypothesis-generation, as Dr. Lin mentioned, and evidence that would persuade people in a disinterested way.

DR. TEICHER: I understand your point. Please understand mine. If you will look at broad categories, like change in a rating scale, and find no difference, it does not mean that all the patients on the drug who experienced it were placebo responders or that the drug was inactive or inert. For a lot of this kind of information, what would be much more

useful is blind rechallenge data. A test-retest paradigm would be more powerful in picking this up than the controlled trials.

Now, as far as controlled studies, I was going to cite the Rouen data to indicate that -- to go back to the Avery data, where, if you compare incidence on ECT versus adequate-dose tricyclic versus placebo, you find some interesting differences, that there is a much lower incidence of suicide attempts in patients who are treated with ECT versus adequate dose of tricyclics, or the available drugs at the time. There is a tenfold greater incidence of suicide attempts on tricyclic treatment. It is particularly noteworthy in patients who had no previous known suicide attempts. Those data are there as well.

As far as some data that have been bandied about showing no change in suicidal ideation, that is, the Rosenbaum and Fauva data from my colleagues at Mass General, those data are interesting as well. Those data did not actually have power to pick up the difference between, say, a 1-percent incidence and a 3.5-percent incidence, which were preexisting literature values.

If you pool those data and compare all patients who received fluoxetine as part of their treatment regime versus all patients who did not receive fluoxetine as part of their treatment regime, you get a threefold difference in the

incidence of emergent suicidal ideation, and that difference is significant. Again, it is not double-blind placebo-controlled, but it was uninformed retrospective analysis.

So I think that there are some data. It is plausible and we can get into specific mechanisms and --

DR. LEBER: Again, maybe it would be useful if you would say precisely where these data that show an excess risk for fluoxetine actually are cited or published; in other words, referenced, because that would help us.

DR. TEICHER: I will be happy to show you. May I show you a couple of slides?

DR. CASEY: I would rather not get into fluoxetine and --

DR. TEICHER: No, these are data that are published. This is a reanalysis of the Fauve and Rosenbaum data.

DR. LEBER: I see, the survey. Right.

DR. CASEY: Let us stick with question number i. I would like to offer my opinion -- everyone else has offered an opinion -- and then call the question, form a question for us to vote on.

I do not find from the evidence today that there is credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or the intensification of suicidality and/or other violent behaviors. Given that statement, I share the concerns that everyone else here has

raised, that the way we asked the question so far may not be able to allow us to detect people who are at risk for the very tragic experiences that we heard about this morning.

But given that, which then leads us to later questions, I do not believe there is credible evidence to date to support the idea that antidepressant drugs cause intensification of suicidality.

Dr. Temple has a comment. You cannot resist.

DR. TEMPLE: I cannot. It is a comment and a question. I have heard pretty much the uniform view that there is not such credible evidence, and that has been well expressed and the reasons have been given for it. I would like to make an assertion about that and see whether people agree that this is what they are saying.

The analysis of controlled trials is straightforward: You cannot detect an increased risk in those. That is fairly obvious and seems to rule out a very large risk.

But to reach the conclusion that there is not credible evidence, it seems to me one has to conclude that the descriptions of individual cases by Dr. Teicher and by the individuals who spoke this morning are at least compatible with the natural history of whatever disease they had. That is, you may not know that for sure, but at this point it is not persuasively shown that these events could not have been

spontaneous change.

I just want to be sure that that is what people -- you may tell me that is the wrong question, feel free, but I think that is equivalent to saying that, and I would like to hear that explicitly, if that is what people mean.

DR. CASEY: My response to that is your explanation of not being able to distinguish from the natural course of the disease is one possibility, but another possibility is that we are not able to distinguish other causes as well from the natural course of the illness.

DR. TEMPLE: That is compatible.

DR. CASEY: It is compatible with, but not the sole explanation of.

DR. CLAGHORN: About what illness are we speaking? You know, in a sense, Dr. Teicher is telling us that he has a group of people that he has seen, on average, for six years, who have been nonresponders, who have multiple problems, who have possible physical problems as well, and he observed a phenomenon in those people that we seem not to find in a population we normally think of when we talk about the depressed population.

His observation may be quite valid. The question is, how would you go about evaluating it vis-a-vis it is almost as if he is talking about an utterly separate and minutely small group. It may be true that if you could

somehow devise tighter criteria for identifying this particular group of people you might find this with greater regularity, maybe 50-60-80 percent of such individuals would have such a response. That would be very, very valuable.

But I do not know that that is the way in which our question is posed right now. Our question right now is posed in terms of the universe of depressed patients as we ordinarily see them, who are really quite a bit different from this group of people. Would we expect this phenomenon to occur with any kind of regularity at all? That is one comment.

The other comment is just the very basic one that, my God, none of these drugs works on everybody. Some of these drugs, no matter which one you use, some people are not going to respond to. I mean, the fundamentals of working with a patient, listening to him, paying attention to what he says and responding appropriately to what he generates as information does not go away because of a statistical analysis. It is just another way of looking at the problem, which does not lend itself -- I mean, it is an experiment of one, it is always an N of one. You have to approach it in terms of making intelligent decisions about some one person.

I think there is a valuable lesson gleaned here about what not to do to certain individuals about aggressive dosing, escalations, and so forth, but it does not really

address question i., which is, in the universe of depressed patients as we normally think about them, does this information answer any questions for us?

DR. CASEY: I will ask the committee to vote on the following statement. It will be a true or false statement, since our usual efforts at voting on efficacy and safety of drugs is reshaped because of the nature of the problem: There is credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors.

Those in favor of that statement, vote yes.

(No response)

Those opposed to that statement, no.

(There was a show of hands.)

And Dr. Dunner has left a proxy, which makes it unanimous at 10 to 0.

The next question is: Is there evidence to indicate that a particular drug or drug class poses a greater risk than others?

DR. LIEBERMAN: I would like to begin by asking Dr. Teicher a couple of questions as a follow-up to his comments before. The mechanisms that you describe, I think, are very thoughtful and plausible in terms of a means by which the pharmacologic effects of drugs might lead to an end point of suicide or destructive behavior. Is it your notion that this

is a hypothesis that might apply to all antidepressant drugs, or specifically to fluoxetine?

DR. TEICHER: I do not know if you even go through all of them. I think that all antidepressant drugs carry some risks. For certain side effects fluoxetine has, perhaps, a higher risks; for other side effects, fluoxetine has lower risks. I think if you slash the pie, you will find that it will vary between class and nature of the antidepressant drug, depending on the side effects that you look at.

DR. LIEBERMAN: With fluoxetine we have a limited experience that we can deal with in terms of when it began to be used in time. With the broad range of antidepressants, we have a much larger experience to look at. Still, within the limitations of the sensitivity of the reporting methodology and monitoring methodology, it would seem that if these various mechanisms were significantly prevalent, that there would be a greater amount of evidence associating antidepressant drugs with suicidal behavior to date.

Apart from the roll-back phenomenon, which is something that is not definitively proven as a bona fide entity but exists as a clinically observed phenomenon -- it has not been proven beyond doubt -- apart from sporadic reports in the literature, there are not large numbers of cases, let alone data from controlled trials which associate standard antidepressant drugs with suicidal behavior.

DR. TEICHER: That is a very good point. I think part of the problem, though, is we really have not carefully looked. I do not think it has been a major academic interest of many people to look at that. I do ask you to look at the Avery data. This is one of the few times it has been looked at. Those data are very interesting. In these patients who were treated with a variety of different treatments, ECT, conventional antidepressants, or neither ECT nor conventional antidepressants, if you look at suicide attempts in the hospital or during six months of follow-up, it was tenfold higher in the group that received antidepressant drugs compared to ECT.

If you look at the group of patients who made no suicide attempts prior to coming into the hospital, there was a higher incidence of suicide attempts in patients receiving adequate antidepressant treatment than in patients receiving neither ECT nor antidepressant. The Rouen data show, again, a higher incidence on drug compared to placebo. So these things may be out there; we really have not looked at it very carefully in these kinds of comparisons.

DR. LEBER: May I ask something? How were patients assigned to ECT versus those assigned to drug treatment? Isn't that a potential biasing issue, that there is a nonrandomized comparison?

DR. TEICHER: You bet.

DR. LEBER: So, then, what can you conclude from the data?

DR. TEICHER: But how do you think it is nonrandom? Do you think that the healthier patients were assigned to ECT?

DR. LEBER: Not at all. I am suggesting that you have a confounding --

DR. TEICHER: Okay, but if you assume that the sicker patients were perhaps at greater suicide risk, then why would you expect to see a tenfold reduction in their suicidal incidence? They are just interesting data. It needs to be done with random assignment, surely.

DR. CASEY: I think one of your earlier comments will surely be an outgrowth of today's meeting and all the other interest in this topic, is that there will be more research. At least I certainly hope so.

DR. MONTGOMERY: May I try and throw some light on this question in a class-by-class way? Take, first of all, the class of 5HT uptake inhibitors. We have one advantage over you in England, which is that we have four different 5HT uptake inhibitors available to us and we have substantial experience with one that was withdrawn, zymeledine [phonetic], and so there is a lot of experience in England.

One of the things that we have been privileged to be able to look at is the possible provocation or not of suicidal thoughts and acts with other 5HT uptake inhibitors. This was

referred to in the presentations today and I just wanted to confirm that I have myself been able to look at those data. They are, to all intents and purposes, similar to the data that you saw today on fluoxetine. So from my perspective, it would seem that the 5HT uptake inhibitors as a class in these analyses on controlled double-blind trials against placebo show more or less exactly the same thing that we have seen here today. So, therefore, I would conclude that as a class the 5HT uptake inhibitors are not associated with the provocation of suicidal behavior or suicidal thoughts, taken from the double-blind data.

DR. CASEY: Thank you. I am glad to hear there is only one advantage that England has over America.

(Laughter)

DR. MANN: I want to endorse the need for better data sets to operate from. But using those imperfect data sets that are available to us and playing with the numbers, it does appear that, looking across the tricyclics that are broken out in the poison centers and the toxicology data compared to the new antidepressants such as trazadone and fluoxetine, there really is not evidence, using IMS prescription rates, that one class of antidepressants is associated with more attempts than another class.

However, if you look within those data at the question of if a patient presents to an emergency room having

swallowed some pills, what is the probability of survival, then you certainly do not see a disadvantage for the patients who have taken the newer generation antidepressants; you see an advantage, which is statistically significant.

If anything, the drug that is hanging out there as the most unfortunate choice is desipramine, for reasons that I cannot understand pharmacologically. But if we take Dr. Teicher's approach to statistically significant data, we can predict with some degree of confidence that if you swallow drugs such as the tricyclics, that have significant cardiotoxicity, you are much more likely to kill yourself than if you swallow drugs that do not have the same cardiac toxicity, and that explanation would be consistent with the observation that, controlling for number of attempts, you are more likely to die if you have taken one of the more cardiotoxic classes of antidepressants than the other class.

This kind of puts a different slant on the discussion. It raises the question not only of the probability of feeling paradoxically more suicidal or making an actual suicide attempt; it also raises the question of if you are on antidepressants and you take it, what are your chances of survival?

DR. CASPER: I would like to do something which we are all used to more, perhaps, than answering questions categorically, namely, to generate hypotheses. I would like

to address question number ii. in a different way, because I believe we are talking today about suicidality or suicidal thoughts or acts as if they occur in a vacuum. I do not believe they occur alone; they occur in connection with other phenomena, with other experiences and feelings.

I think we have heard this morning, actually, in the patient reports, a number of events or experiences occurred prior to the suicide in these patients. So I would like to ask the question a slightly different way, namely, do certain antidepressants perhaps increase the risk factors for suicide? Or risk factors for aggression, since we are talking about both these behaviors?

We all know fluoxetine has a very good side-effect profile. Generally, the side effects are fewer than with other antidepressant medications which are usually prescribed. On the other hand, it has the side-effect profile which is not unlike that of a stimulant drug. What we have heard this morning is that one of the side effects is the occurrence of agitation, of anxiety, of panic attacks, and of insomnia.

If we listened to Dr. Fawcett's presentation about the risk factors in suicide, I think we need to keep those side effects in mind. He presented the data -- and I think he just left -- as increasing the risk for suicide. I do not want to leave the impression that I believe that we have data to support this hypothesis, but I think it is very worthwhile

to design a study looking, in a very small, probably, proportion of people who take Prozac and who develop these symptoms, at the profile of these symptoms, whether they develop agitation related to the depression, for instance. We know that sometimes a retarded depression can move into an agitated depression.

But what we have also heard this morning is some developed clear-cut panic attacks and those might be associated with suicide. My suggestion is that these studies need to be done.

I think my answer to number ii. would be that, given our current knowledge, I do not think we have the studies available to say that a particular drug poses a greater risk, but I think we ought to be mindful that a particular drug poses or might create risk factors, which, in the end, might pose a greater risk for a subset of patients which might be minuscule, but is not minuscule, as we have heard this morning, for the families of those patients who have reported. It might be a true phenomenon, but this has not been studied.

DR. LIN: Related to what has just been said, I would like to ask a question about the unit dose of Prozac. A number of people have mentioned that Prozac may cause akathisia and one of the ways that you cope with it is by reducing the dosage. Some reports have mentioned that patients on 20 mg of Prozac have developed akathisia or have

excessive anxiety symptoms.

Because the dosage that is on the market, the minimum, is 20 mg, it may discourage people from decreasing the dosage. I do not know whether this question is appropriate to bring up here for discussion, but it seems to me that if it is in a smaller dosage form, that may be helpful for the clinicians to cope with that kind of problem.

DR. CASEY: I think that is somewhat of a different issue, but you are correct that it is an important area for discussion.

I would like to bring a rephrased question ii. to the committee and say there is evidence to indicate that a particular drug or drug class poses a greater risk for the emergence and/or intensification of suicidal thoughts and acts and/or other violent behaviors.

Those in favor of that statement, please vote "yes."

(No response)

Those against that statement, vote "no."

(There was a show of hands)

It is unanimous.

One can abstain if he would like to abstain. Those who wish to abstain?

(No response)

Zero.

DR. SCHOOLER: The comment I wish to make is that

while I agree that the evidence does not indicate that any particular drug or drug class poses a greater risk, I am not convinced that all of the appropriate data and analyses have been done, and the same kind of issue that Dr. Casper raised that has been the theme throughout these earlier questions, I think that most of us feel like there is a fifth question that needs to be asked at the end, which is what would we like in addition to what we now have. Somehow, for me, the responses to this end up being always with that caveat, at least so far.

DR. CASEY: Yes, I think that is a common theme that has come up today.

DR. TEICHER: Could I make a comment, please?

DR. CASEY: Can you make it a brief comment?

DR. TEICHER: I will make it very brief. I should have said something before, but I know it would not have changed the vote. But let me give you a completely different response. In terms of is there a class that may have a different effect, there was an hypothesis put forth by Burstein and Jackish that selective noradrenergic agents would have greater risk for this roll-back phenomenon by energizing patients more and suppressing serotonin, and Montgomery criticized the hypothesis very roundly and presented some good information.

But there have been data that have come up since then to suggest, one, in the one study where there is perhaps

differential data regarding placebo, that maprotiline is worse than placebo, that if you look at the coroners' data here, desipramine and nortriptyline are of higher incidence than the mixed amine inhibitors, and that if you take the Great Britain data from coroners and correct them by the toxicity of the data, the LD50 divided by the therapeutic dose, you find, also, that the noradrenergic drugs come out way on top.

So at least in terms of who winds up in the coroner with it in their blood stream, there may be some data actually pointing to noradrenergic agents which probably should be studied.

DR. CASEY: We certainly agree with the last comment.

DR. MONTGOMERY: May I make a request?

DR. CASEY: You should at least have a chance to respond, since your work was commented on.

DR. MONTGOMERY: I have published a paper which contradicts my previous stand. I now do believe that noradrenalin uptake inhibitors probably are the group that are likely to provoke suicide. What I would like this committee to ask for -- not today, because it is impossible -- is that the same analysis that has been done with the 5HT uptake inhibitors should also be requested for these other drugs to see if there are some data present in those companies to help to elucidate this.

It does not change my position, which is, I do not believe that there are sufficient data yet available from controlled trials to alter the position, but I think the hypothesis now stands and I think it is fair enough to ask questions specifically to it.

DR. CASEY: Thank you.

Given the situation as we have it, with the limited data that we have, balanced by the personal reports in the first half of today, what advice can we give the agency as to what they should do? I do not mean which studies should be designed, because that really is more properly done in a conference that is set up specifically to do that and will take, probably, a few days to do. It is a very important question.

But given what we have, what do we recommend to the agency what they should do?

DR. HAMER: Are we on question iv. now? We sort of skipped iii., because --

DR. CASEY: No, iii. and iv. belong together. I propose to put iii. and iv. together and try to give some sense of direction from the committee's recommendations and advice as to what the agency should do. We have options all the way from nothing to recommending withdrawing the compound immediately, or something anywhere between those.

DR. LEBER: Change labeling is probably --

DR. CASEY: Well, change labeling is in the middle.

DR. REGIER: I think one of the questions that comes up, now that we have dealt with some of the scientific evidence, is the issue of good clinical practice, and is there anything that the FDA should do to assist with good clinical practice? As has been said, for none of these disorders do we have perfect response rates to any of these treatments.

I guess the question would be, if a physician is in Dr. Teicher's shoes and a patient comes in who has escalating suicidal ideation, regardless of his diagnosis, do you simply say to yourself there cannot be any causal link between the medication and these symptoms and, therefore, I will continue to push the medication higher and higher in order to finally break through this depression and get to a therapeutic response?

The way it has been phrased so far, the emergence of suicidal thoughts may, in fact, be a representation of a continuation of the illness. However, from a clinical standpoint, what it may mean is that the illness, then, is not being appropriately affected by this particular treatment, and one would do well to cease at a given point and to withdraw the patient from a given medication.

The question, then, is, if we do not have a causal link to the emergence of either suicidal ideation or increased agitation or violent behavior, if that behavior does emerge in

the course of treatment, is there something in the PDR that should advise individuals to be cautious, that this response might benefit from a trial with a different medication or a different type of treatment?

I think that is the clinical question, whether or not, in fact, there is something that would be helpful to the practicing physicians that we might draw from the anecdotal experience and from the clinical experience that we have had today.

DR. HAMER: It perhaps is a little pompous of me as a statistician to comment on clinical practice of physicians but, on the other hand, since physicians have never hesitated to tell me what to do about my statistical analyses --

(Laughter)

-- it seems to me that, given the clinical practices of physicians with whom I have worked for many years, that if a patient comes to you and says, "I feel awful, I'm panicking, I'm going to kill myself, something terrible is going to happen," good clinical practice would be to listen to that and maybe take some action upon it.

It seems to me that that is sort of advice we have just been given by two people, at least, and that is entirely consistent with good normal clinical practice.

DR. MANN: Given the vote of the committee on the first two questions, in my personal view I think that it would

be difficult to move from there to take any action in terms of labeling and so on, withdrawal of the drug or drugs, and certainly it would be difficult to, say, withdraw one drug as opposed to another, after having decided that there is no real difference between one drug and another.

I think, however, there are a lot of clinicians out in the field who are wondering what to do and what to make of the situation. At the risk of reducing the forest of the U.S., I think it is worth sending some information to the medical profession indicating where this committee arrived at in its conclusions and to remind them of their responsibility as clinicians to do precisely as was just suggested, to listen very carefully to what their patients are telling them (as they are no doubt doing anyway) when they are treating them with antidepressants for depression, to monitor closely the fluctuations in the severity of the depression and the suicidal ideation, and to act as they would normally have done, size up the situation, change the dose, change the drug, change the patient's setting from an outpatient to an inpatient setting, as appropriate, and, in the meantime, we will try and develop better methods for finding out what is going on.

DR. CASEY: Would you change labeling or would you prefer to send out a "Dear Doctor" letter?

DR. MANN: I think a "Dear Doctor" letter seems

appropriate, since there are inclusions already in the labeling that address these very areas, and what we are doing is really placing those existing components of the current package inserts, we are reminding physicians of where they fit into the current picture.

DR. CASEY: There was recently sent a "Dear Doctor" letter. Should another one go?

DR. MANN: After the deliberations of this committee, that would be an appropriate action.

DR. LEBER: I want to point out a little bit of background. There has always been a tension between using labeling as a place to provide a comprehensive rich enumeration of facts about the drug and the use of the drug and the other side of the coin, which is exhorting physicians to good practice, turning labeling into a place to instruct physicians and practitioners in the arts of medicine. That is a very difficult road to travel, because in one breath you are almost on the verge of telling people to be prudent, be wise, do the right thing, and yet you do not have the informational base on which to tell them what to do. You alert them to the difficulty of their situation, which anyone who has practiced medicine knows what is like. There is great difficulty with one of these patients, because they do not know what to do.

You tell them what they already know, but you have no concrete recommendations, no conditional probabilities,

nothing. You can postulate that it is akathisia, insomnia, the noradrenergic tone, the time of day, circadian rhythms, interactions with -- and yet you hesitate to do that, because you could be wrong.

So the question is, where do we want to be? How does the committee as a whole feel about this? I know that there will be a part of the community, no matter what you recommend, who is going to disagree with you. That is my bet.

DR. CASEY: Dr. Laughren pointed out that we do not have to establish causality of something to have some issues raised in the labeling. Because of our first two votes we are not prohibited from making suggestions regarding labeling.

From my point of view, I sense that my answer to Dr. Stadel's presentation this morning is that, yes, there is a signal there. The problem is, what does the signal mean and how do we read it better than we have been able to read it so far? One answer is through more research. Another answer, another possibility, that will somewhat disagree with my professional colleagues this morning, is that I am not sure they have the evidence to convince us that if you change the labeling or increase the warnings that you really do scare people away from treatment. They presented it as if it is fact, and I am not sure that that fact is any more established than any other issue that was raised today.

I would not be so troubled by the possibility of

relabeling and possibly raising in the labeling the question that this issue is not yet fully answered to our satisfaction, that the data so far do not identify special patients at risk but good clinical medicine suggests that vigilance is in order and actions should follow vigilance, however the agency chooses to word that more specifically.

DR. TEMPLE: A very important consideration in what you do to therapy is whether you think that should be a general warning for antidepressants or for a particular drug. Which did you mean?

DR. CASEY: I would like to think about that for a minute, while someone else --

DR. TEMPLE: While you think about it, it clearly has the potential to influence therapy if you single out a particular drug for a comment of that kind, unless you mean to do so. It is okay to influence therapy, if that is what you were trying to do, but the presence of a warning -- dark print or otherwise -- on one member of a group and not on the others carries a fairly clear implication that this is something to think about with one of the group and not the others. So one does need to address that.

DR. CASEY: I have had enough time to think. I think it is more likely to be a class issue than a specific drug issue, because I do not think we have adequate information on the other antidepressants besides Prozac, in

general, or the serotonin uptake inhibitors, specifically, but I can see the hands are raising quickly, and there are other opinions to express. I just wanted to start with that one.

DR. ESCOBAR: I agree that the signal is there and I agree with you -- I mean, I would not object to doing something to the label. In fact, the signal is there to such an extent that, as a clinician, if I were going to be facing tomorrow a number of patients who have some of these features, I would think twice before I did something. I think it is just fair to move that forward a warn the practitioners.

DR. TEMPLE: What are you warning them about? I do not understand how that fits with numbers i. and ii.

DR. CASEY: How can we raise the concern to our colleagues that there may be something there, after we have just said that we cannot find in the evidence that there is something there? I think the spirit to reflect is that the evidence so far does not give us clear evidence of an increased risk of suicidality but there is a concern that the issue has been raised -- you can state the issue has been raised, that there are not yet complete answers.

DR. TEMPLE: Is what you want to convey to people that time -- at least shortly after therapy is initiated is the time to be particularly careful, whether because people are not better yet or because of other phenomena, and that great attention should be paid to the patients, or something

of a general nature like that?

DR. CASEY: I do not think it is a time-specific issue, but it may be other risk-factor-related issues, a failure to respond, those kinds of things, after adequate drug exposure, whatever that is.

DR. LIEBERMAN: I think that we voted on questions i. and ii., indicating that no credible evidence existed to associate increase for suicidality in antidepressant drug use in general, and then in connection with fluoxetine in particular. Because of the limited amount of information with fluoxetine, I, for one, felt a little less confident about the certainty of the decision with regard to question ii. than question i., but, nevertheless, on the weight of the evidence, that is how we concluded.

In terms of what should be done, given this situation, I think that what remains of concern to me, and to the committee, I presume, is the fact that fluoxetine is still relatively new in terms of our experience. We are still learning about what the full extent of its clinical properties are, and there is this troubling number of cases that Dr. Teicher and others have described, and we heard described in vivid detail this morning, that make this a greater concern.

The question then becomes how can we respond to that in a way which will be useful in the guidelines of the FDA mechanisms? Dr. Mann raised the issue of a "Dear Doctor"

letter. One has gone out. What would another one do and what should it state? I am not sure. I mean, I guess one thing that could be done is to, at this point, dispel the controversy to the extent that the committee's deliberation can do that, by indicating what the outcome of their review has been and, at the same time, also noting that despite the fact that we feel there is evidence for increased risk, there still is the potential, given the limited amount of information and the existence of a series of case reports, which warrant concern.

Beyond that, the other thought that came to my mind was that it would clearly be of importance to have the opportunity to verify any additional cases that may come to light through the spontaneous reporting system or to the pharmaceutical company subsequently in terms of obtaining additional information to verify the association between fluoxetine and the adverse behavioral reaction.

With clozapine I know that when the issue of agranulocytosis is discussed then there has been an increased effort to try and verify the legitimacy of cases that have been reported. Whether something comparable might be done here, I am not sure.

DR. CASEY: Dr. Lieberman, I am a little confused about your recommendation for a "Dear Doctor" letter but not a recommendation for a labeling change. I am not advocating

either, but if you feel strongly enough the need for alerting physicians to the possibility of a linkage in a "Dear Doctor" letter, why would you not propose something a little more permanent in nature like a labeling change?

DR. LIEBERMAN: I am not recommending a "Dear Doctor" letter. I was commenting on what Dr. Mann had raised, because there was a question of what would the purpose and content of it be. What I wanted to state was the fact that although we felt that there is no credible evidence that there is, because of the limited experience, still, the potential for concern and continued surveillance, how could that be effected? The major way in which I was speculating it might be was through the spontaneous reporting system and seeing if there were ways of obtaining additional information beyond what goes into the data base ordinarily.

DR. LEBER: There is an important thing that I would like to point out, that Jeff is using the word "limited" information vis-a-vis fluoxetine. It is true that the duration of marketing of the drug is short compared to that of the tricyclics and the monoamine oxidase inhibitors, but that is not the only thing that deals with informational content.

In terms of the volume of subjects entered into rigorous controlled trial, actually there may be a relative excess of data on fluoxetine compared to the drugs that were developed in the 1960s and the 1970s. You have got to be

careful about that. I agree that we may not have all the evidence that you want, but you are sort of establishing as a fact that there is a relative paucity of information about fluoxetine, and I am not so sure that is true -- certainly in terms of experience and reports in the anecdotal literature -- but for imipramine, for example, just to pick on a drug that was recently marketed here, it had a long-standing history of very high risk of seizure that was never emphasized, yet it was well known, I believe, throughout the U.K.

There are things that are out there about those drugs that are not necessarily appreciated and never detected in the controlled trials, because they were not subjected to the same level or intensity of scrutiny. Where is this information going to come from to resolve the matter?

I become concerned at this point that we are sort of in the situation where we have heard only part of the evidence. You here have candled fluoxetine, it has been the focus of intensive speculation and interest, and then we have all these other areas where we have not systematically done anything with the same degree of intensity.

If you now move and make a statement, you will have effects. You may displace people from the use of fluoxetine to other drugs about which you know less, not more. That has consequences, and I would want the committee to face that

possibility -- at least address it (I am not telling you where to come out). But be aware that no action is unaccompanied by some reaction, I think, is an old physical principle.

DR. LIEBERMAN: Let me finish staking out my position, which is that, in terms of the labeling change, I do not think that is the appropriate action to take.

DR. CASEY: Thank you.

DR. MONTGOMERY: I wanted to make a small point. You have voted on these two issues and I was surprised by the unanimous nature of the vote. You totally agreed that there is no class phenomenon, that the thing does not exist. It seems to me, therefore, very difficult to do a labeling change on the one set of data that you have got the best evidence from that you will get, that the 5HT uptake inhibitors have been subjected to very thorough examination on this specific issue.

The questions we have been looking at elsewhere that are much more indicative of some labeling change it would be much harder to get those data for, and it would seem to me that if you are going to go for labeling phenomena, you must do it for all antidepressants rather than to pick out the group where we have got very reasonable data that they are okay.

I would have thought myself that it is going to be very difficult to do labeling that does not undermine your two

previous decisions. The only sort of labeling you could have would be advice to physicians.

In the U.K., our licensing authority would eschew this argument completely, because we do not advise physicians. We simply license the drugs. We have to back away very much on how the drugs are going to be used by physicians, once they get them into their hands, and we know perfectly well that they use them in somewhat peculiar ways, in doses outside the recommended ranges, in conditions that we do not approve of, and that is their decision. But our licensing decision in the U.K. would simply say it is for this indication.

We have in this indication some warning or not. We have examined the data today and the evidence is fairly clear-cut that we have not got enough data in our hands to say that there is any credible evidence that antidepressants are associated with it or that there is a class phenomenon.

DR. STANLEY: If I could comment briefly, I agree with Dr. Montgomery on the point. It seems that once we have settled the issue of questions i. and ii., which, as I see it, were based largely on a review of the controlled clinical trials, then you move to the question where you collapsed iii. and iv. together and, as Tom mentioned, you can hold out the possibility, still, for a change. That seems to be based more on the case vignettes that are either published in the literature or information that we heard here this morning in

this room.

The thing that impressed me, and I think it was mentioned by other panel members here, is the tremendous amount of heterogeneity of the individual cases that were, again, either published or presented here. I do not necessarily agree that there is a signal. I am not sure. But with such a heterogeneous clinical group, I do not know how you could go ahead and formulate any change in labeling. I do not know what direction you would take.

Just a note on the clinical cases that were reported here. As a nonpsychiatrist and nonbiostatistician, I am probably best qualified to comment on clinical care.

(Laughter)

I have to say that in many of the cases that I heard this morning, I was frankly very appalled by the lack of clinical care that some of the patients received, whether they were getting Prozac or anything. It just seemed to me a very bad level of care, somebody walking in with a rash all over his body and being sent home. Anyway --

DR. CASEY: I would agree with you about the last comment, some of the care people were receiving this morning. If we would put on the fronts of the PDR or on any other journal that we would be sure that would be read and heeded, we would say to the patients, "Get yourself a good doctor," and we would say to the doctor, "Be a good doctor." But I do

not think that will help.

It really is very important that people feel free to ask their physicians many questions and to be probing and not to be in the position where they feel they just must accept what they are told or that they must take what they are given without question.

DR. TAMMINGA: There are a number of us who are formulating positions different from our chair, but taking that risk, I would also -- it would be my opinion not to address the problems that we are discussing through a labeling change, but through some other mechanism, particularly since the field must be hypersensitive now and a labeling change might have even an exaggerated effect, given all of the publicity and questions that have been asked, particularly about fluoxetine.

Given the possibility that was generated in my mind this morning from listening to people outline their experiences with the drug, accepting the possibility that there might exist some rare idiosyncratic response to fluoxetine, what mechanisms does the FDA have already in place that would allow something like a periodic review, or does one just leave that to the field to come up with through articles like Dr. Teicher's article and things like that?

DR. LEBER: We have a continuous review process going on. As I said in my opening remarks, the fact that we

are having this meeting at this point in time does not mean we are suspending our surveillance operations or dropping negotiations with the sponsor. In fact, we will continue doing what we ordinarily do.

The question that is before you is -- there are two types of labeling changes. One labeling change is specific to fluoxetine. The other, as Dr. Temple pointed out, is a general labeling change for all antidepressant drug products that might provide more of the, I would say, educational exhortatory detailed response to what it means to be a good physician. There is a tension. There is. It is the do what is right, prima non nocere type thing, "think drug if things go wrong," all the other things.

What it cannot do, unfortunately, is tell you what to do when things go wrong. But it can certainly commiserate with you and urge you to think about it. I do not know how to write that. I hope I do not get the job.

DR. CLAGHORN: I think there is a feeling that most of us have, as everyone has talked about, the patients' descriptions, and so forth, that somehow we do not want, albeit we lack a level of evidence that gives us a sense of certitude and would move us to take some sort of drastic steps, to find some way to alert people who are not as attuned to this kind of information as this group is.

I have scratched a very simple short paragraph which

I intended as something that might be said about every antidepressant, whatever it was, that would go something like this. In a small number of patients, depressive symptoms have worsened during therapy, including the emergence of suicidal thoughts and attempts. Surveillance throughout treatment is recommended.

It is a very generic kind of statement that says, hey, keep in mind that not everybody who gets these things gets better. Some people get worse, some people get a lot worse. Pay attention.

DR. LEBER: Would you go so far as to suggest that, in fact, the drug may be causally responsible?

DR. CLAGHORN: Oh, no, not at all.

DR. LEBER: Any drug? This is a generic statement.

DR. CLAGHORN: Absolutely not, and the statement does not make any assumptions as to what is going on. It simply says this phenomenon does occur: People get worse even though you are treating them.

DR. LEBER: We almost have that in labeling now. Suicide, "the possibility of a suicide attempt" -- this is in the "Precautions" section -- "is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions of" -- (fill in the blank) -- "should be written for the smallest quantity of capsules

consistent with good patient management in order to reduce the risk of overdose." Now, that is already generically in labeling.

DR. CLAGHORN: The only difference would be to include the statement that sometimes people actually get worse in the course of that therapy and may -- blah, blah -- but you are right.

DR. LEBER: This becomes a critical point. You do not want to suggest that the drug might be responsible, because that would lead to shifting, possibly, to another drug. So you might want to open the door on that or not open the door on that.

DR. CLAGHORN: I think we just say we do not have any evidence for that.

DR. LEBER: Well, you are raising the possibility that it might. If patients are worsening, it is either the disease -- what is the implication for the reader if the prescriber is faced with that point?

DR. CLAGHORN: I am being atheoretical --

DR. LEBER: But you are asking them to make an inference, and I want to see if the inference could be anything other than the consideration that possibly the drug did it.

DR. CLAGHORN: We do not believe the drug caused it.

DR. CASEY: Yes, there is another inference, and

that is, this medicine is not helping this person. It does not necessarily mean the drug is doing it; it could mean it is failing to provide benefit.

DR. HAMER: And, also, his recommendation was for all antidepressants, not for a specific one.

DR. CASPER: I would like to support our chair's position and wonder whether really recommending a labeling change would be so inconsistent with saying there is no evidence right now that antidepressants or particular antidepressants is really related to the emergence of suicidal ideation.

I think we need to consider whether the phenomenon we have heard about today is a real one and is one which needs to be studied. I have said I believe, from listening to what we have heard this morning, it needs to be studied further. I think there are two ways to do this. One is to design controlled studies and do the appropriate studies, which will probably take another five or 10 years before they are fully completed and analyzed.

Another would be to raise awareness, especially in our colleagues' minds, and give them the information in a very general way which is available to us, namely, the patients need to be -- and I would suggest, perhaps, in very general terms -- after the initiation of antidepressant drug treatment, the patients' symptoms ought to be closely

monitored, and perhaps say something about in the case of worsening of symptoms the patients need to be reevaluated.

I do not know whether another antidepressant drug would be the right step. I think the patient needs to be reevaluated if the patient does not get better. There might be another reason why the patient does not get better; the patient might have an organic brain syndrome. We do not know.

I would speak in support of the labeling.

DR. HELLANDER: As far as the current labeling, I think one thing that is important is it really does not address the issue of people who are taking it for other reasons than depression. As we have heard today, a lot of people are taking it for weight loss, smoking cessation, mild mood disorders, eating disorders, everything under the sun. So if you only talk about the proper treatment of depression and closely monitor your patients and there might be some emergence of some suicidal symptoms related to their underlying diseases, well, then, you miss a third or so of patients who are currently on Prozac who might be susceptible to some adverse reaction of the drug.

Another thing I want to point out, and one of the reasons that we wrote for a labeling change, although we were ourselves very concerned about possibly people not undergoing treatment because they were afraid of what you are warning of or of restigmatizing depression, because so many people say,

whatever drug it is, "I was not told that there were possible side effects" -- I think today we heard that 10 or 15 times -- "My doctor told me this was a wonder drug, there are no side effects."

Forget about suicidal ideation. They are not even told about anxiety and insomnia. You know, 10 to 15 percent of people on Prozac get these side effects. As we have also heard, these are possible factors that might increase the risk of suicide. It seems to me that there should be something in the label that would let people know at least that this committee still has some concerns and that they can find that for themselves, too, that they are not -- I am not saying this as well as I wanted to.

If you sent out a "Dear Doctor" letter, I think one of the topics of it should also be that this meeting has not cleared Prozac or any other antidepressant and said we have no concerns about it, we are completely convinced nobody has a bad reaction to it. In fact, people have expressed that we are concerned about these reports, we do not quite know what to make of them, we have heard from the public, things are going on, we are not quite sure what is going on, we would like to know more.

I think what is going to happen is, you know, you are so unanimous on those two questions that there is a possibility that this will be conveyed as, well, you know,

everything is over, the controversy is resolved.

DR. LEBER: I have one concern, however, Dr. Hellander, that you also are putting your spin on what has gone on in this meeting to this point. It seems to me that if you were to read the record so far, all credible sources of evidence fail to indict. We have all said that the failure to have, if you will, compelling evidence of guilt does not in itself prove you guiltless.

On the other hand, people's lingering doubts do not translate into a specific indictment of fluoxetine. As a matter of fact, one of the controlled trials indicts maprotiline, if you want. The others are speculations.

One of the concerns that I think we have to address is what are you going to get into labeling? Who is going to send this "Dear Doctor" letter? Is it going to be Eli Lilly or all the manufacturers who market drugs? What is the topic going to be? What kind of advice are we going to give? What is the truth?

One of the things that I would hope this committee could decide is one simple set of dichotomies: Should there be a labeling change, yay or nay, and if you recommend a labeling change, will it be specific to fluoxetine, yes or no, and if not, should it be general? I think at least give us that much direction.

How people will interpret the dicta from this

meeting is going to be a function of what they probably believe, to begin with, where they want to go, and the usual things given to how people read these kinds of transcripts. But I think the record of votes at this point really suggests nobody found anything. They simply are acknowledging the possibility that something may be there, but that is true of everything. Something may be there for every drug out there, and that is what my concern is. It is sort of a no-win situation for Prozac, because it has been in the public eye and people have accused it and, therefore, it may be guilty. That is certainly true, or it may be, but there is no compelling body of evidence. We do not know what to do.

I would like you now to give us some specific recommendations on how to deal with this.

DR. LAUGHREN: Several committee members have expressed concern about a physician who tells a patient at the outset of treatment that this drug is without any side effects. It is not clear what one does to improve the behavior of a physician like that through a labeling change.

DR. SCHOOLER: I think that what we are hearing in the conversation now is a sense of malaise, possibly induced by the time of day, but I think more likely induced by the fact that we are not completely comfortable, and the question is how to deal with that discomfort. Some of the discomfort, which has been expressed with great articulation, is, I think,

that people are concerned about the quality of medical practice that they have heard related here.

One would like to believe that these are the extreme, extreme cases and that the reason these cases have been as dreadful and as unfortunate as we have heard has been in some measure due to the fact that the quality of the practice was as unusual as the quality of the outcomes appear to be when we relate these outcomes to the kinds of general, more scientifically based, perhaps, data that we have heard.

My concern is that the kinds of issues that have been raised as concerns are not going to be redressed by labeling, because they really are concerns that have more to do with do a better job, pay more attention, listen to the patient, if someone does not improve after four or five weeks, think about why that might be, and so forth.

The only answer that I can find for myself is one that I think Dr. Casper raised, which is, we really do need to obtain more data. In fact, we probably have more data about fluoxetine, as Dr. Leber suggested, than about most other drugs. But we really do need to know more about these drugs generally in studies that focus fairly specifically on issues of suicidality and suicidal thought.

At one level, you have to think that it is a fairly sorry state where we are picking one item from the Hamilton Depression Scale and one item from the Symptom Checklist 90 as

indicating what we are going to find out about suicidality, and that the item from the Hamilton Depression Scale is one with which I think many of us might quarrel with the labeling of the anchor points, much less other issues.

It seems to me that it is not clear that the concerns we are expressing can be resolved by labeling, although they are very real concerns.

DR. CASEY: Would you recommend a change of labeling?

DR. SCHOOLER: No.

DR. MANN: A couple of quick comments. The first is another argument in favor of the "Dear Doctor" letter and that is that following this meeting I would much rather see the conclusions drawn here summarized by the FDA and distributed to the American medical profession rather than by the various drug companies. I think that is a very critical point. It allows the agency to place its more impartial view on the table in front of medical practitioners before the drug company representatives get to them with their own version of what happened here. That is point number one.

Point number two relates to the question of the discomfort that the committee has felt about the data availability. There are 32,000 to 33,000 suicides reported in this country every year. That means in two years more people die from suicide than died in the Vietnam war. That is a

major source of information that could be tapped by this committee and other related committees.

For example, I think it would be valuable for us to know which of these patients was taking what specific antidepressant and the next time a committee like this has to convene, those kinds of data will be available.

DR. CASEY: I would propose that we address our malaise with a few specific questions, as Dr. Leber has asked for. I will ask the committee to vote, first, on the issue of should there be a labeling change in general.

We will take it in two questions. First, the general question, and then the second question, whether it should be specific to a compound or class.

The first question is, should there be a labeling change? Those in favor, vote "yes."

(There was a show of hands)

Three.

Those against?

(There was a show of hands.)

Six.

Abstaining?

(No response)

None.

The next issue, I think, is specific only to those three who voted "yes" on the first question.

PARTICIPANT: A minority vote.

DR. LEBER: That is fine. That is getting their opinions.

DR. CASEY: For those who think a labeling change should be considered, should it be for the class of drugs? Those in favor of a class of drugs, vote "yes."

(There was a show of hands)

Three out of three.

Those "no?"

(No response)

Good. It is zero.

DR. LEBER: But you still have to ask how many want it specifically.

DR. CASEY: Is there anybody on the committee who feels specific labeling to a particular compound should be addressed?

(No response)

No.

DR. SCHOOLER: The one other comment I would like to make is that is that I think Dr. Mann's suggestion that the deliberations of this committee be reflected in a communication that goes to the field of physician providers would be very, very valuable.

DR. LEBER: The mechanism and the content may not be so easily identified.

DR. CASEY: What would you say in it?

DR. SCHOOLER: What we said here today, which has been so well recorded because --

DR. LEBER: Welcome to the committee, Nina, how would you like to join a subcommittee?

(Laughter)

DR. SCHOOLER: Which has been so well recorded by the fact that we have spoken directly into the microphones.

DR. LAUGHREN: Before you take a vote on something like a "Dear Doctor" letter, I would like to hear a little bit more about what you would want to go in it and what you would want it to achieve, keeping in mind that it is a one-shot thing and it does not really have much of a lasting impact.

DR. CASPER: Maybe I could help Dr. Schooler. What has been in our minds is to raise this particular question which we have raised today, and to raise this in other physicians' minds, namely, are antidepressant drugs -- have they been associated with adverse events beyond those described during treatment? Just to raise the question as a question, not as a fact.

DR. LAUGHREN: If you have enough suspicion about that possibility and you feel strongly that physicians ought to be informed about that, why would you not put it in labeling?

DR. CASPER: Oh, I would put it in labeling.

DR. LAUGHREN: Okay. Well, I guess this is addressed to the people who have suggested a "Dear Doctor" letter and do not want a labeling change.

DR. SCHOOLER: I will try to defend that a bit. It seemed to me that Dr. Mann made the case very persuasively -- I am sorry that he had to leave, because I hoped that he would also want to speak to this. The major concern that I had in not being in favor of labeling change was the two votes that we took and I came to believe the decisions that we made suggested that there was not credible evidence, but one of the issues that was my reservation throughout that process was that I felt we were working with half a deck in terms of data, that the best data we had were regarding fluoxetine and we had very, very few data regarding other drugs.

So saying that we are not comfortable with the amount of data that we have, which is a very comfortable position for me as a nonphysician, I do not have to make decisions that may be life-and-death decisions for patients, it seems to me that physicians who do have to make such decisions ought to be alerted about that.

DR. LEBER: I think the conclusion of the committee today is not proven in the sense of the Scottish jury's verdict. It is not the same as not guilty. The problem is that, having reached that conclusion, you now want to convey something of utility and value to the practitioner who knows

he is in trouble because the patient is not responding, not doing well, and behaving atypically. Given our uncertainty, given the lack of knowledge, just what do you say? How do you give advice in a situation that is inherently a dyadic one between the practitioner and the patient? You do not know the facts, you do not have a generic principle: What is it you want to say? Beware, you may be wrong? Beware, you may be raising the dose when you should be dropping it? Beware that things may be going wrong and you perhaps should seek consultation with those more experienced than you?

I mean, there are a lot of possibilities. Beware, hospitalize the patient, this is a signal. That is the problem for us. How do you translate the good intention into something that we could practically do? For the record, we do not issue "Dear Doctor" letters, ordinarily. We probably could write "talk" papers, but even then, as Dr. Temple says, the content of them is what becomes so difficult. Maybe it is worth a couple of minutes trying to find out how, in the context of what I have just said -- what do you want us to say?

DR. LIN: I would not be opposed to the idea of sending out a letter. I think perhaps it could serve two different purposes. First of all, it would serve to communicate what has been talked about here that in some way would be reassuring to the clinicians in terms of the general

conclusion that we have reached today.

At the same time, I think after doing that we can also have a paragraph saying that while there is no evidence, we should continue to monitor the possibility of maybe a very small group of patients may have paradoxical reactions, even though there is no evidence at all. I think that would be a reasonable approach to take.

DR. TEMPLE: That is difficult advice for us to follow. The first part, that is, reassuring people on the basis of the results here, becomes perilously close to Lilly's job, and they can take care of that.

The second part of it fills me with a sense of contradiction. If we did not think -- we could put something, or urge Lilly to put something in the labeling, even if it is not proof positive. We could do that. But the committee has, for the most part, said do not do that. To then, instead of putting it in labeling, where it becomes part of promotion and part of the environment in which the drug will be given and just put it in a "Dear Doctor" letter, a one-shot thing, so it passes quickly, does not make sense. If it is worth doing, then we could do it. But if it is not worth doing, we do not really balm our conscience very much by just kind of passing it quickly.

DR. TEICHER: I guess the one point I was going to make, Dr. Casey, is that the average clinician, when he

encounters a patient having a side effect on medication, frequently refers to the package labeling or the PDR to look and see is this a reported side effect. If it is a reported side effect, he may discontinue the drug or change treatments in some way. If it is not a reported side effect, he may say, no, the medication cannot be causing it, stay on the medication, it is something else.

DR. TEMPLE: They are in labeling now. If that is what one --

DR. TEICHER: No, no, I understand that. But what is going to happen, based on the results of the committee vote, which is a very honest vote that I am happy with, people are going to say it is free of all blame, it is free of all risk, and I think for the committee to communicate in some way that there is at least a small measure of uncertainty and there is a small desire to see more data is useful to communicate to clinicians. It is not absolute, it is not black and white, and it is still in the process of further evaluation.

DR. CASEY: To Drs. Leber and Temple, I think this is an issue that some of us feel more affectively than the kind of thing that you can palpate. We are struggling with giving you language, because we are not yet sure how to say it ourselves.

DR. LEBER: The likelihood is that we will probably,

as is customary, write a talk paper at some point on behalf of the agency which will contain our distillation of the advice given here today. It will probably say what is obvious from the votes, and that people -- reasonably -- remain concerned about the possibility that there are areas of information that we need that we do not have and we will pursue things as we ordinarily do.

Some people will think, of course, that all this accomplishes is once again saying we are not acting when we should be acting, but I think we would probably want to emphasize -- I want to make sure I have this right, that we are not urged to act by this committee. I think that is a very important bottom line on the other side. You did not tell us to go out and do something because failure to do something would precipitate a major -- you know, it is unconscionable or bad for the public health.

DR. TEMPLE: There were several people who thought that some sort of labeling perhaps might be useful. Any time there is a divided committee, we can consider both parts. If people want to write in to us quickly -- soon, that is -- the particular words, we can certainly consider them.

DR. CASEY: From the committee.

DR. TEMPLE: From the committee.

(Laughter)

The possibility of some kind of labeling change does

not have to be ruled out. There was enough discussion so that obviously people could have gone one way or the other, but still it is, obviously, very difficult to know what to put in.

DR. HAMER: I wanted to say, as we listened to the stories this morning, many of which were really heartbreaking and, in my pompous, nonphysician manner, would certainly have to say sounded like bad medical care, I think what many of us were feeling was that we would like somehow to give advice to improve that medical care. That is probably not something that the FDA can do in a "Dear Doctor" letter or anything like that to tell people, "Pay attention to your patients. If the patient appears to be having a terrible time, do something different."

Maybe that is what people would like to see done and there is just no way for the FDA to do that.

DR. MONTGOMERY: I wanted to say my reaction to this morning's presentations. I thought they were terrible individual testaments to the evil nature of depressive illness, that depression is something which people assume is easy to treat, they assume that if they do not have it treated, it will go away of its own accord. It is a very nasty condition, and what I took from this morning was a description by individuals that they had expected that, having started on medication, that it would automatically resolve and it did not.

It seems to me that one of the things that came out this morning quite clearly was that there was a need to inform patients about the terrible nature of depressive illness itself, rather than trying to ascribe blame to a drug or something else. It seems to me that that is what the testament was really saying to us. They were seeking largely to blame a drug, but they were actually describing a very nasty illness, and that is something which I think we should pay attention to.

DR. CASEY: I would agree. In summary, depression is common, it has morbidity, it is dangerous, it has mortality, it is torturing, it is often unrecognized, and often untreated or poorly treated. Given that, you are correct in urging that treatment of depression be improved. There have to be other ways in this country to do that besides through labeling and through the FDA, and some of those efforts are going on.

I appreciate your international perspective in coming as an "outsider" to listen to what we were wrestling with and bringing your advice.

We are getting close to closing. Unless someone has the burning urge to make additional comments, I would like to, first, thank the visiting members of the committee for their efforts, thank the committee members, thank Mr. Bernstein for all his efforts in making this meeting run smoothly -- he has

done a very good job -- thank all the people who came this morning to present, thank the people from Lilly, who have spent a lot of time and effort to bring new information to us. I now bring the meeting to a close.

DR. LEBER: Before you do, we have one other person to thank. Tom Laughren and I, on behalf of the Division and the agency, want to say something about you. This is your swan song and this is your last time to serve as chair of this committee. I think each of us who has had the privilege of serving with you knows what it is to have a good chairman. You have done a fantastic job, you have been fair, you have been straight on, you have done the right thing, and you have kept us out of trouble, and I want to thank you for it all.

(Applause)

DR. CASEY: Thank you very much. I have been with the committee for four-and-a-half years and it has really truly been both a personal and professional very positive experience. It has been very rewarding to work with both the agency and all my committee members over the years. Thank you very much.

We are adjourned.

(Whereupon, at 5:40 p.m., the meeting was concluded.)

C-E-R-T-I-F-I-C-A-T-E

I, D. Gavrisheff , the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

D. Gavrisheff

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