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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION

PSYCHOPHARMACOLOGICAL DRUGS  
 ADVISORY COMMITTEE

DEPT'S MANAGEMENT BRANCH  
 91 OCT - PM 3:35

Friday, September 20, 1991

Conference Rooms D/E  
 Parklawn Building  
 Rockville, Maryland

## P A R T I C I P A N T S

COMMITTEE:

Casey, Daniel, M.D., Chairman

**Claghorn**, James, M.D.

Dunner, David, M.D.

**Escobar**, Javier, **M.Sc.**, M.D.

Lieberman, Jeffry, M.D.

Hamer, Robert, Ph.D.

Tamminga, Carol, M.D.

Lin, Keh-Ming, M.D.

Casper, Regina, **M.D.**

**Schooler**, Nina, Ph.D.

CONSULTANTS:

**Hellander**, Ida, M.D.

'Mann, John, M.D.

Montgomery, Stewart, M.D.

**Regier**, Darrel, M.D.

Stanley, Michael, Ph.D.

Teicher, Martin, M.D., Ph.D.

FDA STAFF:

Bernstein, Michael, M.P.H., Executive Secretary

**Leber**, Paul, M.D.

Temple, Robert, M.D.

Laughren, Thomas, M.D.

**Stadel**, Bruce, M.D., M.P.H.

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## P R O C E E D I N G S

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

1 Nutrition.

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

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

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

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

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

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

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

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

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

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

1 DR. **HAMER:** Robert Hamer of the Department of  
2 Psychiatry and Department of Biostatistics, Medical College o  
3 Virginia, Virginia Commonwealth University.

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

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

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

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

14 OPENING COMMENTS

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

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

24 On the table by the entry are handouts of the  
25 agenda, question list, and roster of committee membership. 1

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

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

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

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

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

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

11 To ensure an efficient use of time in the open  
 12 public hearing the following system will be employed. There  
 13 will be two active microphones. The 50 individuals have been  
 14 granted an opportunity to make a public verbal statement.  
 15 Specifically, the first 50 to apply to the Executive Secretar  
 16 have been arranged in alphabetical order and given an **assigne**  
 17 number. Those with odd numbers will use the microphone at th  
 18 right, those with even numbers, the microphone on the left.  
 19 When a speaker at one microphone completes his or her  
 20 statement or when five minutes elapse, whichever occurs first  
 21 that microphone will be turned off and the speaker at the  
 22 alternate microphone will be asked to begin his or her  
 23 statement.

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

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

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

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

13 (Administrative announcements)

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

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

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

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

11 In order to preserve the integrity of the objectives  
12 of the agenda and to preserve fairness, all members and  
13 consultants are requested to limit any issue discussed to  
14 class action considerations at this meeting. However, while  
15 it is not the objective of the meeting to advise FDA regarding  
16 possible actions that could potentially affect all  
17 manufacturers of antidepressant products, it is possible that  
18 such recommendation could result from this meeting.

19 Therefore, FDA has taken the additional precaution of granting  
20 class action waivers for members and consultants who have any  
21 reported active financial interest in any manufacturer of  
22 antidepressant drug products.

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

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

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

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

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

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

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

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

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

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

23 Thank you for your attention. This concludes my  
24 comments.

DR. CASEY: Thank you, Michael.

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

5 (Administrative announcement )

6 OPEN PUBLIC HEARING

7 MR. BERNSTEIN: Is **Maryles** Allen here?

8 (No response)

9 DR. CASEY: Next will be Burton Appleton.

10 (No response)

11 DR. CASEY: Marian Badovinac?

12 (No response)

13 DR. CASEY: Sally Barrett?

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

22 This story has to do with our youngest daughter,  
23 Jennifer, and our experience with the drug **Prozac**. On Januar  
24 25, 1970, Jenny entered our lives and captured the hearts of  
her mom and dad, like her older sister had. She was a child

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

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

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

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

1 started having terrorizing nightmares, frightening the whole  
2 family with her outcries. Jenny's behavior began to change  
3 dramatically and drastically. She started shoplifting in the  
A stores, a strange and unusual act which we could not  
E 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 --  
1( the second time that she was placed on **Prozac** she secretly  
1: purchased a gun on August 25 and shot herself in the head and  
1: died on August 27.

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

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

1 loved one to use this drug.

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

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

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

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

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

1 please.

2 (No response)

3 Dr. Peter **Breggin**, please?

4 (No response)

5 **Pallie** Carries?

6 MS. CARNES: Good morning. My name is **Pallie**  
7 Carries. I am the Director of the Prozac Survivors Support  
8 Group of Covington, Georgia.

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

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

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

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

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

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

23           I was a different person while I was taking **Prozac**.  
24 I was a zombie. I would sit and stare. I was completely  
25 without emotions. If you can only realize how this feels, no

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

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

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

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

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

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

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

19 My husband stuck by me, my family and friends have  
20 stuck by me. They have seen what it's done to me and it's  
21 just not worth it. I plead for you to just take a second 100  
22 at this drug and see what it's doing. Don't the numbers coun  
23 for themselves? Don't the people here today, average normal  
24 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

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

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

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

18 Before I expand on this point, let me point out to  
19 you that in the last week the Council of Europe, representing  
20 23 member countries in Europe, has, by written declaration,  
21 called for the discontinuance of Prozac in Europe. In Holland  
22 this week an advisory commission for the side effects of drug  
23 started an official government investigation into the problems  
24 with Prozac. In addition, the government agencies in Sweden  
and Norway have refused to register Prozac for sale in their

1 country.

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

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

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

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

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

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

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

14 MS. SHANNON: Lee Ann Westover.

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

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

17 I am the widow of Charles Westover, also known as  
18 Del Shannon. My husband was given Prozac on January 24 of  
19 1990. On the evening of February 8, 1990, he killed himself.  
20 I am told his death was instantaneous, but I believe his cleat  
21 actually began the moment he took his first dose of Prozac.

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

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

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

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

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

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

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

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

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

13 Sharyn DeGeronimo, please.

14 (No response)

15 Susan Dime-Meenan, please.

16 MS. DIME-MEENAN: Mr. Chairman and members of the  
 17 advisory committee: My name is Susan Dime-Meenan and I am  
 18 Executive Director of the National Depressive and Manic-  
 19 Depressive Association. I am here today representing over  
 20 35,000 members who are patients with depressive illness. The  
 21 National Depressive and Manic-Depressive Association is the  
 22 only patient-run organization, membership-based, in this  
 23 country. Through our 250 local chapters we aim to increase  
 24 research, education, and public welfare. We aim to end stigm  
 25 and discrimination against those who suffer from these

1 medical, treatable disorders.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 atrocity.

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

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

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

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

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

23 MR. DONNELLY: In fairness? I'm a taxpayer. I need  
24 30 more seconds to finish.

(The microphone is turned off)

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. CASEY: Thank you. Debra Douglas?

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

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

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

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

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

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

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

21 I had finished my work day at the port for the  
22 cruise line which I have worked for, for almost four years  
23 now, and love working for, met my family at the **ballfield** for  
24 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

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

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

10 I was given a slow schedule of reduction from the 8  
11 mg. "The next day after my release another explosive headache  
12 episode occurred, with the same intensity, out of the blue, a  
13 the first one. I was again rushed to emergency, more tests,  
14 and a longer hospital stay. Again, no real findings other  
15 than the suggestion by the neurologist that these headache  
16 episodes were emotion-related.

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

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

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

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

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

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

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

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

16 As you hear the many stories today, you can see we  
17 are real people, not small percentage numbers of a minority  
18 suffering these silenced adverse effects. Please look at us,  
19 listen to us, take this Prozac off the market until it can be  
20 proven 100-percent free against violent turns in personality,  
21 until Eli Lilly can give assurance that the psychiatrists and  
22 general practitioners that are so quick to hand out this  
23 prescription are aware of all side effects, and information is  
24 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 DR. CASEY: Thank you.

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

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

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

1 reported concern of significant adverse reactions.

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

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

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

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

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

1 and I am substituting today for Ms. Flynn.

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

4 (Mr. Bernstein consulted with officials. )

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

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

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

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

15 MR. FIDELI: Thank you very much.

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

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

1 about the devastation associated with his or her untreated  
2 condition.

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

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

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

5           Some suggest that the side effects are tragically

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

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

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

On behalf of our membership and the millions more

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

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

8 MR. BERNSTEIN: Suzanne Francis, **Sonja** Lovett, and  
9 Mark Lovett.

10 (No response)

11 DR. CASEY: Dr. Burton Goldstein, please.

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

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

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

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

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

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

1 only 20 to 25 percent of depressed patients are treated.

2           The seriousness and high-disability aspects of  
3 depression were cited in another segment of the medical  
4 outpatient studies. Twenty-one percent, or 2400, of over  
5 11,000 patients from nearly 400 medical practices throughout  
6 the country met the criteria for major depressive illness or  
7 severe depressive symptomatology.

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

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

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

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

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

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

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

20           MS. **GUARDINO**: My name is Mary Guardino and I am the  
21 Executive Director and Founder of Freedom from Fear, a  
22 nonprofit organization that is dedicated to aiding and  
23 counseling individuals and their families who suffer from  
24 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

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

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

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

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

A recent survey conducted by Freedom from Fear of

1 245 of its members nationwide found that 78 percent of the  
2 people felt that the media has a great to moderate influence  
3 on public understanding of psychiatric disorders and 69  
4 percent felt the media often represents a sensationalized view  
5 of psychiatric disorders. When asked to give an example of  
6 this, the key incident cited was the media attack on Prozac.

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

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

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

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

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

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

16 (Laughter)

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

19 Melinda Harris, please?

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

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

\_m-

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

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

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

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

2           To watch an 8-inch-long wound about 3 or 4 inches  
- 2 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

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

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

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

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

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

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

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

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

12 No one can bring my father back at the young age of  
13 55, but I can help others live and I can talk about it. I  
14 know my dad would have liked me coming here today and he would  
15 have said, "That's daddy's little girl." No one can justify  
16 the violent suicides and murders Prozac has provoked. This is  
17 a real story, and God bless the people who believe and  
18 understand that Prozac does kill. Thank you.

19 DR. CASEY: Thank you. Shirley Jarrott?

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

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

1 MR. BERNSTEIN: No, we do not.

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

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

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

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

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

12 MS. TRACY: Certainly.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 Looking back, the emotional side effects began  
22 immediately. My wild spending started within a week of my  
23 ingestion of Prozac. I began lending sums of money to  
24 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

1 purchased a opera length black gamma mink coat.

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

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

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

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

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

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

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

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

5 DR. CASEY: One minute, please.

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

13 DR. CASEY: Thank you. Kathleen Kessen?

14 (No response)

15 Ron Klemme?

16 (No response)

17 Bonnie Leitsch?

18 MS. LEITSCH: I am the National Director for the  
19 Prozac Survivors Support Group, an organization consisting of  
20 Prozac survivors and the families of people who did not  
21 survive. I personally have interviewed and talked with over  
22 400 people who have been prescribed Prozac for various  
23 reasons, for weight loss, to stop smoking, and the scenario i  
24 the same. They are free of suicide before they go on the dru  
and when they are on the drug they become suicidal. They go

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

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

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

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

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

7           And if all of this isn't tragic enough, we are  
8 referred to as anecdotal. What does that mean? Does that  
9 mean that the people that died on this drug is not equally as  
10 dead? Does it mean that Sally Padoor, who's grieving the 10Ss  
11 of her son, is not just as grieved? I think not. What that  
12 really means is that we were not in the paid-for studies of  
13 Eli Lilly. We are the real people. Anecdotal are the real  
14 people. This is the people that you have unleashed this drug  
15 on.

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

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

1 3.5 percent, fine, have at it. But the general public does  
2 not want to be that 3.5 percent.

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

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

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

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

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

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

10           Prompt restoration of thiamine to their diet  
11 resulted in a complete improvement of their symptoms.

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

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

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

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

5 DR. CASEY: Would you please conclude?

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

10 DR. CASEY: Thank you. Heidi Lovett?

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

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

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

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

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

18 Counseling was part of his treatment and in April of  
19 1988 Prozac was the other primary component of his therapy.  
20 His physician psychiatrist put him on 20 mg of Prozac twice a  
21 day and that's what he was taking up to the day of his death.

22 Like many victims of depression, my husband was no  
23 stranger to occasional thoughts of suicide. However, he did

- 24 not hesitate to signal the fact of suicidal thoughts to me or  
to his sister and others close to him. Aware of his

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

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

13 Partly because his suicide came so unexpectedly and  
14 partly because we have heard from media sources about a  
15 potential link between Prozac and suicide, I requested an  
16 autopsy and toxicology on my husband. I was, to put it  
17 frankly, extremely troubled and angered by the results. The  
18 toxicology report showed that the blood Prozac quantitation  
19 was at a level of 4100 ng. The reference range listed is a  
20 mere 91 to 302 ng. The blood norfluoxetine quantitation was  
21 3200 ng. The reference range is at 72 to 258 ng. I am  
22 appending a copy of this toxicology report. I mentioned this  
23 Prozac level to my husband's psychiatrist. I did not  
- 24 anticipate his reaction. Upon hearing the level, he said, "My

God, how could it get that high?"

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

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

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

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

20 DR. CASEY: Thank you. James Lucas?

21 (No response)

22 Maria Malakoff?

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

1 husband was suffering a little depression.

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

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

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

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

24 DR. CASEY: Thank you for your comments. Margaret

25 McCaffrey?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10           (No response)

11           Betty Prentice?

12           (No response)

13           Marvin Pulliam?

14           MS. PRENTICE: I'm Betty Prentice.

15           DR. CASEY: Please go to the microphone.

16           MS. PRENTICE: My name is Betty Prentice.

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

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

21           DR. CASEY: Thank you. Go ahead.

22           MS. PRENTICE: I've been off Prozac for two years  
23 and I have to deal every day with not getting a gun or taking  
24 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

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

4 Now my doctor, my psychiatrist, in Atlanta would no  
5 give me my records. I have finally gotten them, but too late  
6 to bring them to show you. Something has to be done and this  
7 is just not -- this is something that's real. My doctor told  
8 me it would be fatal. I moved from Atlanta to Sacramento,  
9 California. He told me it would be fatal if I went cold  
10 turkey and dropped the drug, but I went off of it and I have  
11 a pill bottle here to show you. That was my last one,  
12 September 3rd in '89.

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

18 DR. CASEY : Thank you, Ms. Prentice. Mrs. Frederic  
19 Richardson?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 The investigators had searched the apartment,  
6 questioned everyone who knew him. They already had concluded  
7 that my son lived a clean life. He did not drink or smoke no  
8 did he take drugs. They had overruled a newspaper account  
9 that it was a cult or a prowler or a crime of passion. Their  
10 findings made them more mystified.

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

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

24 DR. CASEY: Thank you. Suzanne Robbins?

MS. ROBBINS: I am head of the Indiana **Prozac**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Depressive Association in dealing with the allegations and  
2 concerns raised.

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

7 As you know well, depression is a serious and grave  
8 disorder. It is a disease that has not only enormous  
9 morbidity and cost to society, but also an important and  
10 devastating mortality as well. We have certainly heard some  
11 very 'sad, troubling, and tragic stories and anecdotes this  
12 morning. We also know that when depression is untreated, som  
13 15 percent of patients will kill themselves, additional  
14 tragedies, and many more suffer from untreated depression who  
15 do not suicide.

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

21 But the treatment of depression, as in all other  
22 medical conditions, is not without some risk. Medications an  
23 psychotherapy can have some side effects, some of which can b  
24 serious, just as can other medications for other medical  
25 illnesses . In addition, there is the possibility that some

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Before I appeared before this committee, I had an

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

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

18 DR. CASEY: Thank you. Harry Samith?

19 (No response)

20 Robin Schott?

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

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

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

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

25 I entered therapy and was pressured into taking an

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

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

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

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

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

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

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

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

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

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

1 and I hope that you heard what I said.

2 DR. CASEY: Thank you. John Smith?

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

5 (Laughter)

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

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

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

1 these medications is adequate and describes potential side  
2 effects.

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

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

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

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

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

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

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

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

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

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

10 The FDA underscored this point recently, on August  
11 1st, "when it denied a petition to withdraw Prozac from the  
12 market. The FDA ruled that, "The data or information  
13 available at this time do not indicate that Prozac causes  
14 suicidal or violent behavior. " We believe the FDA is an  
15 effective mechanism to screen, approve, and monitor  
16 prescription medications. The National Mental Health  
17 Association praised the recent FDA ruling and we continue to  
18 believe that antidepressants are extremely useful drug  
19 therapies in the treatment of depression.

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

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

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

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

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

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

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

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

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

9 I am also board-certified in internal medicine, **wit**  
10 a specialty in endocrinology, and board-certified in nuclear  
11 medic'ine. This gives me a broad aspect in terms of the  
12 approach to medical diseases, of which depression is one  
13 terrible example.

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

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

25 Let us recall the recent Time magazine proposal --

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

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

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

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

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

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

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

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

1 committee.

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

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

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

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

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

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

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

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

1 I was terrified to go on living.

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

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

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

My therapist explained that the Prozac had severely

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

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

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

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

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

2 DR. CASEY: Thank you. Sara Thomas?

3 (No response)

4 Nancy Veasey?

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

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

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

19 Through the fall and winter of 1990 and the fall of  
20 1991 until today I met with and talked with by phone 15 people  
21 directly and indirectly affected by the drug, not a very  
22 impressive group, but what is impressive is that out of the 1  
23 there are five deaths recorded in my notes. These are the  
24 facts.

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

1 attempted suicide by impulsively ingesting a toxic dose of  
2 medication.

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

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

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

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

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

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

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

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

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

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

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

23 DR. CASEY: Thank you. Nedra **Walnum**?

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

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

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

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

23 I appeared to be doing well on Prozac until June 25  
24 1990. This was the date of my first suicide attempt. Five  
25 days prior to June 25, 1990, I have little or close to no

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

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

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

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

E -

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

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

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

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

17 Lindsay's mother began taking Prozac in August of  
18 1988 for treatment of depression and alcoholism. She became  
19 very suicidal on the drug. She was a slight woman, she  
20 weighed 98 pounds. She was kind of **hyper**, to begin with, and  
21 the drug made her very, very aggravated. I looked it up in  
22 the dictionary: Aggravation is "to make worse, to annoy or t  
23 irritate. " So essentially Prozac made her problems worse.  
24 She ultimately committed suicide.

25 One woman earlier spoke of nearly committing **suicid**

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

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

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

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

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

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

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

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

19           No one has ever really explained what Prozac does.  
20 I've heard that it taps neurons in the brain. Well, perhaps  
21 it taps certain neurons in certain people's brains that tap  
22 suicidal ideation. Who knows? No one has ever explained  
23 that. All I've heard is the **Scientology** issue. I'm not a  
24 **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,  
1 that I should be here when everybody else did such a good job

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

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

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

3 DR. CASEY: Thank you. Richard Wontorski?

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

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

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

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

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

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

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

21 DR. CASEY: Thank you. This concludes the open  
22 public hearing session. I would like to offer everyone in the  
23 room and on the committee a three-minute stand-up-and-stretch  
24 break. Because of security reasons, I will ask all the  
25 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.

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

4 FDA PRESENTATIONS: INTRODUCTION AND PURPOSE

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

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

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

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

1 they do.

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

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

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

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

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

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

20           It is for these reasons and others that assessments  
21 of the potential of drugs to cause harm are ordinarily only  
22 deemed reliable in the scientific community if they are  
23 derived from clinical sources of evidence that allow a  
24 comparison, and it is a comparison of the incidence and  
25 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,

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

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

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

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

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

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

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

25 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 on 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### BACKGROUND INFORMATION

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

6 The NDA was originally submitted in September of  
7 1983. This drug was classified as IB. Basically what that  
8 means is that we consider this to represent a modest  
9 therapeutic gain, and the reason was that it was the first  
10 drug of the fairly specific **serotonin** reuptake inhibitors to  
11 come "in under an NDA.

12 We did a preliminary review and we brought Prozac to  
13 an advisory committee in October of 1985 and that committee  
14 recommended that we approve the drug. Over the next year we  
15 received a substantial amount of additional safety data, which  
16 we reviewed. In fact, the safety data base for Prozac was one  
17 of the largest we had ever seen. There were approximately  
18 8000 patients exposed to this drug during the premarketing  
19 trials, including 6000 in the United States and 2000 from  
20 foreign sources.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- 24 received prior to this meeting.

The other petition was from Public Citizens Health

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

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

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

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

21 DATA FROM FDA'S SPONTANEOUS REPORTING SYSTEM

22 DR. STADEL: Thank you.

23 (Slide)

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

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

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

14 There is another group of reports where an event is  
15 in the drug's label but the manufacturer receives a sudden  
16 increase in frequency of reports. They also send those within  
17 15 days. We have been monitoring all these types of reports  
18 on a regular basis for **fluoxetine** for some time.

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

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

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

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

18 (Slide)

19 This represents the different drugs, proportion of  
20 the market. We are talking about fluoxetine, trazodone,  
21 amitriptyline, desipramine, and maprotiline, because these  
22 were drugs that for various reasons were thought worth 100kin  
23 at all reports in the suicide-attempt category and other  
24 categories that I will be showing you, so it is to get some  
25 idea of what the experience across antidepressants has been,

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

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

7           (Slide)

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

18           (Slide)

19           This gives you the overall numbers I will be talkin  
20 about and shows, of course, the very large number of reports  
21 that have been received for **fluoxetine**. Those numbers add up  
22 to a very large number. They, in fact, represent a total of  
23 880 **unduplicated** reports, that is, more than one term can  
24 appear in a report, so you can have something listed under  
25 suicide attempt that is also counted under overdose, because

1 of the nature of the counting process.

2           The comments, I think, that bear here, in  
3 particular, have to do with year of marketing, which has a big  
4 impact on reporting, 1988 for **fluoxetine**, 1982 for trazodone,  
5 1961 for **amitriptyline**, 1971 for **desipramine**, and 1981 for  
6 maprotiline. Actually, trazodone and maprotiline are included  
7 in our considerations partly because they were marketed closer  
8 in time to **fluoxetine**, so if we did try to make any sort of  
9 comparisons, they would be somewhat better. I think the  
10 comparisons are, nonetheless, quite difficult and quite  
11 limit-ed among the drugs, as we will see.

12           (Slide)

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

18           (Slide)

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

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

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

7 (Slide)

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

23 (Slide)

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

1 and suicide attempts would have been coded. The line  
2 categories, I think, are pretty self-explanatory. Remember  
3 that the term "suicide attempt" was introduced in January of  
4 1989 when you are looking at the graph.

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

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

21 (Slide)

22 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

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

7 (Slide)

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

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

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

1 1988 category for **fluoxetine** includes a small proportion, a  
2 little under a third, that are in the category of psychotic  
3 depression (I will discuss that more a little later). The  
4 overall picture, as you see, is, if anything, higher **first-**  
5 year reporting for trazodone, a very abrupt drop -- more  
6 abrupt than we usually see for most drugs from the first to  
7 second years -- whereas in fluoxetine you have the first year  
8 being similar, or smaller, and then the increase especially  
9 taking off in 1990, which I previously related to the events  
10 in publicity.

11 (Slide)

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

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

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

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

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

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

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

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

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

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

23           Thank you.

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

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

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

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

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

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

1 separate events.

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

5 DR. STADEL: I do not have any information.

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

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

18 The other thing is, did you look at the Valium  
19 data? There was an article in JAMA, I guess in about 1976,  
20 that was very similar to what The American Journal of  
21 Psychiatry reported, that looked at development of suicidal  
22 ideation in individuals taking Valium to see if after that  
23 report there was a widespread change in the amount of  
24 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 reduplicate, yes. We make considerable effort at reduplication. 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

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

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

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

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

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

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

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

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

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

10 (Laughter)

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

17 You cannot get below an incidence rate of, say,  
18 somewhere between -- on a log scale -- 1 in 1000, 1 in  
19 10,000. You get down to a rate where we do not have  
20 mechanisms for quantitative determination. Of course, if you  
21 have a drug that is widely enough used, if there were a very  
22 small subgroup, it would result in a comparatively large  
23 number of people over a period of time, so it becomes a very  
24 difficult thing, where, on the one hand, spontaneous reports  
25 might be the first place that you would pick something up

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

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

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

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

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

1 looked like some cofactor were an important risk factor, then

1 one would say, well, maybe if I am going to do a clinical

1 trial or a **rechallenge** study, I should try to selectively

1 recruit people who might have some factor that would give the.

1 a differential susceptibility.

1 If it can be, I think, a guide to further work, it

1 is useful. It is very difficult when you have it alone to go

1 beyond that, I think.

1 DR. LEBER: I think one of the points that has to b

1 made about the quality of the system that is important is tha

2 the breadth, depth, and detail provided in the 1639 report is

2 rarely enough to allow you to decide whether or not the

2 **phenomenology** exhibited by patients compares or does not

2 compare to, say, a unique form of -- it is not like growing

2 feathers on your arm, as Feinstein described, where there is

2 no question about the event being related causally.

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

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

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

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

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

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

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

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

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

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

13 As to percent of incidence that these data  
14 represent, one of the things I said is that I do not know.  
15 Underreporting for almost everything associated with drugs,  
16 when it has been studied, in those instances where it has bee  
17 studied, is very high. That is, if the coincidence of taking  
18 a drug A and having disease B is at some rate, only a small  
19 fraction of that, in general, will be reported as an  
20 association between drug A and disease B. That is just  
21 generally true, like underreporting is on the order of 85 to  
22 90 percent in those areas where it has been studied.

23 Even, for example, the one I personally know best  
24 was that in the United Kingdom there was a study of the exter  
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 overdose and suicide. When you report those two categories for the tricyclic antidepressants, how do you report overdose on your reporting form? If it is reported as an overdose and not as a suicide attempt, do you categorize this as overdose but not a suicide attempt? If it is reported as a suicide attempt and overdose, 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

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

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

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

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

1 suicide attempts.

2 DR. STADEL: And they are coded as that.

3 DR. CASPER: Are they coded this way if they are no  
4 reported this way?

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

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

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

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

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

25 DR. STADEL: Six people looked at the reports that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 DR. REGIER: To compare the reports from this syste  
15 with other potential systems where we can look at rates of  
16 suicidal behavior, it is obviously helpful to have a clear  
17 numerator and a clear denominator. In order to do that, if w  
18 assume that the three behaviors, the suicide attempt, the  
19 O.D., and the psychotic depression all could potentially cove  
20 the range of suicidal activities, we would be talking about  
21 800 events.

22 The question is, over what time period can we place  
23 these events? Can we place them, for example, say, 500 of th  
24 800, over a single 12-month time period, so that we would be  
able to then estimate the number of people on Prozac during

1 that same 12-month time period and be able to get some kind of  
2 rate against which we could compare rates in clinical studies  
3 or **epidemiological** studies?

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

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

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

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

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

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

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

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

8 DR. **STADEL**: The computer system is called Oracle.

9 (Laughter)

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

19 (Laughter)

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

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

1 DR. STADEL: Surely, I will.

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

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

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

18 **NIMH PRESENTATION: STATEMENT ON BEHALF OF ADAMHA-NIMH**

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

1 National Institute of Mental Health, which falls under ADAMHA

2 (Slide)

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

10 This illness is highly lethal in untreated patients  
11 Comparing on the subgroup of patients, it can vary from maybe  
12 10 percent up to more than 20 percent in bipolar disorder, an  
13 we know -- and certainly one of the major tasks of ADAMHA ove  
14 the last 20 years has been to fund much of the research --  
15 that there are highly effective treatments available.

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

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

23 (Slide)

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

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

9 (Slide)

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

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

21 (Slide)

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

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

5 (Slide)

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

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

21 These are the data provided by Lilly. There were  
22 about 3 million people over the last three years, perhaps, in  
23 this country on **fluoxetine**. We have taken an estimate that  
24 two-thirds of them might have met diagnosis for depression.

The data are not broken down that way, but that seems a

1 reasonable assumption.

2           Using the ECA data, which, again, Dr. Regier could  
3 address more specifically, that we have from the National  
4 Institute of Mental Health, we find a 3.65-percent likelihood  
5 of prevalence per year of people attempting suicide. If you  
6 take the multiplier, then, out of these 2 million with  
7 depression treated with the drug, you would expect about  
8 73,000 to make a suicide attempt.

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

18           (Slide)

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

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

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

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

10 (Slide)

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

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

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

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

8 (Slide)

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

18 (Slide)

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

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

8 Thank you for your time.

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

14 DR. HAMER: Back on the slide you had in which you  
15 showed approximately 2 million prescriptions and approximately  
16 73,000 expected attempted suicides and approximately 500  
17 reported, if that population had been a nondiagnosed, normal  
18 population of 2 million people, what would the expected number  
19 of suicides in that population be?

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

23 DR. REGIER: It is less than 1 percent.

24 DR. POTTER: About the same, actually.

DR. REGIER: No, it is considerably less.

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

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

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

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

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

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

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

20 DR. POTTER: That is suicide attempts, not complete  
21 suicides.

22 DR. TEICHER: This is attempts?

23 DR. POTTER: That is correct.

24 DR. TEICHER: The data are 3 per 1000, not 3 per  
25 100, in a massive amount of other literature. I do not think

1 that number is correct. It does not jibe even with the 15-  
 2 percent lifetime for untreated depression if you are having  
 3 3.65 percent per year. I do not think that is an accurate  
 4 number.

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

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

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

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

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

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

3 DR. TEICHER: They range from a variety of studies.  
4 If you look at -- first, look at the data, say, for the large-  
5 scale epidemiological study where mianserin was used, where  
6 amitriptyline was used, you have instances where you have 11  
7 per 1000, 15 per 1000 for suicide attempts. If you look at  
8 the maprotiline data --

9 DR. LEBER: I am a little confused. An  
10 epidemiologic study would not ordinarily be using a drug.  
11 Perhaps you are talking to large-scale multicenter trials that  
12 you conducted over short intervals of time.

13 DR. TEICHER: No, these are studies where they have  
14 looked at physician use in the general population. They are  
15 not large-scale trials.

16 DR. LEBER: So they are actually sampling what?  
17 See, I think part of the argument here is that people derive  
18 estimates from different sources and it is consistent that you  
19 would have very widely varying estimators, because you are not  
20 specifying what the source precisely is. The rates of 3.65  
21 percent of suicide attempt per year come from what?

22 DR. REGIER: That comes from the epidemiologic  
23 catchment area, which is a sample of 20,000 representatives,  
24 adult, both institutionalized and community residents, and it  
25 is standardized, then, to the age-sex-race characteristics of

1 the U.S. adult population.

2 DR. TEICHER: What about Dr. Fawcett's data? Is he  
3 here?

4 DR. CASEY: Could we save part of this discussion  
5 for later on? We will come back to it, because it is an  
6 important topic. I want to give everyone a chance to ask Dr.  
7 Potter questions.

8 DR. HELLANDER: I just wanted to note that those wa  
9 very interesting data you just presented on the undertreatmen  
10 of depression, but perhaps the quote by Styron was not so wel  
11 chosen, considering that he has considered his **suicidality** to  
12 have been induced by **Halcion** and wrote about it in Darkness  
13 Visible and was **rechallenged** with **Halcion** after back surgery  
14 and became suicidal again. He now writes and speaks about th  
15 dangers of **Halcion**, and in one recent editorial concluded tha  
16 he avoids **Halcion** as if it is cyanide. Anyway, I just wanted  
17 to say that that maybe was not the best choice.

18 DR. POTTER: I thank you for the comment, because i  
19 one is interested in packaging the best sales pitch, I agree  
20 with you, one would like to line up testimonials from  
21 witnesses and all, but the point that Styron makes -- and  
22 Styron is not an expert on pharmacology, so do not ask Mr.  
23 Styron to be an expert on pharmacology -- he is, however,  
24 someone who expressed very well the question of stigma and ha  
25 become a major spokesperson for that. And that is a very

1 important issue.

2 We do not ask our depressed patients, we do not ask  
3 our cancer patients, we do not ask our heart disease patients  
4 to be the critics of the drugs they take and their best  
5 treatments per se, but we do ask them to speak to the major  
6 issues, and Mr. Styron has done that.

7 DR. CASPER: I was intrigued by your slide about the  
8 public's interest to take medication or not to take  
9 medication. I am wondering how you derived the data for your  
10 column on depression, because most everyone has had a  
11 headache, but very few people know what a depression is like,  
12 what we could call, currently, diagnostically, a major  
13 depressive disorder is like.

14 Therefore, I think it would be very difficult to  
15 make a judgment about their willingness to take medication fo:  
16 it. I think we should be very careful about asking whether  
17 patients who might feel depressed would be willing to take  
18 medication, and I think we should be very careful to advocate  
19 taking medication for feelings of depression. I do not  
20 believe you wanted to transmit that message -- I hope.

21 DR. POTTER: No. Thank you very much. I think the  
22 clarification is extraordinarily well taken. Obviously, when  
23 you do a survey like this, people who have had experience of  
24 headache will know what we are talking about. A lot of people  
will never experience a severe **syndromal** depression or

1 melancholic depression and really will not know what you are  
2 asking about, so your point is well taken.

3           Again, though, these graphs are to dramatize the  
4 problem with which we have been confronted, that the people  
5 who really do have severe **syndromal** depression are not **seeking**  
6 treatment at the level which one would expect, given the  
7 efficacy of known treatments.

8           DR. CASEY: Bill, you commented from the data that  
9 there are 500 reports of attempted suicide over an estimated  
10 --

11           DR. POTTER: On an annual basis there were **800-and-**  
12 something cases. You have just been having this discussion,  
13 actually, a few minutes ago, and it goes back and forth with  
14 how you do those numbers.

15           DR. CASEY: Given those numbers, is it possible to  
16 detect a signal from that information one way or the other  
17 about whether **fluoxetine**, or any other drug, is having an  
18 effect, since we are getting less than 1 percent of the  
19 information? You said perhaps the drugs are having an  
20 intended anti-suicidal effect, and I wonder if the information  
21 is clear enough there, or strong enough, to allow us to say  
22 one way or another what they mean?

23           DR. POTTER: I have heard only a little of the  
24 discussion this morning, but the analysis is not at the level  
25 of scientific data that would allow us to draw a scientific

1 conclusion of a preventive or protective effect. But it  
2 certainly is not of the scientific level that would suggest to  
3 us that there is a problem in the other direction. Really,  
4 what we were looking at the data to ascertain was should we be  
5 worried, and what we are trying to say is, the signal here for  
6 us to worry that we have a new dangerous problem on our hands  
7 is not there.

8 DR. TEMPLE: Bill, if I understand you, you took 2  
9 million people as a sort of estimate of patient years of  
10 therapy, is that right?

11 DR. POTTER: No, the data available to us from Eli  
12 Lilly was that about 3 million people in the United States had  
13 been on **fluoxetine**. We guessed that maybe two-thirds of them  
14 would have had depression, and this is over a three-year  
15 period, so this is the cumulative three-year exposure of  
16 everybody who has had a prescription written, whether they  
17 actually took it or not, whether they had it for one day, one  
18 week, or a year. That is what that is.

19 DR. TEMPLE: I guess I would think that to make an  
20 estimate of how many expected suicides there would be, you  
21 would need some kind of estimate of patient years of therapy  
22 to apply your rate per year to.

23 DR. POTTER: That is quite correct.

24 DR. TEMPLE: Mind you, I think that would be  
difficult.

1 DR. POTTER: Exactly, and we have had hours of these  
2 debates internally already. You are obviously going to have  
3 hours more. Again, if someone wishes to do an elaborate  
4 mathematical model about what the various potential estimates  
5 would be, that would be fine. But, again, in any way that  
6 anybody has looked at these data that we know, and we have  
7 asked many people, many experts who are statistical and  
8 epidemiologic experts, there is not a sufficient signal. That  
9 is what we are saying.

10 We agree the data are not great quality data.

11 DR. TEMPLE: We have ways, and people here might  
12 talk to you about it, of estimating the average duration of  
13 therapy associated with prescriptions.

14 DR. POTTER: Actually, I think Dr. Regier made some  
15 attempts to gather this information. Apparently, it was not  
16 available on short notice.

17 DR. TEMPLE: It "ain't" great, either, but it is  
18 something.

19 As a comment on what Dr. Casey was saying, if I hear  
20 the thrust of this, what you are, in part, responding to is  
21 what we have been told by a lot of people, which is, look at  
22 how many there are. Five hundred people. Doesn't that make  
23 any difference to you? What you are saying is that in the  
24 ordinary course of people's lives who have severe depression,  
25 a much larger number of suicide attempts can be anticipated.

1 The number that has been reported is a very small fraction of  
2 that.

3 I must say, whatever way you slice the numbers and  
4 however you correct it, that figure still seems to be true.

5 DR. POTTER: Thank you, Dr. Temple. Actually, I  
6 will do something that the other speaker was not willing to  
7 do. I will personalize this a little bit, and I think most of  
8 the clinicians around the table who treat a lot of depressed  
9 patients might do that, too. Out of the few hundred depressed  
10 patients that I have known well enough to be aware of their  
11 treatment in my lifetime, I would say five or six have  
12 committed suicide, so a higher percentage than the report.  
13 Those are aggressively treated patients, being treated at  
14 research centers by expert clinicians and everything else.  
15 People do commit suicide on this, so it is not surprising to  
16 me, as a clinician -- not as a government representative, but  
17 as a clinician -- that there are this many suicide attempts or  
18 suicides.

19 DR. SCHOOLER: I wanted to raise one other caveat  
20 with your pie chart. That is that I do not believe that the  
21 system that was described allows the discrimination of  
22 diagnosis.

23 DR. POTTER: You are correct.

- 24 DR. SCHOOLER: So that, essentially, dividing into  
the smaller number that represents the diagnosis is not

1 precisely fair.

2 DR. POTTER: That is quite correct. It would be  
3 very useful -- the agency would like it very much if the  
4 pharmaceutical industry would take on the burden of somehow  
5 tracking the actual diagnoses for which people prescribe  
6 drugs, but my guess is that would be a very expensive process.

7 DR. MONTGOMERY: A small point. I found that  
8 presentation very interesting and take the point that you make  
9 that there is no signal in a worrying direction, which I think  
10 is very similar to the statement that was made by the previous  
11 speakers. I just wanted to say that it really would seem, in  
12 this circumstance, better to turn to the controlled studies  
13 with placebo and compare the data to get that full message  
14 across.

15 DR. POTTER: Absolutely. Precisely. Actually,  
16 since Dr. Montgomery raised something about what should alert  
17 us -- you did not quite do this, but I will take the license  
18 to move one step further -- without going into the science of  
19 it, there is, in fact, a substantial body of highly replicate  
20 data suggesting that a low amount of a serotonin metabolize in  
21 this drug **fluoxetine** affects a neurotransmitter called  
22 serotonin, the low amount of that is supposed to be associate  
23 with more **impulsivity, aggressivity, suicidality**, and so on,  
24 so, if anything, this class of drugs, if you wanted to work  
from a theoretical perspective, if anything, this class of

1 drugs should be better anti-suicidal agents, given where our  
2 biological science is today.

3 That is another factor, which is very complex to  
4 explain, but I will mention it, too, that enters into our  
5 thinking.

6 DR. CASEY: Thank you very much. We appreciate you  
7 time.

8 Next we will move to the phase where we offer the  
9 opportunity to the pharmaceutical industry to make  
10 presentations, and members of the Eli Lilly Company came  
11 forward, so we will hear from them. The first speaker will be  
12 Dr. Robert Zerby.

13 PHARMACEUTICAL COMPANY PRESENTATIONS

14 ELI LILLY AND COMPANY: INTRODUCTION

15 DR. ZERBY: Dr. Casey, Dr. Temple, Dr. Leber, Dr.  
16 Laughren, and members and guests of the committee: Eli Lilly  
17 and Company appreciates the opportunity to present our data  
18 today for thorough scientific review and analysis of the fact  
19 surrounding the topic of suicidality and depression.

20 This advisory committee is an appropriate forum for  
21 such a discussion. Had the well-intended anecdotal reports  
22 been allowed to undergo the usual scrutiny in the scientific  
23 community without the attendant lay publicity, a clear  
24 consensus would have emerged, without creating unwarranted  
25 fear in the minds of depressed patients and their families.

1 Consistent with this view that scientific questions  
2 should be addressed by scientists, we have submitted our data  
3 for publication in peer-reviewed journals. The first of these  
4 papers, that describing a **meta-analysis** of our large U.S.  
5 clinical trial data base, just appeared in The British Medical  
6 Journal. Others will follow soon.

7 In addition, we are continuing to study the **problem**  
8 of **suicidality** and depression. In collaboration with the FDA  
9 and outside consultants, we have just initiated a study **which**  
10 will better characterize patients in whom suicidal ideation  
11 **emerges** during various forms of treatment.

12 Our presentation today will be made by three  
13 speakers. First, Dr. Jan Fawcett, Professor and Chair,  
14 Department of Psychiatry, Rush Presbyterian Saint Luke's  
15 Medical Center, is one of the world's experts in the area of  
16 suicide and violence. Dr. Fawcett will review the association  
17 of suicide and depression.

18 Next, Dr. Charles **Nemeroff**, Professor and Chair,  
19 Department of Psychiatry, Emory University, will review the  
20 available literature on the emergence of **suicidality** during  
21 treatment of depression. Dr. **Nemeroff** has published  
22 extensively in the area of affective disorders.

23 Last, Dr. Gary **Tollefson**, Executive Director, Lilly  
24 Research Laboratories, will review the Lilly data.

We will make the following points in this series of

1 presentations: One, **suicidality** is part of the disease of  
2 depression and the greatest risk of **suicidality** occurs when  
3 the disease is undertreated.

4 Two, there is no consistent pattern among anecdotal  
5 reports and postmarketing adverse event reporting of suicide  
6 and violence. Furthermore, these are not unique to any  
7 specific product. They do not provide adequate scientific  
8 evidence of a causal association between suicide or violence  
9 and any specific form of antidepressant therapy.

10 Three, **fluoxetine** is especially valuable in the  
11 treatment of suicidal patients because of its safety record in  
12 overdose.

13 Four, epidemiologic data and controlled clinical  
14 trials have not demonstrated induction of **suicidality** due to  
15 treatment. To the contrary: Antidepressants are shown to be  
16 effective in lowering suicidal ideation.

17 Five, the labeling of antidepressants already  
18 accurately represents the state of knowledge and **appropriately**  
19 warns of the risk of suicide in depression.

20 Finally, speculative labeling changes based solely  
21 on anecdotal data will be distorted by special interest groups  
22 and create unnecessary barriers to treatment.

23 Dr. Fawcett?

- 24 **THE RELATIONSHIP BETWEEN DEPRESSION, SUICIDALITY, AND TREATMENT!**

25 DR. FAWCETT: Thank you, Dr. **Zerby**.

1 (Slide)

2 I am happy to be here to contribute to today's  
3 discussion and because I am bringing you coals to Newcastle,  
4 as it were, delivering a message to you that has been  
5 delivered repeatedly by previous speakers, I will try to do it  
6 rapidly.

7 I am here to bring you four major points. The **first**  
8 is one that has been echoed and re-echoed, and that is  
9 suicide, a very tragic and preventable occurrence, is inherent  
10 to the disease of depression.

11 Secondly, the treatment of depression, especially  
12 the primary affective disorders, can prevent suicide.

13 Thirdly, the failure to have access to treatment, to  
14 proper diagnosis, or effective treatment can increase suicide  
15 rates in depression.

16 Lastly, even with today's antidepressant treatments  
17 that we have developed and even with the progress that we have  
18 made, there are substantial numbers of patients who will  
19 still, unfortunately, suicide and not respond to treatment,  
20 and may suicide with treatment.

21 (Slide)

22 The prevalence of depression in the U.S. population  
23 and its morbidity have already been discussed by Dr. Potter  
24 -- with much nicer slides, I might add -- showing the  
tremendous effects on productivity compared to other medical

1 illnesses, as in the Rand study.

2 (Slide)

3 The fact that depression leads to suicide in the  
4 Guze and Robins review of over 15 studies leads to a 15-  
5 percent lifetime suicide rate has also been discussed. What  
6 has not been mentioned so far with regard to this is the fact  
7 that in the first two to three years of follow-up the percent  
8 of death from suicide in these studies, in the 11 studies that  
9 were published before the introduction of any antidepressant  
10 drugs, before 1960, showed 60 to 70 percent of all deaths were  
11 related to suicide in the first two to three years, falling to  
12 about 50 percent in three to eight years of follow-up, with a  
13 planing out of the asymptote of that curve, out to 20 years,  
14 at around 15 percent of deaths.

15 I think that if you contrast that with our  
16 collaborative study, data from the NIMH collaborative study,  
17 where we have a 10-year follow-up, our 10-year rate of suicide  
18 compared to, let us say, Loker's study, which showed rates of  
19 7 or 8 percent (we are not talking about percent of deaths  
20 now, we are talking about percent of the sample) committing  
21 suicide, we have a 3.5 percent rate of suicide at 10 years  
22 follow-up so far.

23 The representation of depression in suicides, as has  
24 already been attested to, is very highly associated with  
depression.

1 (Slide)

2 We have also reviewed the data on the epidemiologic  
3 **catchment** area data base, it has been thoroughly discussed.  
4 We know that there is a certain lifetime prevalence of **suicide**  
5 attempts in an untreated community population and that  
6 psychiatric diagnoses are the strongest risk factor,  
7 especially depression.

8 (Slide)

9 Suicidal ideation and acts or behaviors, of course,  
10 are symptoms of depression. This is one of the reasons we see  
11 suicide during antidepressant treatment, of course, and this  
12 has been repeated over and over, again, today. I will not  
13 push it any further.

14 (Slide)

15 The current status of antidepressant therapy is an  
16 important point here. Inadequate care resulting from a lack  
17 of understanding or misunderstanding of depression is  
18 expensive and many of these people are undertreated or have no  
19 access to treatment. I would like to mention two fresh data  
20 sets, one from a study of adolescent suicide, by Dr. David  
21 Clarke, an NIMH-funded study in Chicago, in the three-county  
22 area around Chicagoland, where he has followed up and  
23 interviewed the families and friends of 86 adolescent  
24 suicides. Thus far, the antidepressant medication treatment  
rate in those 86 suicides is 7 percent. Thirty-three percent

1 of the suicides had been in mental health treatment at the  
2 time of their suicide, and only 7 percent were receiving any  
3 antidepressant drugs. About 10 percent were receiving any  
4 psychoactive drugs at the time of their suicide.

5 In another study in our suicide prevention research  
6 center by Dr. Clarke in geriatric suicide, in 56 geriatric  
7 suicides (over 65), only 5 percent of these patients were  
8 receiving antidepressant treatment. Only 13 percent had ever  
9 had psychiatric treatment, even though 40 percent of these  
10 people had seen a doctor within one week of suicide.

11 We have a tragically low incidence of treatment with  
12 antidepressant medications, not an indication that the  
13 treatment is causing the suicide; quite the reverse, that  
14 undertreatment is obviously causing suicide.

15 (Slide)

16 In our controlled study, the collaborative study,  
17 another **NIMH-funded** study which gave us a prospective follow-  
18 up of 954 patients with major affective disorder collected in  
19 five university centers, we saw 25 suicides in the first four  
20 to five years and 34 suicides by the time of our 10-year  
21 follow-up, for a final rate that I gave you.

22 Thirty-two percent of those suicides occurred in the  
23 six months after study entrance and 52 percent after the first  
24 year of study entrance. Clinical predictors of suicide,

25 **comparingthesuicides** with all the nonsuicides, include high

1 hopelessness scores, loss of pleasure and interest scores,  
2 cycling within an episode in those patients with bipolar  
3 illness, and also double abuse, abuse of alcohol plus one  
4 other drug, increased the rate of suicide long term by 10  
5 times in this sample, and not having a child under 18 also  
6 biased toward suicide, even though sometimes I think having  
7 children under 18 may bias toward suicide -- or homicide.

8 (Laughter)

9 (Slide)

10 Other risk factors associated with **suicidality** have  
11 been 'reported in the literature. I will let you read these.  
12 They include severity, length of episode, previous suicide  
13 attempts, concomitant psychotic ideation (which also turned u  
14 in our collaborative study, I did not mention it), and  
15 hopelessness . Beck has also done prospective studies, of  
16 which not enough have been done, and has found hopelessness a  
17 high predictor of suicide.

18 (Slide)

19 Another risk factor associated with **suicidality** is  
20 the so-called roll-back phenomenon, which, I think, is very  
21 important and known to clinicians. This is the notion that  
22 often when patients are treated for depression they show an  
23 increase in energy and their capacity to make decisions befor  
24 their hopelessness lifts, and the risk of suicide is great at  
that time. Anyone treating depressed patients should know

1 this and should take this into account. This is a question of  
2 physician education in terms of the treatment of depression.

3 (Slide)

4 Other factors that you have seen related to suicide  
5 are history of violent behavior, emergence of bipolarity or,  
6 as we call it, mood cycling. Alcohol abuse we saw just prior  
7 to suicide as a short-term predictor. Anxiety we saw in our  
8 prospective study as not only a predictor, but a modifiable  
9 predictor that was a short-term predictor, within the first  
10 year. Recent studies by Dr. Katie Bush in our department of  
11 patie'nts who suicide inpatient, inpatient suicides, have show  
12 very high levels of anxiety, reflected in staff nursing notes  
13 prior to suicide in our inpatient suicide sample.

14 (Slide)

15 Is suicide predictable? That is the major problem  
16 we have in preventing suicide, is that it is very difficult to  
17 predict. Our recent prospective study allowed us to look at  
18 time-related predictors and, at least in our data, the 954  
19 cases with the 34 suicides, we found that anxiety, panic  
20 attacks, poor concentration, and insomnia formed a cluster  
21 which predicted suicide within a year of the patient's  
22 interview as opposed to the predictors that we have all been  
23 taught to look for, such as hopelessness, prior suicide  
24 attempts, and suicidal ideation communicated to a clinician,  
25 which only predicted long-term suicide in our study and not

1 short-term suicide.

2 So we may need to refocus our predictors to be more  
3 effective at predicting suicide and preventing it as  
4 clinicians.

5 (Slide)

6 What are the reasons for suicide during  
7 antidepressant treatment? We see, first of all, depression  
8 waxes and wanes in severity and frequently we are not  
9 affecting the natural history of depression with our  
10 treatment, especially early on, and the depression may get  
11 better spontaneously -- that is why we do controlled studies  
12 -- and it may get much worse after we introduce treatment,  
13 having nothing to do with the treatment or nontreatment.

14 (Slide)

15 Patient noncompliance is another major barrier to  
16 treatment and it does not do any good, of course, if patients  
17 are frightened of the drugs they are being treated with. I  
18 know anecdotally of two patients who stopped their Prozac,  
19 because of such fears conveyed to them by well-meaning friends  
20 and relatives, who committed suicide weeks later, having  
21 recurrences of their depression.

22 (Slide)

23 I am going to go through these slides in the  
24 interests of the committee's time and get to the last one,  
25 listing all the reasons for treatment failure. There are man

1 reasons for the failure of antidepressant treatment. I  
2 mentioned patient noncompliance. I should say something about  
3 inadequate dosing. It has been shown recently by the studies  
4 of **Thrace** and **Cupfer** that patients maintained at too low a  
5 dose for maintenance treatment (and this was shown in earlier  
6 studies as well) often will relapse and have recurrences of  
7 depression when they are inadequately treated. This raises  
8 the risk of recurrence and suicide.

9           Refractory depression is still a significant  
10 problem. We estimate that up to 20 percent of patients  
11 respond to no antidepressant treatments, pushing us to look  
12 for other ways of combining drugs to get better responses in  
13 these patients. My reading of the pharmacologic literature,  
14 which uses improvement, not recovery, as a criterion,  
15 frequently, is that another 3 percent of patients who show  
16 improvement are still not well, they are not back to their  
17 normal sense.

18           A person with a Hamilton score of 10 is not a  
19 patient who is recovered; he is a patient who still has  
20 symptoms. There is evidence that these **patients** are more  
21 likely to recur who have partial responses.

22           Intercurrent life events is self-explanatory,  
23 because depressed patients, of course, are more sensitive to  
24 any stress and unable to cope with it and frequently will show  
25 exacerbations of both depression and suicidal ideation in the

1 face of negative life events which are unpredictable --  
2 especially real estate developers in this current economic  
3 atmosphere, since the tax law of 1986.

4 (Laughter)

5 Concomitant drug abuse is probably one of our  
6 greatest problems. In his recent testimony before the NIMH  
7 meeting on severe mental illness and hopelessness in Chicago,  
8 actor Rod Stieger testified about his eight-year depression  
9 following open-heart surgery and how he did not respond -- it  
10 took him four years to get diagnosed (not a person who did not  
11 have "access to the health care system, certainly) and another  
12 four years to get a response -- he told me this personally.  
13 It took him four years to have someone convince him or  
14 identify and convince him to stop drinking before his  
15 antidepressants worked, and he did respond, he told me, to  
16 desipramine and he considers himself well now.

17 Concomitant drug abuse or alcohol abuse is **certainly**  
18 another factor. Many of these factors, of course, defeat  
19 treatment and make treatment seem not so great in some  
20 patients and not such a tremendous outcome, and yet if we can  
21 overcome some of these comorbid and other aspects and have  
22 better treatments, we should be able to save more lives with  
23 treatment.

24 (Slide)

25 Our conclusions are, of course, that depressive

1 disorders are very common. Suicide is a clear symptom of  
2 depression and is difficult to dissociate from it, except with  
3 adequate care and treatment. The increased risk of suicide in  
4 patients with depression goes up to 30-fold in certain  
5 studies. patients will manifest suicidal acts or ideations as  
6 part of the natural history of the disease, even under the  
7 treatment. We still have a long way to go in being effective  
8 at even predicting suicide, even the so-called experts. We  
9 have a lot more to do and we should not be hindered any more  
10 than we absolutely have to be by restrictions and things that  
11 are going to frighten people from accepting treatment.

12 Thank you very much.

13 DR. CASEY: Thank you. The next presentation will  
14 be by Dr. Charles Nemeroff, Emory University.

15 A REVIEW OF LITERATURE OF SUICIDAL IDEATION OR  
16 ACTIONS DURING TREATMENT OF DEPRESSION

17 DR. NEMEROFF: Thank you, Dr. Casey.

18 (Slide)

19 I hope you find this quote a bit more to your  
20 liking. This is a quote by Dr. Kraepelin, the father of the  
21 current Western psychiatric nosology, who describes  
22 suicidality in his patients with depression. This severe type  
23 of suicidal ideation has been known for centuries. It is not  
24 new. Dr. Kraepelin stated: "The patients, therefore, often  
25 try to starve themselves, to hang themselves, to cut their

1 arteries. They beg that they may be buried alive, driven out  
2 into the woods and there allowed to die. One of my patients  
3 struck his neck so often on the edge of a chisel fixed that on  
4 the ground that all the soft parts were cut through to the  
5 vertebrae. "

6 This is the behavior that we see as clinicians in  
7 our depressed patients, in our untreated depressed patients.

8 (Slide)

9 What I will attempt to do in the next very few  
10 minutes is to review the literature that is currently  
11 available on the emergence of **suicidality** or the attenuation  
12 of **suicidality** during active treatment for depression.

13 (Slide)

14 I would like to start off with a few brief points,  
15 if I could. First, anecdotal reports fail to establish cause  
16 and effect, and I think this is the cornerstone of what the  
17 panel must come to grips with today, because essentially the  
18 COSTART system is uncontrolled data. It is data, but it is  
19 difficult to interpret.

20 The real issue is how can we, scientifically, as a  
21 profession, come to grips with this difficult issue? Clearly,  
22 what we need are double-blind placebo-controlled trials. I  
23 would like to read a quote from David Kessler, Commissioner o:  
24 the FDA. In his recent article in the New England Journal of  
Medicine, he said, "scientific rigor requires that data

1 presented during an activity be reliable, that is, capable of  
2 forming an appropriate basis for medical decision making.  
3 Scientifically rigorous data are developed through study  
4 designs that minimize bias. Anecdotal evidence and  
5 unsupported opinion should play no part in a scientifically  
6 rigorous program. "

7           So the issue, then, is what, on the one hand, can we  
8 learn from case reports and anecdotal data, and I think it can  
9 give us a signal for prospective studies. I remind all of you  
10 that the history of medicine is replete with examples of  
11 medical decision making based on anecdotal case reports, to  
12 wit, the use of widespread tonsillectomies in all of our  
13 children -- at least not our children, but there are very few  
14 people in this room who have tonsils. We have now discovered  
15 that that was unnecessary surgery, and how did we discover  
16 it? By prospective controlled trials.

17           Indeed, we have to determine what the current  
18 evidence is, and I shall quickly review this for you.

19           (Slide)

20           Dr. Montgomery, one of the invited panelists today,  
21 said in an article in 1987, "The only evidence that would be  
22 acceptable is the demonstration in a prospective double-blind  
23 trial that a difference in suicide rates was consistently seen  
24 with a specific therapeutic agent."

(Slide)

1           Let me now quickly review these data. There are 16  
2 published reports of suicidal ideation occurring in patients  
3 receiving **fluoxetine**. Please take that in the background of  
4 4 million patients having taken this drug worldwide and the  
5 data that Dr. Potter and Dr. Fawcett presented about the fact  
6 that **suicidality** is part and parcel of this illness.

7           (Slide)

8           I would like to take this opportunity to briefly  
9 review the Teicher report, which essentially has launched a  
10 maelstrom of activity in the lay press and controversy about  
11 this 'drug. There were six patients reported. These patients  
12 had multiple complicating factors. Let me speak to a few of  
13 these issues.

14           They were, by and large, treatment-resistant. They  
15 are not your run-of-the-mill patient with simple major  
16 depression treated by a family practitioner or by a private  
17 practice psychiatrist. They were patients referred to a  
18 tertiary medical center for treatment resistance. They had a  
19 number of complicating factors, including **comorbidity**, other  
20 diagnoses, multiple personality disorders, other personality  
21 disorders known to be associated with **suicidality**, alcohol  
22 abuse, temporal lobe epilepsy.

23           A recent letter in The American Journal of  
24 Psychiatry by Dowries, et al., raised the question of whether  
25 these patients did not have frank brain disease by virtue of

1 abnormal EEGs and **limbic** dysfunction. In this reply, Teicher  
2 stated that, yes, indeed, many did have abnormal EEGs and that  
3 they likely did have **limbic** brain dysfunction.

4           Shall we draw conclusions about the efficacy of an  
5 antidepressant on the basis of six extremely unusual,  
6 complicated, treatment-resistant cases? Three of the six  
7 patients had previous suicidal gestures. They were impulsive  
8 and they were on a bewilderingly large number of concomitant  
9 medications, including antipsychotic drugs and  
10 benzodiazepines, themselves implicated in some untoward side  
11 effects.

12           Of course, the greatest criticism, that Dr. Teicher  
13 himself acknowledges, is that this was retrospective and  
14 uncontrolled.

15           (Slide)

16           Are there other pieces of evidence in the  
17 literature? There are two cases reported by Masand. One was  
18 a treatment-resistant patient to imipramine, another a patient  
19 who received concomitant treatment with **alprazolam**, and a case  
20 by Dasgupta.

21           (Slide)

22           There was a case originally reported by Hoover, but  
23 since that time Hoover has retracted the suggestion that the  
24 suicidal ideation originally reported in this patient was  
secondary to **fluoxetine**. Hoover says, "It is unlikely that

1 fluoxetine has any relationship to the development of suicidal  
2 ideation. "

3 What else in the literature might support this  
4 notion that fluoxetine is associated with suicidality?

5 (Slide)

6 There are six cases by King in six adolescents with  
7 obsessive-compulsive disorder but a number of other  
8 complicating organic factors were identified and the authors  
9 themselves acknowledge that the association might well have  
10 been coincidental. Then there is a single case by Koizumi.

11 (Slide)

12 What about other antidepressants, stepping away from  
13 fluoxetine for the moment? There is the often-quoted Damluji  
14 and Ferguson report published in The Journal of Clinical  
15 Psychopharmacology, four patients who became suicidal during  
16 treatment, a phenomenon not unknown to any clinician in this  
17 room. Two of these patients, surprisingly enough, after being  
18 removed from desipramine, responded quite well to fluoxetine  
19 and, in fact, their suicidality was associated, as we would  
20 expect, with depression and not with a particular  
21 pharmacological agent.

22 (Slide)

23 What about other agents? There is a single report  
24 of amitriptyline in a double-blind study. Fifteen refractory  
borderline patients receiving amitriptyline showed an increase

1 in suicidal threats, paranoid ideation, and the like, compared  
2 to 14 nonresponding patients.

3 Taken all together, with these anecdotal data one  
4 has to raise the obvious question. It seems likely that what  
5 we have here is a situation that we are taught in medical  
6 school . Things can be true, true and unrelated. Patients can  
7 be suicidal, patients can be being treated with an  
8 antidepressant, yet there is no cause-and-effect relationship.  
9 At best, these are anecdotal reports.

10 Let us now look to see the other side of the coin,  
11 what "I think to be considerable evidence that active,  
12 aggressive antidepressant treatment, as Dr. Potter described  
13 it, is associated with an amelioration of **suicidality**.

14 (Slide)

15 In a study reported by **Helmut Beckman** and **Christine**  
16 **Schmouze**, two well-respected European investigators,  
17 **amitriptyline** was compared with promethazine in 50 severely  
18 depressed inpatients over a one-month treatment period. Not  
19 only was imipramine clinically superior but, in fact, it was  
20 superior not only in overall global ratings for major  
21 depression but for suicidal ideation as well.

22 (Slide)

23 **Nomofensin**, an antidepressant drug unrelated to the  
- 24 serotonin uptake blockers, 757 patients were classified into  
four different subgroups and nomofensin was a superior agent

1 over placebo, yet, surprisingly, perhaps, in view of this  
2 overall controversy, suicidal depressions, the most severe  
3 subtype, were the best predictors of response to nomofensin.

4 (Slide)

5 Recently Dr. **Tollefson** has analyzed a double-blind  
6 placebo-controlled series of antidepressants, 226 patients  
7 randomized to placebo or an active antidepressant for seven  
8 weeks.

9 (Slide)

10 The results were rather clear. There was an  
11 increase in suicidal ideation in the placebo group compared to  
12 the controls. No other class of antidepressant studied was  
13 associated with **suicidality**.

14 (Slide)

15 Even more importantly, not a single case of this  
16 ego-dystonic suicidal preoccupation that Dr. Teicher reported  
17 was observed in any of those studies.

18 I might add, on a personal note, that of the several  
19 hundred patients whom I have treated with **fluoxetine** and other  
20 related antidepressants, I have not observed this type of ego-  
21 syntonic suicidal behavior, either.

22 (Slide)

23 There is, of course, active investigation of other  
24 antidepressants. Another serotonin uptake blocker is the drug  
pyroxetine [phonetic], the **SmithKline-Beecham** drug, clearly,

1 in Europe, an efficacious antidepressant. In a study  
2 published by Dunbar and Mewett of almost 3000 patients who  
3 received pyroxitine, 554 with placebo, and almost 1200 with  
4 other antidepressants, in patients with no or mild suicidal  
5 thoughts, pyroxitine did not cause a worsening of suicidal  
6 ideation.

7 (Slide)

8 In fact, **suicidality** as an adverse event was no more  
9 frequent in pyroxitine-treated patients than those treated  
10 with placebo or active control. Thus, there was no evidence  
11 from 'these very large N's studied that serotonin uptake  
12 blockade per se is associated with increased **suicidality**.

13 (Slide)

14 Fluvoxamine, a drug currently under investigation by  
15 Solvay and Upjohn, has been studied by a number of  
16 investigators, including Dr. Montgomery. **Fluvoxamine** is  
17 significantly more effective, at least in these two studies,  
18 than imipramine in reducing suicidal ideation.

19 (Slide)

20 Similarly, **sertraline**, the Pfizer drug, the  
21 Psychopharmacologic Drugs Advisory Committee at its 33rd  
22 meeting stated the emergence of substantial suicidal ideation  
23 was low in all treatment groups and placebo rates exceeded the  
24 rates for active agents.

(Slide)

1           Although Dr. **Tollefson** will review the Lilly data  
2 per se, I did want to include some published **fluoxetine** data.  
3 In the study by Mueijer in 1988, suicidal feelings, as  
4 estimated by the HAMD-3 item, was significantly reduced among  
5 14 fluoxetine-treated patients compared to 16 or 14 placebo or  
6 mianserin-treated patients two weeks after therapy.

7           (Slide)

8           One can use anecdotal data in any way one wishes .  
9 I simply want to show you how one can do that. This is a  
10 report published in The American Journal of Psychiatry by  
11 Cornelius, which suggested that five patients with borderline  
12 personality disorder and recurrent self-injurious behavior  
13 could be treated successfully with **fluoxetine**. They suggested  
14 that fluoxetine should be the treatment of choice for  
15 patients with depressive and impulsive symptoms in the  
16 context of a diagnosis of borderline personality disorder.

17           I would suggest to you that I have as little  
18 confidence in these anecdotal reports as I do in the anecdotal  
19 report of Teicher, and that, in fact, there is no substitute  
20 for controlled prospective double-blind clinical trials.

21           (Slide)

22           The last **fluoxetine** report to review is Sacchetti's  
23 of 62 patients receiving a range of 20 to 60 mg and, in fact,  
24 the patients who responded best were the patients who had a  
history of suicide attempt. Again, this would argue against

1 the notion that serotonin uptake blockers in general and  
2 fluoxetine in particular would be associated with an increase  
3 in suicidality.

4 (Slide)

5 In conclusion, there is simply no scientific  
6 evidence whatsoever, no placebo-controlled double-blind study  
7 that has established a cause-and-effect relationship between  
8 antidepressant pharmacotherapy of any class and suicidal acts  
9 or ideation.

10 As Drs. Potter and Fawcett have suggested, limiting  
11 the availability of antidepressants could have a very profound  
12 adverse effect in terms of increasing the morbidity and, in  
13 fact, mortality associated with untreated or undertreated  
14 depression.

15 Thanks very much.

16 DR. CASEY: Thank you, Dr. Nemeroff. There may be  
17 some questions, but I will ask the committee to hold their  
18 questions until all the representatives from Lilly have  
19 presented, so that the Lilly Company can have the benefit of  
20 the cohesiveness of their presentation.

21 Next will be Dr. Gary Tollefson from Lilly Research  
22 laboratories.

23 A REVIEW OF THE LILLY DATA BASE REGARDING **FLUOXETINE**

24 DR. TOLLEFSON: Thank you. I would like to thank  
25 the FDA for the opportunity to present data from our

1 controlled clinical trials of **fluoxetine**.

2 (Slide)

3 During our presentation of our **Lilly** controlled  
4 blinded studies we will overview four topics: an analysis of  
5 **suicidality** during depression; an analysis of **suicidality** in  
6 non-mood disorder trials; an evaluation of our clinical data  
7 base for evidence of paradoxical or clinical worsening; and a  
8 similar evaluation looking for any evidence of violence or  
9 aggressive behavior associated with pharmacotherapy.

10 (Slide)

11 In approaching evaluation of these potential  
12 associations of suicidal acts, ideas, of violent behavior  
13 during the pharmacologic treatment of depression, we have  
14 evaluated multiple data sources.

15 (Slide)

16 These include spontaneous adverse event monitoring,  
17 prospective suicide studies as a possibility, **epidemiological**  
18 data bases, and controlled clinical trials.

19 (Slide)

20 We have carefully evaluated spontaneous adverse  
21 event data and share the conclusions that there are  
22 significant limitations in this type of reporting system. We  
23 will be reviewing adverse events in the controlled blinded  
24 trials with fluoxetine later in the presentation.

25 (Slide)

1 Spontaneous adverse event data, as you have heard,  
2 suffer from having no reliable denominator. At best, only a  
3 gross estimate can be made based on sales or prescriptions  
4 provided. Events also are reported regardless of causality.  
5 On careful review, as you have heard, the majority of **Prozac-**  
6 related adverse events appear unrelated or noncausal to the  
7 drug itself. Spontaneous adverse event data also do not put  
8 events into context with other suitable comparative drugs.  
9 Thus we lose a sense of relativity.

10 (Slide)

11 In addition, reporting, as you have heard, is highly  
12 influenced by a variety of variables. Webber has already  
13 published that peak reporting occurs approximately two years  
14 after a product's launch and thereafter decreases. Reporting  
15 is also influenced highly by the volume of product used. **Thus**  
16 the more popular a product is, the greater the number of  
17 absolute adverse events that are likely to be reported. Also,  
18 a variety of examples illustrate that the number and the  
19 nature of adverse events are substantially influenced by  
20 publicity. This has been well demonstrated several months  
21 following the publication of **Teicher, et al.**

22 (Slide)

23 We view data that are generated from spontaneous  
24 event reporting and case reports to be hypothesis-generating.

25 We have chosen to test these hypotheses based upon the

1 remaining three methods of study that I have cited.

2 (Slide)

3 These alternatives include prospective **suicide-**  
4 **specific** trials, **epidemiological** data bases, and detailed  
5 studies drawn from controlled double-blind clinical trials.  
6 In consultation with the Food and Drug Administration and  
7 noted external experts in the fields of depression and  
8 **suicidality**, we have already generated a series of protocols  
9 to better characterize patients who experience an increase in  
10 suicidal ideation during pharmacotherapy or other forms of  
11 treatment.

12 The first of these protocols has already been  
13 initiated.

14 (Slide)

15 We have also evaluated a variety of leading  
16 **epidemiological** data bases. These data bases have the caveat  
17 that they are not always well equipped to detect or capture  
18 **mental health-** or **mental illness-**related events such as  
19 suicidal ideation.

20 (Slide)

21 The first of these **epidemiological** data bases that  
22 I would share is the Drug Safety Research Unit's Prescription  
23 Event Monitoring System, or PEMS. This is a system under the  
24 direction of Dr. William Inman in the United Kingdom. This  
group has analyzed over 12,731 patients prescribed **fluoxetine**

1 and concluded that there was no evidence of **fluoxetine-induce**  
2 suicide attempts.

3 The second data base that I would like to attend to  
4 is the Drug Abuse Warning Network, or DAWN. DAWN collects  
5 information on emergency room and medical examiner mentions i  
6 association with drug use, either illicit or prescription.  
7 The number of emergency room mentions with regard to  
8 fluoxetine are not disproportionate when adjusted for the  
9 number of prescriptions written.

10 Regarding the number of medical examiner mentions  
11 with **fluoxetine**, again, relative to the number of  
12 prescriptions written, DAWN has concluded that the **fluoxetine**  
13 experience is substantially lower than that with other  
14 antidepressant agents.

15 A third data set comes from the National Center for  
16 Health Care Statistics. This has indicated that there has  
17 been a consistent, albeit modest, decline in the absolute  
18 number of suicide deaths and the rates of completed suicide  
19 per 100,000 individuals since the introduction of **fluoxetine**  
20 in January of 1988.

21 (Slide)

22 The focus of today's presentation, however, is on  
23 the large and comprehensive controlled clinical trials and  
24 data from Eli Lilly and Company. We approached these  
25 controlled clinical trials with three specific questions in

1 mind: Is pharmacotherapy associated with an increase in the  
2 rate of suicidal acts; is pharmacotherapy associated with an  
3 increase in the emergence of substantial suicidal ideation;  
4 and, thirdly, is pharmacotherapy associated with an actual  
5 reduction in suicidal ideation amongst depressed patients?

6 (Slide)

7 The initial analysis that I will present to you is  
8 from our mood disorders trials. In these clinical  
9 investigations of depressive disorders we had the luxury of  
10 two different clinical data bases. Together, as you can see,  
11 the N is quite impressive; over 5600 patients were studied in  
12 the clinical trials.

13 These two data sets differ in some very important  
14 clinical aspects, which we will be discussing momentarily.  
15 Data set number one is drawn from the U.S. IND for fluoxetine  
16 and data set number two is studies done outside of the United  
17 States, referred to as international trials. You can see  
18 these include placebo-controlled, comparative-controlled, and  
19 three-armed studies with both compared and placebo controls.

20 (Slide)

21 We are looking at three principal outcome measures  
22 here in these studies. The first one is a suicide act. The  
23 definition here is that we have defined a suicide act as  
24 behavior judged to be purposefully undertaken to produce an  
outcome of self-harm. The second outcome measure, to attempt

1 to capture what has been described in the literature as a  
2 clinical phenomenon by **Teicher, et al.** , we have called the  
3 emergence of substantial suicidal ideation. This is defined  
4 as individuals who, at base line in clinical trials, had an  
5 item 3 score from the Hamilton Depression Rating Scale score  
6 of 0 or 1 that increased at any time during clinical trials to  
7 a 3 or 4 (that is during the double-blind component of those  
8 trials).

9           Just for a moment I would like to review what item  
10 3 is. From the Hamilton Depression Rating Scale item 3 is a  
11 five-point scale ranging from a score of 0 -- as you can see,  
12 the absence of suicidal symptoms -- to a maximum score of 4,  
13 which is indicative of a suicide attempt. The third outcome  
14 measure was improvement. We defined improvements of suicidal  
15 ideation as a decrease in the Hamilton item 3 score from base  
16 line to patient's last clinical visit.

17           The first statistical method that was applied in the  
18 analysis of the U.S. IND depression data base was the Pearson  
19 chi-square test. This was performed to compare all treatment  
20 groups that you saw in the earlier slide. Again, we will  
21 focus initially on just the U.S. IND clinical characteristics  
22 and I would point out that the patient characteristics at base  
23 line in the U.S. IND trials were comparable with respect to  
24 patient age, patient gender, total depression severity at base  
25 line, and item 3, **suicidality.**

1 (Slide)

2 On this slide you see the incidence of suicidal  
3 acts from the pooled U.S. IND trials. The first point that I  
4 would make is that the rate of suicidal acts in controlled  
5 clinical trials was low. There, as you can see, was no  
6 statistically significant difference between any form of  
7 therapy. I would also point out that in an analysis of fixed-  
8 dose trials with fluoxetine there was absolutely no difference  
9 in the rate of suicidal acts that did occur in that particular  
10 cohort relative to the dosage of the drug administered.

11 Presentation of these post-randomization data does  
12 not include one additional important observation. That is,  
13 there were three individuals who had suicide acts, one of  
14 which was fatal, that occurred during the placebo lead-in  
15 component of these trials.

16 (Slide)

17 I now move on to the emergence of substantial  
18 suicidal ideation. This is based on the same clinical data  
19 set, with one exception. You can see the denominator has  
20 changed here. That is based upon the fact that we are  
21 examining patients who, at base line, had an item 3 score of  
22 0 or 1 in order to meet the criteria of the emergence of  
23 substantial suicidal ideation.

24 I would like to emphasize in this analysis,  
consistent with the observation of **suicidality** as a symptom o

1 depression, that approximately one-third of the total U.S. IN  
2 data base had item 3 scores of 2 or greater at base-line  
3 randomization. This, of course, underscores the presence of  
4 some degree of suicidal ideation that was in existence prior  
5 to drug therapy as part of the disease course.

6 As you can see here, significantly -- statistically  
7 significantly -- fewer patients had the emergence of  
8 substantial suicidal ideation with **fluoxetine** than either  
9 placebo or comparative **tricyclic** antidepressants in the U.S.  
10 IND trials.

11 (Slide)

12 This slide reflects the third outcome measure, and  
13 that is improvement from base line to last study visit. These  
14 data demonstrate convincingly that approximately two-thirds o  
15 patients improved when receiving active pharmacologic  
16 treatment for depression, either fluoxetine or **tricyclic**  
17 antidepressants.

18 I would also like to emphasize that **fluoxetine** is  
19 statistically and significantly associated with more  
20 improvement in item 3 scores than was placebo.

21 (Slide)

22 In summary, in the U.S. IND studies on **Prozac**, there  
23 were no statistically significant differences among **fluoxetin**  
24 (or **Prozac**), placebo, or comparative **tricyclic** antidepressant  
25 in the rate of suicidal acts.

1            Secondly, **fluoxetine** was actually associated with  
2 significantly fewer cases of the emergence of substantial  
3 suicidal ideation than either placebo or comparative **tricyclic**  
4 antidepressants .

5            Thirdly, an important point to clinicians and to  
6 public health in general, active pharmacologic treatment with  
7 either **fluoxetine** or **tricyclics** was associated with  
8 significantly better performance than placebo regarding  
9 improvement in suicidal ideation as measured by item 3.

10            (Slide)

11            Now I am going to move on to our international  
12 controlled trials in depression.

13            (Slide)

14            You have seen this slide previously. I would point  
15 out that, as one might expect, the international trials in  
16 depression were more heterogeneous from site to site and they  
17 obviously reflected the cultural and the scientific diversity  
18 that one would see in a multinational study.

19            (Slide)

20            Again, patient characteristics were completely  
21 comparable in the analyses by these same four parameters.

22            (Slide)

23            The statistical methodology, recognizing these  
24 significant heterogeneity and international trials of  
depression, led us to investigate the consistency of results,

1 investigator to investigator, by using the **Mantel-Haenzel**  
2 incidence difference test. This method allowed us to analyze  
3 treatments with respect to select variables after stratifying  
4 by protocol.

5 (Slide)

6 In our worldwide trials, we have, then, two head-to  
7 head comparisons to share with you: **fluoxetine** versus **placeb**  
8 and **fluoxetine** versus **tricyclic** antidepressant medications.

9 (Slide)

10 This first slide looks at the incidence of suicidal  
11 acts "by **Mantel-Haenzel**, providing, from your left to your  
12 right, the data analysis in the U.S. IND trials, the  
13 international trials of **fluoxetine** in depression and, thirdly  
14 a pooled, worldwide experience in over 5000 patients.

15 (Slide)

16 As you can see here, this method was used and  
17 provided evidence that there was no statistically significant  
18 difference regarding the emergence of suicidal acts between  
19 **fluoxetine** and placebo in the U.S., international, or  
20 worldwide studies.

21 You can see that the percentages are slightly highe  
22 in the international data base and that, in fact, reflects  
23 that in the international trials we had a greater number of  
24 inpatients, we had a higher rate of base-line **suicidality** at  
25 study randomization, and patients generally, in the European

1 experience, tended to be continued in trials despite having  
2 suicidal ideation longer than their counterparts in the U.S.  
3 might normally practice.

4 One other important observation is that in the  
5 international trials more than 40 percent of the individuals  
6 randomized had base-line suicidal ideation present.

7 (Slide)

8 Now we look at the emergence of substantial suicidal  
9 ideation. You will note that the U.S. data and the  
10 international data appear similar regarding the rates of ESSi,  
11 or emergence of substantial suicidal ideation. The rate is  
12 numerically lower with **fluoxetine** when contrasted with  
13 placebo, and that achieved, statistically, a trend within the  
14 U.S. IND data. When all of the data are pooled between the  
15 United States and the international trials, you can see that  
16 statistical significance at 0.03 was achieved, whereby more  
17 emergence of substantial suicidal ideation during clinical  
18 double-blind trials was associated with placebo than with  
19 active drug therapy.

20 (Slide)

21 Once again, we also visit the third outcome measure  
22 of improvement in item 3 scores. As you can see, **fluoxetine**  
23 was significantly statistically better than placebo in these  
24 trials, both within the U.S. experience and the pooled U.S.  
25 and international or worldwide data. Once again, more than

1 two-thirds, approaching three-fourths, of all patients  
2 experienced an improvement in their item 3 scores, base line  
3 to last visit, while receiving active treatment.

4 (Slide)

5 We will now focus on an evaluation, as you remember  
6 from the Mantel-Haenzel, of a comparison between fluoxetine  
7 and other standard tricyclic antidepressants. Again, overall,  
8 we observed a very low incidence of suicidal acts. You can  
9 see there was no statistically significant difference between  
10 fluoxetine or tricyclic antidepressants in the U.S., the  
11 international, or the pooled worldwide data bases.

12 Regarding the emergence of substantial suicidal  
13 ideation, the absolute prevalence, fluoxetine appeared  
14 somewhat better than the tricyclic antidepressants in the U.S.  
15 and the worldwide data bases. However, overall, the results  
16 demonstrated no statistically significant differences in the  
17 two different treatment assignments.

18 (Slide)

19 Regarding improvement in item 3, item 3 improvement  
20 was comparable between fluoxetine and TCAS within the U.S. INI  
21 data base. However, in the international data base, tricyclic  
22 antidepressants appeared to have significantly more  
23 improvements than did fluoxetine. I would remind you, though,  
24 that fluoxetine had statistically and significantly greater  
25 improvement in ideation than had placebo. A caveat in

1 interpreting this particular individual analysis is that there  
2 was statistical evidence of significant heterogeneity trial by  
3 trial. Thus the pooling of these particular data in this  
4 analysis might be in some question. We show it, nonetheless,  
5 to give you that comparison.

6 (Slide)

7 In summary, the international data replicated our  
8 Us. IND experience. It demonstrated no statistically  
9 significant difference between **fluoxetine** or **tricyclics** in the  
10 occurrence of suicidal acts and no difference from the base-  
11 line 'rate with placebo. **Fluoxetine** was superior to placebo in  
12 the prevention of emergence of substantial suicidal ideation  
13 and there was no difference in substantial suicidal ideation  
14 emergence between fluoxetine and **tricyclic** antidepressants.  
15 **Fluoxetine** was superior to placebo in the improvement of item  
16 3 suicide ideation scores.

17 (Slide)

18 Returning to our original three questions regarding  
19 the pharmacotherapy of depression, is there evidence that  
20 pharmacotherapy increased suicidal acts based on this over  
21 5000-patient-sample data base? The answer was no.

22 Is there any evidence that there was an increase in  
23 the emergence of substantial suicidal ideation with the  
24 introduction of pharmacologic treatment? Again, from this  
data base you can see the answer was no.

1           The third and a very important question, was active  
2 pharmacologic therapy associated with a reduction in the  
3 majority of patients with suicidal ideation? The answer was  
4 a resounding yes.

5           (Slide)

6           I would now like to turn your attention to the  
7 trials that were done on non-mood disorders, nondepressive  
8 disorders.

9           (Slide)

10           As you can see here, the hypothesis of why we did  
11 this "data analysis was that if antidepressant medication  
12 carried the inherent risk of promoting suicide or hostile and  
13 aggressive events -- and that was apart from the natural  
14 history of the disease that it was being prescribed for, i.e.,  
15 depression -- then one would expect that drug-induced effect  
16 to emerge in other disorders where it is prescribed.

17           (Slide)

18           What we did was, we looked at our U.S. IND data  
19 bases for three clinical disorders: bulimia nervosa; obesity;  
20 and obsessive-compulsive disorders. These three trials  
21 represent over 5000 patients who were investigated.

22           (Slide)

23           Once again, in **these** non-mood disorders, patients  
24 were comparable across the assignment to either **fluoxetine** or  
25 placebo.

1 (Slide)

2 Here we, first, look at the incidence of suicidal  
3 acts. As you can see, there is no statistically significant  
4 difference between **fluoxetine** and placebo regarding the  
5 incidence of suicidal acts with bulimia, obesity, or  
6 obsessive-compulsive disorder: In fact, there were no acts in  
7 trials of OCD.

8 (Slide)

9 In review of the data for emergence of suicidal  
10 ideation during **pharmacotherapy**, as you can see here, there,  
11 again", was no statistically significant differentiation  
12 between placebo and **fluoxetine** with regard to suicidal  
13 ideation in any of the three non-mood-disorder trials.

14 (Slide)

15 In summary, there was no evidence of an increase in  
16 suicidal acts in non-mood-disorder patients receiving  
17 fluoxetine. There was no evidence of an increase in suicidal  
18 ideation during administration of **fluoxetine** to non-mood-  
19 disordered patients.

20 (Slide)

21 Thus we would summarize that there is no suggestion  
22 that **fluoxetine** induced suicidal acts or clinically  
23 significant ideation in a non-mood-disordered cohort.

— 24 (Slide)

25 There has also been some discussion in the

1 literature about a hypothetical clinical worsening amongst a  
2 very small number of patients receiving antidepressant  
3 medications. This has been labeled a so-called paradoxical  
4 reaction. The next few slides examine that hypothesis.

5 (Slide)

6 We used the following definitions to examine that  
7 hypothesis in our **mood-** and non-mood-disordered trials in the  
8 U.S. IND. These definitions, in fact, for the most part,  
9 reflect the mirror image, or the opposite, of what are typical  
10 response definitions.

11 First of all, in depression, a 50-percent-or-greater  
12 increase in the 17-item Hamilton Depression Score from base  
13 **line** to any point during study; in bulimia nervosa trials, at  
14 least a 50-percent increase in bingeing or vomiting at any  
15 point during clinical trials; in trials with obesity, based  
16 upon **outliers** beyond the 99th percent of weight gain in  
17 placebo recipients, a greater than 12-pound or equal-to-12-  
18 pound weight gain during eight to 12 weeks of drug therapy  
19 and; lastly, in obsessive-compulsive disorder, a 25-percent-  
20 or-greater increase in the Yale-Brown Obsessive-Compulsive  
21 Scale, again, at any time during clinical trials.

22 (Slide)

23 As you can see, in the analysis for possible  
24 paradoxical worsening, in fluoxetine versus placebo and  
25 **fluoxetine versus tricyclics**, there was no statistically

1 significant differentiation between either placebo and  
2 **fluoxetine** or fluoxetine and **tricyclic** antidepressants,  
3 suggesting there is no evidence of worsening with either  
4 active drug that differentiated them from placebo.

5 (Slide)

6 We now move on to the bulimia trials. The first  
7 outcome measure, an increase in vomiting, you can see there  
8 was statistical significance and, of note, that statistical  
9 significance was such that there were fewer paradoxical  
10 worsening amongst bulimic patients receiving active drug  
11 treatment with **fluoxetine** than with placebo.

12 (Slide)

13 The same statistical significance held true in  
14 looking for binge eating. There were fewer paradoxical  
15 worsening with active drug therapy than with placebo.

16 (Slide)

17 The same statistical significance held true in  
18 obesity trials. There were fewer paradoxical or unanticipated  
19 and unexpected weight gains in patients receiving **fluoxetine**  
20 than in placebo recipients.

21 (Slide)

22 Last, but not least, in the assessment of  
23 paradoxical worsening in obsessive-compulsive disorders,  
24 there was no statistically significant differentiation of  
25 **fluoxetine** or placebo regarding unexpected worsening.

1 (Slide)

2 In conclusion, looking at these U.S. IND depression  
3 and non-mood-disorder trials, we saw no evidence of  
4 paradoxical worsening in fluoxetine-treated patients.

5 (Slide)

6 I said I would briefly share with you studies  
7 looking at discontinuation rates during the controlled  
8 clinical trials. As you can see here, and as one often would  
9 expect with the use of any active pharmacologic agent, adverse  
10 event experience is more common with active treatments than  
11 with "placebo. I would point out, though, that **fluoxetine** was  
12 statistically and significantly associated with fewer side  
13 effects leading to discontinuation of treatment than  
14 comparator **tricyclic** antidepressant agents.

15 (Slide)

16 I will show you a perhaps equal or of greater  
17 importance slide, and that is retention in study. These are  
18 discontinuation rates for any reason, looking at fluoxetine  
19 versus placebo and **fluoxetine** versus **tricyclic**  
20 antidepressants. As you can see here, there was a  
21 statistically significantly greater number of patients, over  
22 half, who received **fluoxetine** and were able -- I am sorry, let  
23 me restate that. There were a statistically significant  
24 number of patients who failed to discontinue, or, in other  
25 words, stayed in the studies, receiving **fluoxetine** and, when

1 compared with **tricyclic** antidepressants, once **again**, there  
2 were significantly fewer patients who discontinued clinical  
3 studies.

4 One can conclude that, compared to placebo, active  
5 therapy was associated with longer study retention.  
6 Specifically, head to head, fluoxetine performed significantly  
7 better than placebo or **tricyclic** antidepressants.

8 (Slide)

9 In summary, there were no significant relationships  
10 that were seen. We took that one step further, though. As we  
11 have 'heard, there are possible hypotheses that have been  
12 generated considering that there may be a certain **association**  
13 in rare patients between an adverse event experienced and an  
14 increase in suicidal ideation.

15 Accordingly, we analyzed this entire data base of  
16 over 500 patients with depression for their adverse event  
17 experiences . For the sake of time, I will only comment on one  
18 adverse event experience. That was looking at activation,  
19 including the experience of akathisia. In comparison versus  
20 placebo or compared to **tricyclic** antidepressant there was  
21 absolutely no statistical association between **suicidality** and  
22 activation relative to drug assignment or placebo assignments.

23 (Slide)

24 I am going to move on to another question that has  
25 been posed to this committee. It is the final question; that

r s m

1 is, whether or not fluoxetine precipitates aggression or  
2 hostility.

3 (Slide)

4 We used the following method to address this  
5 question. We evaluated the spontaneous adverse event data for  
6 violence or terms that would identify violent, hostile, or  
7 aggressive behaviors. We then applied these terms, the so-  
8 called aggression cluster events, to our double-blind placebo-  
9 controlled trials across all indications, depression and  
10 nondepressive disorders.

11 From that we identified 13 individuals of some  
12 10,000 who experienced an event cluster of aggression.

13 (Slide)

14 Let me emphasize that in those clinical case report  
15 analyses of those 13 individuals there was no evidence that in  
16 any of these cases the aggression led to serious bodily harm  
17 to others. From a clinical perspective, the acts were of  
18 limited significance. But as you can see from the data  
19 analysis, **fluoxetine** was statistically significantly less  
20 likely to have resulted or to have been associated with an  
21 event from an aggression cluster than placebo. The absolute  
22 numbers: nine events with placebo, only four events in  
23 **fluoxetine**; the percentages, 0.65 placebo, only 0.15 with  
24 **fluoxetine** (significant at a 0.008 level).

(Slide)

1           Thus , in the placebo-controlled double-blind  
2 clinical trials, **fluoxetine** was significantly less likely than  
3 placebo to be associated with aggression. In fact, the  
4 evidence suggested that aggression was less likely to have  
5 occurred in patients medicated with an active antidepressant  
6 agent.

7           (Slide)

8           In conclusion, we have reviewed the various data  
9 bases or possible hypothesis-generating methods to look at  
10 these interesting questions posed to the committee. We have  
11 already heard that spontaneous event reporting suffers from  
12 numerous caveats. There are advantages to prospective,  
13 suicide-specific, double-blind controlled studies and, as you  
14 have already heard, these clinical studies looking at  
15 **suicidality** and depression have already been commenced.

16           There are **epidemiological** data bases that can be  
17 reviewed and, as you have heard, there is absolutely no  
18 evidence from those data bases of an increase in suicide rate  
19 since the launch of Prozac, nor any evidence in the DAWN data  
20 base looking at coroner or medical examiner mentions of an  
21 unexpected increase in **fluoxetine** events; in fact, on the  
22 contrary, there were fewer **fluoxetine** mentions than expected  
23 for the number of prescriptions rendered compared to tricyclic  
24 agents.

25           (Slide)

"1           Thus , the overall conclusions that we would leave  
2 you with are, based upon a comprehensive analysis of our data:

3           . **suicidality** is part of the natural history of the  
4 disease of depression;

5           . compared to placebo, **fluoxetine** was not associate  
6 with an increase in the rate of suicidal acts and mood  
7 disorders;

8           . **fluoxetine** was associated with fewer cases of the  
9 emergence of substantial suicidal ideation than were seen with  
10 placebo;

11           . **fluoxetine** was more effective than placebo in  
12 reducing base-line to last-visit item 3 scores (in other  
13 words, improvement in suicidal ideation); --

14           (Slide)

15           -- there also was no evidence of suicidal acts or  
16 ideation in the non-mood disorders, bulimia **nervosa**, obesity,  
17 and obsessive-compulsive disorders;

18           . there was no evidence of a paradoxical or clinics;  
19 decompensation with regard to the treatment of **fluoxetine** in  
20 mood and non-mood disorders compared to the placebo rate that  
21 would be seen, in part, as reflective of the diversity of the  
22 clinical presentation of these disorders; and

23           . aggression or violence was less likely to occur  
24 with fluoxetine than with placebo.

It is our feeling that the major public health

1 concern relative to **suicidality** and depression is the current  
2 stigma, underrecognition, or undertreatment of a very serious  
3 disease and, secondarily, in those patients who do experience  
4 **suicidality** as a part of the disease, the concern about  
5 pharmacologic treatment is specifically the risk of drug  
6 overdosage.

7           With that, I would like to thank you for your time  
8 and return to Dr. Zerby.

9           DR. ZERBY: Thank you, Dr. Tollefson.

10           Let me very briefly summarize our data in reference  
11 to **the** questions posed to the committee. First, the only  
12 scientifically valid approach to the evaluation and treatment  
13 of emergent **suicidality** in depression is through an analysis  
14 of appropriately controlled data. Neither anecdotes or  
15 spontaneous reporting allow distinction between fluctuation of  
16 the severity of the underlying disease and the **treatment-**  
17 induced worsening.

18           No blinded controlled clinical trials have  
19 demonstrated an excess of either **suicidality** or violence  
20 during antidepressant therapy. To the contrary,  
21 antidepressants have been shown to improve suicidal thinking.  
22 Thus , credible scientific data demonstrating a causal  
23 association between antidepressants and **suicidality** do not  
24 exist.

25           Second, the rare anecdotal reports of suspected

1 antidepressant-induced **suicidality** are not unique in either  
2 occurrence or characteristics to any specific agent.

3           In response to the final question, neither the  
4 number of spontaneous events nor the nature of the specific  
5 events justify unsupported changes in labeling. The number of  
6 events observed with **fluoxetine** is entirely compatible with  
7 the age of the product, the extensive clinical use of the  
8 product, Lilly's vigorous reporting policy, and unprecedented  
9 publicity.

10           The anecdotal reports of suicidal ideation have no  
11 features which can reliably be identified as a unique syndrome  
12 beyond the spectrum of depressive illness. While additional  
13 studies, such as those which we have initiated, are  
14 appropriate, speculative labeling changes based on anecdotal  
15 data would benefit no one, while needlessly alarming and  
16 potentially hurting many seriously ill patients.

17           We will be glad to entertain additional questions.

18           DR. CASEY: Thank you, Dr. **Zerby**. I will ask the  
19 committee to now use a few minutes to address specific  
20 questions to the Lilly Company related only to their  
21 presentations, and if there are more general questions about  
22 the issues, we will have the Lilly people available as  
23 resources.

24           DR. DUNNER: It is my understanding that there was  
25 a difference in the reporting system by the company and,

1 therefore, to the FDA for this compound versus other  
2 compounds. That has been alluded to, that the reporting of  
3 adverse events has been more complete since the introduction  
4 of fluoxetine than with other compounds?

5 DR. ZERBY: The reporting system that Lilly has is  
6 applied to all Lilly compounds. There are no unique features  
7 of reporting for fluoxetine. I would hasten to emphasize some  
8 very critical points. We report everything, regardless of  
9 causality. That is all very compatible with FDA standards,  
10 but that point needs to be reemphasized. The conclusion that  
11 because a report exists in the data base the physician or we  
12 conclude that it is causally related is simply not true. Many  
13 of the cases that are in the data base, in fact, specifically  
14 indicate that the physician felt that the event was not  
15 related to fluoxetine, but we report that anyway.

16 The other thing to point out is that in the  
17 reporting we do not -- the patient need not be on the drug at  
18 the time that the event occurred. In other words, we report  
19 events if there has been some exposure to fluoxetine.

20 DR. DUNNER: Therefore, some of the reports that go  
21 into the FDA data base are reports that are coming from the  
22 clinician to the company to the FDA?

23 DR. ZERBY: That is right. In fact, that represent  
24 the majority of reports. Of the reports at the FDA, we think  
25 about 95 percent -- by FOI information -- come from Lilly. I

1 would add that 80 percent of those events are, by FDA  
2 standards, nonserious.

3 DR. DUNNER: So **in** order to understand this 500 to  
4 800 events that we are talking about today in some context,  
5 they could represent a maximal number of events that actually  
6 occurred in the U.S. and they also could represent some  
7 portion of the maximal number, dependent on the thoroughness  
8 of that reporting system on the part of Lilly?

9 DR. ZERBY: Everything we receive is reported to the  
10 FDA in compliance with their standards. I think the issue is  
11 how much information actually gets to us.

12 DR. LIEBERMAN: Dr. Tollefson, you presented some  
13 very thorough and clear analyses, which I presume were based  
14 predominantly on acute treatment studies, controlled acute  
15 treatment studies. Is that right?

16 DR. TOLLEFSON: The data from the depression trials,  
17 the acute double-blind component of the depression trials,  
18 ranged anywhere from four to 13 weeks. I would point out the  
19 reason for looking in the double-blind trial, obviously, is to  
20 try to control for other variables -- that was an advantage.

21 However, we have experience, in the non-mood  
22 disorders, with patients treated anywhere from six to 60  
23 weeks, and then in compassionate use protocols with  
24 **fluoxetine**, or other protocols that have been used outside of  
25 double-blind, there are experiences with well over one year o

1 exposure to the drug.

2 DR. LIEBERMAN: That is essentially what I was going  
3 to ask. If one looked at the controlled trial data solely,  
4 they might not extend through a hypothetical period of risk,  
5 and do you have data for longer periods of time, either  
6 maintenance treatment or --

7 DR. TOLLEFSON: I think that is an excellent  
8 question. What we decided to do is to take what we thought  
9 might be the worst-case scenario, and those were patients, a  
10 very large number, that were put on compassionate use. As you  
11 know," by definition, compassionate use patients are patients  
12 who have not responded to any other vigorous efforts at  
13 treatment and might be considered a high-risk group for  
14 suicide.

15 Looking at those patients, followed a mean of six  
16 months -- but, as I said earlier, the range being out over one  
17 year -- their rate of suicidal acts actually was less than  
18 that that has been reported by Winneker or as Jan Fawcett had  
19 cited, so even in that worst-case scenario the rates were less  
20 than what has been reported in the data as a whole by, again,  
21 Fawcett and Winneker.

22 DR. LIEBERMAN: Can you estimate the number of  
23 patients that may have been followed in that context?

24 DR. TOLLEFSON: It is approximately 800 patients in  
compassionate use trials.

1 DR. LEBER: Jeff, you were going somewhere with that  
2 question, and I wonder if you would like to explain where you  
3 were going? I think I know, but --

4 DR. LIEBERMAN: Why don't you say?

5 (Laughter)

6 DR. LEBER: I am presuming that you are trying to  
7 make the point that if the hazard, that is, the risk of having  
8 an adverse event, is nonuniform across the time of exposure,  
9 that events that have a hazard that rises late may not be  
10 captured, because relatively few people are placed at risk  
11 late; and that these relatively short-term studies lasting  
12 perhaps eight weeks, at most, in the domestic studies, up to  
13 maybe 12 or 13 weeks in non-domestic studies, have not looked  
14 enough at the chronic course of treatment, since episodes of  
15 depression are now treated six months to a year, to rule out  
16 the possibility that there is an emergence of something in the  
17 long run.

18 DR. TOLLEFSON: May I make one other comment on  
19 that, Dr. Leber?

20 DR. LEBER: I think Jeff was going there, and he is  
21 the one who has to tell me that he was.

22 DR. LIEBERMAN: That is exactly right.

23 DR. TOLLEFSON: I was going to say that we did also  
24 analyze the data based upon patient exposure to drug; that was  
25 the entire data base. There was no relationship between

1 suicidal acts and length of exposure.

2 DR. CASPER: I was wondering whether you could  
3 enlighten us whether the patients, I think in the U.S., in the  
4 **four-** to six-week treatment trials, were seen on a regular  
5 basis, probably evaluated weekly, were probably also in some  
6 other form of treatment, perhaps psychotherapy or family  
7 therapy or some other form of treatment, at least regular  
8 contact? That is, these patients did not take Prozac and did  
9 not see either their general practitioner or a psychiatrist  
10 for a prolonged period of time. They were under supervision.  
11 That "is question number one.

12 The second question relates to plasma-level  
13 monitoring. Have you ever considered plasma-level monitoring  
14 or have you done that with **fluoxetine**?

15 DR. TOLLEFSON: Your first question had to do with  
16 the protocol design, and I would say yes and no. The  
17 patients, obviously, as a standard for this type of clinical  
18 investigation, were followed regularly, and most often that  
19 meant a weekly visit. On the other token, they were not  
20 benefiting by other modes of therapy, nondrug therapy, such a  
21 psychotherapy, again, to protect the integrity of the clinics  
22 study of drug versus placebo.

23 Are they different from the patients that might be  
24 encountered in primary care practice as far as the level of  
25 follow-up? Possibly, yes. On the other token, they probably

1 represent a more severely depressed patient population with a  
 2 lot more risk factors for suicide than one would see in a  
 3 standard primary care office practice.

4           Regarding the second question, we have looked at  
 5 **fluoxetine** and its desmethylated metabolize. There is a lack  
 6 of any substantial correlation between those drug  
 7 concentrations and either therapeutic response or,  
 8 particularly, the issue of suicidal acts.

9           DR. ESCOBAR: This may relate to Dr. Lieberman's  
 10 question. In the preamble, I believe it was Dr. Nemeroff who  
 13 revie'wed the evidence for the relationship between suicide  
 12 ideation and the use of other antidepressants in the  
 13 controlled trials. It occurred to me that he did not review  
 14 the very few long-term maintenance studies, such as the one b:  
 15 Dr. Pryan. I would be interested in knowing, since Dr. Pryan  
 16 is here, whether there was any relationship.

17           DR. CASEY: Could we save that to committee  
 18 discussion and keep our questions specifically directed at  
 19 this time to the Lilly people? Bob, will you be available to  
 20 avoid or answer that question later on?

21           DR. PRYAN: Yes, I will be available.

22           DR. CASEY: Thank you.

23           DR. **HAMER**: This also is related to Dr. Lieberman's  
 24 question. I believe, in reading the material, that several o  
 the studies had open-label extensions and you did not analyze

1 -- or at least you did present -- the data from those. Did  
2 you analyze those data and, if so, how long were the open-  
3 label extensions and what kinds of results did you see?

4 DR. ZERBY: We have had patients treated in open-  
5 label extensions and compassionate use for up to **eight-and-a-**  
6 half years. In fact, there are about 2000 patients who have  
7 been treated for more than six months in some monitored way.  
8 The problem with the interpretation and the way that we did  
9 the controlled clinical trials is there is not a suitable  
10 comparator group. The way that we analyzed them is the way  
11 that "Dr. Tollefson mentioned, looking at the rates of  
12 occurrence, and then compared that to an epidemiologic data  
13 base. In reality, the numbers were actually lower than one  
14 would have expected from, for example, Dr. Fawcett's work.

15 DR. REGIER: I wanted to speak about Dr. Fawcett's  
16 presentation. As I understand the presentation, he mentioned  
17 that there were 954 individuals who were entered into that  
18 study and that of those 954 there were 13 who actually  
19 committed suicide within the first year of entry into the  
20 study, which, in relation to Dr. Teicher's question about bas  
21 rates, would amount to a completed suicide rate of 1.4  
22 percent. That is completed suicide as opposed to even suicid  
23 attempts.

24 I wonder if Dr. Fawcett could comment on those rate  
and if he has any information on rates of suicide attempts

1 with this population.

2 DR. FAWCETT: The suicide completion rate was lower  
3 than we had anticipated, based on other studies, although the  
4 percent of deaths was just as high. In other words, if you  
5 take the early studies that were quoted by Guze, we had, in  
6 our first year, 70 percent of the deaths reported were from  
7 suicide. Other studies just with one- or two-year follow-ups  
8 had reports that high, but the actual percent of the sample  
9 seemed quite low for the first year after hospitalization,  
10 although it represented 50 percent of the suicides that we  
11 had.

12 That is the face of our feeling, following  
13 treatment, which we could not match -- it was not controlled  
14 or randomly assigned -- but we felt treatment was not that  
15 intense as we expected in five university centers. So even  
16 with moderate treatment, we saw, I think, a not-too-high  
17 suicide rate. These were 85 percent inpatients that we were  
18 following.

19 They were equivalent to the rates reported way back  
20 by Lowcher in his ECT group, where he compared ECT against  
21 nothing and for 10 years he got a 1.5-percent rate of suicide  
22 in the ECT group versus 7 percent in the no-treatment group,  
23 so they were comparable to his ECT group for the first year.

24 As far as suicide attempts go, I know that about 26  
25 of those patients have made suicide attempts, and I cannot do

1 it by year, but I think in the first five years there were  
2 about 260 attempts, which averages out to about 5 percent a  
3 year, which is very similar to the Avery finding of non-ECT  
4 patients -- I think it was 5 to 7 percent of suicide attempts  
5 in the **Avery-Winneker** study, as I remember it.

6 Does that answer your question?

7 DR. REGIER: Yes. I think it is very important to  
8 deal with the issue, because Dr. **Teicher** had asked for your  
9 data base, and that speaks directly to the issue of what is  
10 the expected base rate in either a community population or in  
11 a clinical population.

12 DR. CLAGHORN: I would like to talk for a moment  
13 about the selection-bias issues. We have got a large sample  
14 of individuals but we have excluded from them people who are  
15 physically ill. We have excluded from them people who have  
16 significant suicidal thinking. We have really taken the lower  
17 end of that, sampled off the bottom end of that part of the  
18 range. We have made some selections on the basis of age. We  
19 have excluded a wide variety of other diagnoses.

20 I think the question emerges in the committee's min  
21 at this point, are we seeing something in our naturalistic  
22 reporting system that reflects a different selection of  
23 individuals than we see in the controlled clinical trials and  
24 therefore, there may be an incompatibility between those two  
lines of information?

1 Is there any way you could address the issue of how  
2 the broad population might differ from this selected  
3 population?

4 DR. ZERBY: That obviously is always a problem when  
5 you are dealing with experimental compounds and using placebo  
6 arms and trying to investigate the safety of a drug. One has  
7 to balance the ethics of putting seriously ill patients, for  
8 example, into the trial.

9 I would have to say, first of all, with regard to  
10 the **suicidality**, to reemphasize the point that Dr. Tollefson  
11 made, ' that really the only exclusion for **suicidality** was in  
12 the view of the investigator that that patient was at high  
13 suicidal risk at the time. Many of the patients, however, by  
14 looking at **HAMD** item 3 had significant suicidal ideation but  
15 were still enrolled.

16 The other thing that I would emphasize is that not  
17 all trials excluded patients even at high suicidal risk.  
18 About 50 percent of the trials outside the U.S. had no such  
19 exclusion and a few within the U.S. had no exclusion. So not  
20 all trials were that restrictive.

21 The other thing, as everyone is doing, we are trying  
22 to open up more widely age limits and so forth. We have an  
23 ongoing geriatric study. We will have a much better idea  
24 about those kinds of populations when that study is finally  
25 broken.

1 DR. CLAGHORN : One follow-up: Have you actually  
2 broken out the studies that did not use that exclusion and  
3 analyze them separately to confirm that they come to the same  
4 conclusion as the trials generally?

5 DR. TOLLEFSON: We looked at protocols that either  
6 included or excluded patients who had suicidal ideation or  
7 high suicide risk, and the data are really indistinguishable  
8 in the two different **subcohorts**.

9 DR. SCHOOLER: I wanted to follow the line of  
10 questioning that Dr. Claghorn was addressing in another way.  
11 One o'f the general problems with clinical trials is exclusions  
12 and who gets into them. From the data base that you have,  
13 which is a very elegant one, I think, approximately what  
14 number of cases would you estimate had been screened in order  
15 to get that number of patients into the studies, given the  
16 kinds of criteria that were set up in each one? Just  
17 roughly. Are you talking about 50 percent? 30?

18 DR. TOLLEFSON: I cannot give you an exact number.  
19 I think, in general, what you are talking about is probably  
20 about one out of two to one out of four patients who would be  
21 included. I do not know if anyone in our group would have  
22 that specific information right now.

23 LILLY REPRESENTATIVE: (Not at microphone). It  
24 varies from protocol to protocol --

DR. TOLLEFSON: The bottom line is there is

1 variation, depending on the protocol.

2 DR. ZERBY: One other thing perhaps worth noting is  
3 in that screening, some patients were screened out not **because**  
4 they are too ill but because they are not ill enough.

5 DR. SCHOOLER: I would say that still would affect  
6 the generalizability in both directions.

7 DR. TOLLEFSON: Outside of the controlled data base  
8 that we presented, I mentioned that we had compassionate use.  
9 There are also studies that have been done in mild depression  
10 or **dysthymia**, for example, so we have looked at a variety of  
11 different mood disorders, without any deviation from the basic  
12 concluding points that were made.

13 DR. MONTGOMERY: I have a comment which may help to  
14 answer Dr. Claghorn's very interesting point, and this is, we  
15 looked at a group -- the data were presented in the recent  
16 Florence meeting -- of 107 patients with a history of repeated  
17 suicide attempts, without major depression (they were largely  
18 personality disorders). We followed them up for six months or  
19 until they attempted suicide and we achieved a suicide attempt  
20 rate of 18 attempts in each group, representing a 35-percent  
21 attempt rate in this population. Clearly, people were  
22 dropping out as they went along, but the life table analysis  
23 that we did showed absolutely no difference in the attempt  
24 rate or in the speed of the attempt on drug or placebo, and  
25 that very largely backs up data in the nonmajor-depression

1 population which you have seen presented today.

2 DR. CASPER: I was amazed by Dr. Montgomery's  
3 comment that the attempt rate under drug was not less than  
4 under placebo conditions. Actually, from the data we have  
5 seen here today, you would expect a lower attempt rate in  
6 patients taking an effective antidepressant medication.

7 DR. MONTGOMERY: These patients were not depressed.  
8 They were not suffering from major depression and so,  
9 therefore, it is testing whether the drug was effective in  
10 those groups who maybe ought not to have received the  
11 antidepressant, and the answer for us was that there was no  
12 provocation of suicide. Neither was there induction of  
13 suicide attempts in that group.

14 DR. CASPER: Did they have any change in any other  
15 symptoms? Or did fluoxetine at the time have no effects on  
16 this population?

17 DR. MONTGOMERY: As far as we could tell, the  
18 difference between the drug and placebo was minimal. They  
19 followed exactly the same course in both groups.

20 DR. CASPER: I have, really, another question, and  
21 that concerns the group of patients who did not complete the  
22 studies. You said that the patients, actually,  
23 proportionately were less in number than those in tricyclic  
24 drug studies. Did you analyze the reasons why patients  
25 discontinued medication, dropped out of the study? I mean,

1 there are obviously many reasons why patients do not continue  
2 a particular drug study, but did you look at this population,  
3 because this might be a population which might be of interest  
4 to our discussion today, since they might have developed some  
5 symptoms or adverse reactions which, indeed, might be side  
6 effects of drugs done in only a very small population.

7 DR. TOLLEFSON: The question, if I understood, was  
8 on the slide that had to do with discontinuation for any  
9 reason or discontinuation due to an adverse event? I was not  
10 sure which one you were referring to.

11 DR. CASPER: Either one.

12 DR. TOLLEFSON: As you remember, the basic  
13 conclusions there were that patients compared to placebo on  
14 either tricyclic or fluoxetine were more likely to experience  
15 an adverse event, which would make sense. Fluoxetine rates,  
16 though, were significantly fewer than were seen with  
17 tricyclics. Then we moved on to a discussion of any  
18 discontinuation from study for any reason and, in fact, there  
19 were far fewer, statistically significantly fewer,  
20 discontinuations with drug therapy with fluoxetine than either  
21 with placebo or tricyclics, meaning more patients were  
22 retained in the study.

2 Now, had, from any of those three assignments,  
2 fluoxetine, placebo, or tricyclic, the patient experienced an  
2 increase in ideation potentially, theoretically, as an adverse

1 event, for example, in the placebo cell, it would have been  
2 captured in the analysis as a clinical worsening or, if the  
3 emergence were substantial it would have been caught in that  
4 ESSI , or emergence of substantial suicidal ideation.

5 Those individuals, remember, as we said in the  
6 definition of the data analysis, we were looking at a  
7 difference from base-line randomization to their last visit  
8 or, for that matter, any visit during the clinical study. So  
9 if they experienced that adverse event at a termination point  
10 of the study, they would have been included in the data  
11 analysis.

12 DR. CASPER: My question also concerned the **analysis**  
13 of adverse events, in general, not just suicidal ideation, but  
14 agitation, restlessness, or other symptoms. Did you look at  
15 those? Did you do an analysis in this population who  
16 discontinued the control trial?

17 DR. TOLLEFSON: For example, at the closure of the  
18 U.S. IND base at the end of 1989, suicidal acts or ideation as  
19 a side effect, if you would map it as such, under active  
20 treatment with **fluoxetine** was not in the top 20 events. The  
21 most common things were the ones that people would encounter  
22 in clinical practice, such as nausea, headache, or  
23 restlessness. We do have that. In fact, we could show you  
24 the rank ordering, if you are interested.

25 DR. MANN: One of the concerns that was expressed 01

1 a placard outside the building was that **Prozac** kills. One of  
2 the problems with the limitations of the data set generally  
3 being presented and discussed here from the controlled  
4 clinical trials and from the various kinds of continuation  
5 data that you have is that there are not any data on deaths  
6 through overdose.

7 I wonder, first, whether you could tell us a little  
8 bit about what in the analysis you might have done, using the  
9 DAWN data set, on actual fatalities due to suicide attempts or  
10 overdoses related to Prozac and, secondly, whether you have  
11 tapped the same data set in order to determine whether there  
12 are any differences between **fluoxetine** and other  
13 antidepressants in terms of presentations to emergency rooms,  
14 for example, with an overdose.

15 DR. TOLLEFSON: I would refer back to our review  
16 that we did do of the **epidemiological** data bases with this  
17 group. First of all, as you recall, when we looked at the PEM  
18 system, the **Inman** group that looked at over 12,700 **fluoxetine**  
19 recipients observed no evidence of **fluoxetine** induction of  
20 **suicidality** or suicidal deaths.

21 We then moved on to the DAWN data and there are two  
22 components that one can analyze within that Drug Abuse Warning  
23 Network. The first one was just general emergency room  
24 mentions. As I commented, in light of the volume or the  
popularity of the medication as a denominator, the DAWN data

1 base concluded there was no disproportionate increase in  
2 mentions of suicide at emergency rooms relative to **fluoxetine**

3           Then we moved to discuss, within the DAWN data, the  
4 other subset, which were medical examiner mentions of deaths  
5 and, in fact -- and we can show you those comparisons -- the  
6 **fluoxetine** experience, when considering, again, popularity by  
7 prescription, was substantially lower in medical examiner  
8 mentions than **tricyclic** antidepressants. That, I think,  
9 definitely reflects the differential therapeutic indices  
10 between conventional **tricyclics** and some of the more novel  
11 **serotonin-selective** uptake inhibitors.

12           Last but not least, is the general point from the  
13 National Center for Health Care Statistics that absolute  
14 numbers of suicides -- lethal, death -- have gone down  
15 somewhat since the launch of the product.

16           DR. ESCOBAR: Going back to the selection of the  
17 samples, I am particularly interested in having a general idea  
18 of the criteria to select particularly the nondepressive  
19 samples, because I have a hunch that in the real world  
20 **fluoxetine** is being used for a large number of nondepressed  
21 patients. Do you have any idea of what proportion of the  
22 individuals who entered those trials were real patients, users  
23 of services, and what percentage or proportion of them were  
24 symptomatic volunteers recruited through newspaper

advertisements and, if so, does your company have a specific

1 policy on those advertisements?

2 DR. TOLLEFSON: That is a very difficult question to  
3 address with regard to the percent of patients, say, derived  
4 from newspaper ads versus normal patient care. I would think  
5 that there would be more patients recruited in that way in the  
6 obesity trials than in the depression trials, the mental  
7 illness trials, and I think, for the most part, those are  
8 centers that are very highly skilled in those areas and have  
9 very selected populations and not generally seeking those from  
10 newspaper ads.

11 DR. ESCOBAR: Some of the companies have policies on  
12 the advertisements that are placed by the P.I.'s. Do you have  
13 any such policy?

14 DR. TOLLEFSON: Let me, just for one second, refer  
15 back to your earlier question. If you were speaking on the  
16 non-mood-disorder trials, obesity, OCD, and bulimia, those are  
17 patients in clinical studies using DSM-III-compatible criteria  
18 for OCD and for bulimia nervosa and defined criteria that are  
19 medically acceptable for obesity; those were not just random  
20 clinical observations.

21 DR. ESCOBAR: It is the way they are recruited, how  
22 they came to the attention of the investigators.

23 DR. TOLLEFSON: Now, again, that would not be a  
24 corporate issue. The corporation does not **recruit** patients.  
25 There are academic investigators who recruit patients. Some

1 academic centers, as you know, may use print advertising.  
2 That print advertising is subject to that institution's  
3 institutional review board policy and it would have to approve  
4 whatever advertisement was used.

5 DR. CASEY: Dr. Lin, please. Again, I ask people to  
6 have just specific comments to Lilly, so we can proceed with  
7 our committee discussion.

8 DR. LIN: I also have a question about the patient  
9 selection and potential bias. I think it is a very important  
10 question and I do not know whether there is an easy answer.  
11 In the case report literature, I think many authors suggested  
12 that patients with atypical depression, however it is defined,  
13 may be more susceptible to this kind of side effect. I wonder  
14 whether you have data to address that or whether there is any  
15 plan to look into that issue?

16 DR. TOLLEFSON: There clearly are published trials,  
17 not necessarily sponsored by Eli Lilly and Company, looking at  
18 selective serotonin-reuptake inhibitors such as **fluoxetine** in  
19 atypical depression. The data suggest, as I am sure you know,  
20 that the selective serotonin-reuptake inhibitors appear as  
21 efficacious as monoamine oxidase inhibitors and better  
22 tolerated and appear superior to **tricyclic** antidepressants in  
23 atypical disease. One would expect that with the classical  
24 features, with **hyperphasia, hypersomnia**, et cetera. They

would seem to be a reasonable option.

1           That is not necessarily based on our Lilly data base  
2 we heard today, but published academic literature.

3           DR. MONTGOMERY: One way of answering Dr. Escobar's  
4 interesting question is to comment on the difference between  
5 the international studies and those conducted in the U.S.A.,  
6 because my understanding is that the international studies did  
7 not have the ability to do recruitment by advertisement; it is  
8 not a technique for raising patients for studies in Europe.

9           I wonder whether you would confirm that, because  
10 that would help Dr. Escobar to answer that question.

11          DR. TOLLEFSON: Yes, that is true. Thank you.

12          DR. HELLANDER: I have a question about the doses of  
13 fluoxetine that were used. I am assuming that it was 20 to 80  
14 mg in all the studies, but could you tell us, perhaps, what  
15 percentage of the patients were on the lower end, 20, and what  
16 percentage were on the higher end, 80? Could you also try to  
17 do the same with estimating the percentage of the patients who  
18 were in the shorter trials, the four- to five-week trials and  
19 those who were in the longer ones, toward the 24-week end?

20          DR. ZERBY: I am only able to give you a  
21 gross estimate -- some of my colleagues may be able to  
22 clarify it. There are a large number of patients at the high  
23 doses of fluoxetine in these trials. Many of the early  
24 trials with fluoxetine were done at higher doses than  
25 subsequent trials, when we looked at fixed doses. My

1 estimate would be that roughly 40 percent were 40 to 60 mg  
2 and probably 20 to 30 percent were at 20 mg.

3 DR. TOLLEFSON: I would like to reiterate the  
4 comment, though, that we did, in the fixed-dose studies, which  
5 ranged from 5 mg to 60 mg, an analysis to see if there was any  
6 association between suicidal acts or ideation and dosage and  
7 there was none.

8 DR. TEICHER: A couple of questions. In terms of  
9 the coroners' data, where you showed the extraordinarily low  
10 frequency of adverse reports with fluoxetine, did this require  
11 that the coroners pick them up on assay and were they all  
12 prepared to do assays on it, or required that it be documented  
13 in some way in terms of medical history? How did they know  
14 that they were on fluoxetine?

15 DR. ZERBY: They did not require assay confirmation..  
16 In fact, it could be as little as some evidence that they were  
17 on the drug would be sufficient as a coroner's mention or  
18 medical examiner's mention.

19 DR. TEICHER: I am interested in the converse. In  
20 some cases, say, with tricyclics, did they say that the  
21 patient was on tricyclic because they had toxicology data, and  
22 were those toxicology data in some instances not available for  
23 fluoxetine?

24 DR. ZERBY: I do not know exactly how one can answer  
25 that. I know assays for fluoxetine now are not uncommon and

1 people can assay for that. I do not think there is any  
2 limitation in the ability to measure it. I guess I would be  
3 almost more concerned, with all the publicity, with even the  
4 coroners being influenced by the recognition, by saying this  
5 patient may have been on Prozac, when, in fact, the patient  
6 was not on Prozac.

7 I think there are issues, too, that emerge with  
8 medical examiner mentions.

9 DR. TEICHER: I think, also, it should be noted in  
10 terms of the trend of the mortality or number of suicides  
11 going down over time, one important fact to filter into that,  
12 that I am sure you are aware of, is that it has always been  
13 reported in epidemiological studies that one thing that  
14 influences the overall rate of suicides is whether the country  
15 is at war or not, and there was a conflagration.

16 The other thing is that in terms of our case report  
17 our first patient was in a Lilly-sponsored trial that we  
18 reported. The interesting thing was, her Hamilton Depression  
19 Score, item 3, was completely insensitive to the change. She  
20 started out with a 3, because she had some very, very mild  
21 suicidal thought. She basically thought for about three  
22 seconds that she wanted to take all her pills, said it was  
23 foolish, and went no further.

— 24 Then, during the course of treatment, it became  
25 obsessive and unrelenting, but it still scored a 3 -- it did

1 not go to a 4 -- and an earlier one was lower than that. If  
2 we looked at most of our cases, that would have been the way  
3 they went. So the Hamilton item itself is not a great fine  
4 screen for suicide; it is a very coarse instrument. That may  
5 be a problem in really interpreting those data.

6 DR. TOLLEFSON: I would just open it up. This  
7 committee has greater expertise than I, but I think if someone  
8 only had a mild, transient thought of suicide, many  
9 investigators would not have scored that a 3.

10 DR. TEICHER: But it was.

11 DR. TOLLEFSON: There is a continuum on the Hamilton  
12 in the absence of suicidality to, on the far end, an act, and  
13 what we tried to capture in the definition of emergence of  
14 substantial suicidal ideation was what I thought your patient  
15 had had, and that is the absence or relative absence of  
16 ideation, going to a very strong, intense ideation, with or  
17 without an act.

18 I would just add, we did look at other indices. In  
19 the international trials we had Dr. Montgomery's scale  
20 available. We also used a patient report, the Hopkins Symptom  
21 Checklist, item 15, subjective patient report, on the  
22 intensity of ideation or on hurting one's self, or thoughts of  
23 death. None of those three outcome measures, the MADRAS  
24 [phonetic], the Hopkins Symptom Checklist, or the Hamilton,  
25 showed any deviant results. They were all entirely

1 consistent.

2 DR. LEBER: I have a clarification. I may have  
3 missed this, because I was out taking care of some  
4 administrative business, but when you were presenting the DAW  
5 mentions from the medical examiners, is there a breakout  
6 between those which are overdose completed suicides and those  
7 which are violent completed suicides? Obviously, there is an  
8 interaction there. The patients are selected for the overdose  
9 suicides by virtue of the other type of antidepressant they  
10 are using, whereas within the, say, violent type, hanging,  
11 shooting, et cetera, that is the group I presume we would want  
12 to look at if we were doing any kind of case control  
13 methodology.

14 DR. ZERBY: To my knowledge, that has not been  
15 broken out, by violent or overdose. It is just the  
16 implication that the drug was involved in some way, but not  
17 necessarily overdose.

18 DR. TOLLEFSON: Although I think one could say that  
19 if the patient -- we are looking at patients in that study,  
20 Dr. Leber, that, given the safety profile of the drug, they  
21 would probably, if they were really truly suicidal and wanted  
22 to end their lives, they would have to find a method other  
23 than **fluoxetine**.

24 DR. LEBER: That was precisely my point, because if  
25 I wanted to look at the cause prevalence, if you will (and yo

1 have to adjust it for market share and the time in the  
 2 calendar year), in the group that committed suicide by a  
 3 violent means (not the group that overdosed, because that wil.  
 4 not give you a sample of fluoxetine exposures), you want to  
 5 look back among those who completed suicide, correcting for  
 6 use of drug in that particular epoch in which they committed  
 7 the suicide, to find out whether there is anything. I do not  
 8 think that has been done yet. I know that other people have  
 9 probably thought of the same thing, but I wondered if you had  
 10 done it.

11 DR. TOLLEFSON: The DAWN data, as far as the  
 1: emergency room mentions, of course, focus on suicidality, but  
 1: the medical examiner mentions are on fatalities and then  
 14 linkages with antidepressants, so it is not unique to just  
 1! have drug overdosing as a method of death.

1! DR. CASEY: Thank you very much. We appreciate your  
 1' time and your presentations. We now move to the phase of the  
 1: meeting where the committee will address the questions put  
 1 forward by the FDA. We are also able to discuss other issues  
 2 which we bring to the table which we think will be relevant.

2 COMMITTEE DISCUSSION/RECOMMENDATION (S)

2 The four questions are:

2 . "i. Is there credible evidence to support a  
 2 conclusion that antidepressant drugs cause the emergence  
 2 and/or intensification of suicidality and/or other violent

1 behaviors?

2 . "ii. If so, does the evidence indicate that a  
3 particular drug or drug class pose a greater risk than others

4 . "iii. If the whole class or a particular drug  
5 cause emergence and/or intensification of **suicidality**, what  
6 actions, if any, should the Agency take?

7 . "iv. Even in the absence of sufficient evidence  
8 to establish causation, do the large volume of reports and/or  
9 the type of reports received justify some Agency action, e.g.  
10 a modification of labeling for some or all antidepressants?"

11 I would like to go to the first question, initially  
12 "Is there credible evidence to support a conclusion that  
13 antidepressant drugs cause the emergence and/or  
14 intensification of **suicidality** and/or other violent  
15 behaviors?" I open the question for discussion by the  
16 committee.

17 DR. **HAMER**: Like everyone else on the committee, I  
18 read all the material very carefully before I came here. I  
19 paid attention carefully to the presentations. These data  
20 have been analyzed very thoroughly, I think. A statistician,  
21 I do not remember exactly who it was -- it may have been John  
22 Tookey -- once said, "If you torture the data, they'll  
23 confess. "

24 I think these data have been tortured thoroughly,  
and they still have not confessed. I mean, there have been s

1 many P values and so few significant ones and so fewer that  
2 showed any indication that antidepressants seemed to play a  
3 role in attempts or emergent suicidal ideation, I would find  
4 a hard time answering "yes" to question i.

5 DR. CASEY: How about answering "no?"

6 (Laughter)

7 DR. HAMER: To answer "no," you are asking me to  
8 accept the null hypothesis. Of course, as a statistician, I  
9 can never accept the null hypothesis. But I am surely coming  
10 close.

11 DR. MONTGOMERY: There is one important study which  
12 has not been discussed today, and that is the study of  
13 maprotiline in long-term treatment, a one-year study looking  
14 at two different doses of maprotiline against placebo. That  
15 study, with 1100 patients in it over a one-year period, has  
16 sufficient power to test for the presence of suicidal acts and  
17 it reported that maprotiline was associated with a significant  
18 increase in suicidal acts compared with placebo.

19 It is a one-off [phonetic] study. It is the only  
20 one I can find in the literature with sufficient power to be  
21 able to test it and it goes to some way, along with the report  
22 of Soloff, who reported, in a very much smaller number of  
23 patients in an acute study, as Dr. Fawcett has said, that  
24 amitriptyline may be associated with an increase.

I would take both of these studies as warnings that

1 the phenomenon may exist for some antidepressants. But I am  
2 not in the habit of accepting data on a single study and I  
3 would commend this committee to watch this situation  
4 relatively closely in the meantime.

5 The other area of concern is that the  
6 benzodiazepines have a labeling for the provocation of  
7 suicidal acts in some places in Europe. That is based very  
8 largely on anecdotal data but there is a study, again, by  
9 Calgary and Gardner, with **alprazolam** provoking suicide  
10 attempts. I would put the benzodiazepines, possibly, in a  
11 **category** which you would need to watch a little bit more  
12 closely.

13 The question you ask, for the data that have been  
14 presented today, I must say that I agree absolutely that the  
15 data are neutral to positive, that there seem to be less  
16 effects than placebo, rather similar to other antidepressants

17 DR. CASEY: The **maprotiline** data, that was a two-  
18 dose study against placebo?

19 DR. MONTGOMERY: Yes.

20 DR. CASEY: Are the results dose-related?

21 DR. MONTGOMERY: No, very interestingly, the doses  
22 that they chose were very low, 37.5 mg versus 75 mg of  
23 maprotiline versus placebo in three equal groups, and the  
24 attempt rates were equal in very low-dose and in the 75-mg  
25 dose groups, so there appears to be no dose relationship

1 there. This is an important study, because it found that botl  
2 doses of maprotiline were better than placebo in reducing  
3 subsequent depressive episodes in this long-term efficacy  
4 trial. So, therefore, it indicates that suicide and suicidal  
5 attempts may be dissociated from the recrudescence of  
6 depression. So that is something that is a warning to us tha  
7 we should carry on looking at these data very carefully.

8 DR. CASEY: Was concomitant medication allowed in  
9 patients in that study?

10 DR. MONTGOMERY: I am afraid that all I have of the  
11 trial' is a French publication and it needs to be examined in  
12 far greater detail.

13 DR. LEBER: I wanted to bring out something that Dr  
14 Montgomery just mentioned that I think that we would want to  
15 emphasize. The evidence presented today includes not only th  
16 evidence from controlled comparisons, but all the other  
17 evidence that we heard, some of which is anecdotal, and that  
18 is not always inappropriate, because it is possible to  
19 conceive of some anecdotal reports as an N of one experiment  
20 in which sequences of events are so improbable in the absence  
21 of treatment that you conclude that the drug might have done  
22 it.

23 I think we are trying to get a broad answer to this  
24 question. We understand that the rates, if they exist (we  
25 came to that conclusion almost unaided) , are probably quite

1 low, but does the possibility still exist in your minds as a  
2 reasonable one? Do you think there is any evidence on the  
3 basis of the reports and anecdotes that you have had and heard  
4 about that it does? For example, Dr. Teicher is here for a  
5 reason. He was convinced. He is a reasonable man, an  
6 academic psychiatrist. Why? What persuaded some of you and  
7 not others?

8 So when you answer this question, I hope you will  
9 focus not only on the controlled trial data, which I think Dr  
10 Lieberman pointed out is covering a small proportion of the  
11 total time-duration of the average treatment course, and look  
12 at all the evidence and see where it is weak and where it is  
13 strong. So with that charge added to it --

14 DR. MANN: In relation to Dr. Leber's cement, what  
15 we can learn from the data that have been presented is that  
16 patients who are on antidepressants are not entirely free from  
17 the problem of suicidal ideation, attempts, or completions.  
18 We are dealing here with probabilities and, from a statistic  
19 standpoint, the drugs basically seem to be ranging between, a  
20 Dr. Montgomery mentioned, neutral and favorable -- some may  
21 say highly favorable.

22 But that still does not mean that there are no  
23 patients in whom one finds suicide attempts, suicide  
24 completions, and perhaps the development of severe distressing  
25 suicidal thoughts. The nature of things being what it is, it

1 is from that group that we hear those very painful stories  
2 this morning. Nevertheless, overall, one would have to look  
3 at things from a statistical standpoint. Is this more than  
4 just the effects of the illness, environment, and a range of  
5 other things that antidepressants cannot completely suppress  
6 in their treatment of depression?

7 At this point, I find it difficult to conclude that  
8 there is specific evidence that the antidepressant plays an  
9 aggravating role. Again, I see these anecdotes, therefore, as  
10 suggestions of areas that need to be looked at very closely,  
11 but in their own right they do not represent sufficient  
12 evidence to act on.

13 DR. TEMPLE: It was Dr. Fawcett, I think, but, in  
14 any event, one of the presenters under the Lilly banner, who  
15 referred to the possibility the so-called roll-back phenomenon  
16 as if it were an established truth. Now, you can call that  
17 unmasking something that was there already, or you can call it  
18 provocation -- it does not really matter which it is,  
19 necessarily -- but it could suggest that people who start on  
20 an antidepressant are placed at increased risk of suicide  
21 because of that.

22 Obviously, I have no knowledge in this area, but it  
23 was presented as if everybody knew this. Is this something  
24 everybody knows, because nothing quite to that effect is  
25 stated in the labeling that says you should watch out when you

1 start someone, because he may not be cured of his problems  
2 right away. It certainly does not say his risk may actually  
3 be increased during that period. I guess I would like to hear  
4 some flavor of that.

5           Then I have one other question to throw out to the  
6 committee, which is this: The discussion we heard earlier  
7 showed that people who commit suicide are highly likely to  
8 have a diagnosis of depression, which means that somebody  
9 identified them as in a high-risk category. But there were  
10 still a significant number of people who committed suicide  
11 without having that sort of diagnosis and I guess I would like  
12 some advice or discussion of who those people are.

13           I ask it for the following reason. The anecdotes  
14 that one hears that are most evocative, to me, anyway, are not  
15 the ones where people have had a 20-year history of suicidal  
16 ideation and then finally do it -- that is not too surprising  
17 -- it is where they assert that there has never been anything  
18 in their minds like that before and yet now they have suddenly  
19 become excessively concerned with suicide and may even do it.  
20 Of course, it is hard to know what was in their minds all  
21 these years, but those are the stories we hear.

22           So those two questions really relate to the same  
23 phenomenon, which is how to evaluate some of the anecdotes,  
24 and are those telling you anything, even if the amassed data  
we have heard are fairly persuasive on the idea that there is

1 nothing going on?

2 DR. REGIER: One of the things that was most  
3 striking about the anecdotes -- 1 should say the personal  
4 stories -- that were presented was that many of them did  
5 exhibit some complications, as does Dr. Teicher's. In  
6 particular, the co-occurrence of substance abuse in a major  
7 depression increases the risk of suicide in the population, a  
8 reflected in some of the epidemiological studies. The risk o  
9 a suicide attempt for somebody with uncomplicated major  
10 depression is about 12 to 13 percent, lifetime. The risk of  
11 a suicide attempt for somebody who has both a major depressio  
12 and a history of use of an addictive substance, either alcoh  
13 or drugs, is double that, or 25 percent.

14 This is something that may be a factor in some of  
15 the uncontrolled case studies that we have, and in Dr.  
16 Teicher's cases we also have some very complicated, both  
17 neurological and personality disorder, cases in which there  
18 may be some interaction, both between the disorders and  
19 increase in suicide risk and an as-of-yet-undetermined  
20 interaction of the medication with those disorders.

21 I think that it is important to have the large  
22 clinical trials to determine the efficacy of the drug and als  
23 the risk of side effects in these controlled trials, but in  
24 routine practice I think it is important to warn, I guess  
practitioners, that where there are concurrent disorders, the

1 there is an additional need to be careful about monitoring  
2 patients who are on these medications and, for that matter,  
3 for those who are not on these medications.

4 DR. CASEY: In relation to that, Dr. Leber has given  
5 me an excerpted translation of the French study that Dr.  
6 Montgomery referred to. In relation to my inquiry about  
7 concomitant medication, it says, "The only possible  
8 therapeutic associations" -- meaning those also allowed --  
9 "were benzodiazepine-type tranquilizers, Clobazam, lorazepam,  
10 and flunitrazepam. " So, once again, we have the complication  
11 that 'the benzodiazepines in that setting make it more  
12 difficult to understand the **maprotiline** data.

13 DR. SCHOOLER: To come back to question i., I have  
14 some concerns about a response to that question, and that is  
15 that it is not clear to me that data have been evaluated with  
16 respect to these questions for the wide range of  
17 antidepressants with the kind of attention that the fluoxetine  
18 data have received. Indeed, it is very clear that within the  
19 FDA's own reporting system terms dealing with suicide have  
20 only been there since 1989. That is one point.

21 The second is, I found myself enormously touched and  
22 responsive to a number of the stories that we heard this  
23 morning and, in particular, to the point Dr. Temple raised, I  
24 think, that many of these seem to be unprovoked in the sense  
25 of having lengthy histories. I guess I would say that the

1 data from the trials that were presented here, I think, are  
2 very convincing as far as they go, but I am not completely  
3 convinced that those are all the data that we need in order t  
4 be able to say, no, there is no credible evidence to support  
5 a conclusion that antidepressants \_\_\_\_\_ -- you know,  
6 complete the sentence.

7 I guess the question that I would raise in turn  
8 would be what would additional data be that we might want to  
9 see that would make it possible for me to say the data -- and  
10 by that I would mean a wide range of data, not just the  
11 clinical trial data -- have been tortured and they have indee  
12 not confessed.

13 DR. CASEY: I agree, and I think you will probably  
14 have a large number of committee members agree. Given the  
15 information that we do have, do you feel that -- that is  
16 related to question i., and I know you want the caveat that "  
17 don't feel I have all the data," but, on the other hand, we  
18 have to live with what we have and we have to make some  
19 decisions and give some guidance.

20 Your last point is really issue number iv., which I  
21 think we can have a creative discussion about: How shall we  
22 go about addressing issues that are now missing from our  
23 information base?

- 24 But given the information base we have now, do you  
feel that there is evidence to conclude that antidepressant

1 drugs cause the emergence and/or intensification of  
2 suicidality?

3 DR. SCHOOLER: I will go a step further, then, which  
4 is that we had a certain amount of data presented here this  
5 morning and this afternoon. Then, just a few minutes ago Dr.  
6 Montgomery mentioned a **maprotiline** trial which was certainly  
7 not familiar to me -- this is not an area of expertise for me  
8 -- but it was my sense that it was not familiar to a large  
9 number of people around the table. My question is, is it that  
10 we are restricted to the data that have been turned up here  
11 today or are we looking more broadly at what evidence there is  
12 available?

13 DR. CASEY: We are not restricted. If you would  
14 like to sit on the fence, it is quite fine.

15 DR. SCHOOLER: For the moment.

16 DR. LEBER: A technical point: Obviously, data are  
17 accumulating. I believe I first heard of this paper this  
18 summer when I was a guest of Dr. Montgomery in July. A paper  
19 appearing this week in The British Journal of Medicine is  
20 going to report on a **meta-analysis** of **fluoxetine** and it will  
21 cite this particular paper. So this particular paper is not  
22 widely known now; it will be shortly. It is available in  
23 French.

24 Are you holding up the BMJ? There we have an  
illustration of it and you are welcome to take a look. This

1 is the meta-analysis that does reference the French paper.

2 The point I was trying to make is that obviously  
3 data keep coming in and we keep looking at them and you will  
4 iterate toward what you believe is the correct position.

5 The one thing I would ask about that one single  
6 case, though, is you have one thing I guess we would call the  
7 experiment-wise error rate. Clearly, we are doing hundreds  
8 and hundreds of controlled comparisons. Surely once in a  
9 while some will turn out to show a difference that  
10 incriminates the drug. I think Stu was making the point that  
11 he does not like one occasion of anything: It is not one  
12 swallow that makes the summer.

13 How does everyone else feel about that? Are these  
14 types of studies going to be persuasive?

15 DR. LIEBERMAN: Let me make a couple of comments by  
16 way of responding to question i. I think if anything has been  
17 driven home today, it is that many more people suffer and die  
18 from not receiving medication for depression than are harmed  
19 or die from receiving treatment with antidepressant  
20 medications .

21 The question then becomes at what cost is this in  
22 terms of adverse effects potential? In terms of the data that  
23 we have heard about today and are aware of from the  
24 literature, there are controlled data, which is the preferred  
25 mode of data, and then there is the spontaneous reporting

1 system, or anecdotal data. Both have their various  
2 limitations.

3 The controlled data have limitations, maybe, in  
4 terms of generalizability and in terms of not extending  
5 entirely through the period of risk. Spontaneous reporting  
6 system data and the anecdotal or case report data have  
7 inherent limitations in them, but reflect the mass of  
8 information that is known to date.

9 Based on both sets, it is hard to say that there  
10 appears to be any credible evidence indicating an increased  
11 risk 'for antidepressants inducing suicidal behavior. The mos  
12 compelling evidence clearly was the very dramatic and tragic  
13 testimonials by individuals this morning which have impacted  
14 terribly on their lives, and that is hard to ignore. Placing  
15 that against the objective evidence that is normally evaluate  
16 scientifically, it still seems that there is not a credible  
17 basis on which to determine that there is an increased risk o  
18 antidepressant drugs, unless the methodology that has been  
19 used heretofore to evaluate that -- and it may be that  
20 clinical trial methodology is less sensitive to indices of  
21 suicidal behavior -- but unless the methodology was greatly  
22 flawed, it does not seem to have turned up in a very  
23 conspicuous way.

- 24 DR. STANLEY: To actually continue on with Jeff's  
point about the methodology, it has been suggested that

1 perhaps the assessments of suicidal ideation or acts may not  
2 be as sensitive as we would like in some of the controlled  
3 trials . As someone who works in this field, we grapple with  
4 this all the time in trying to come up with adequate measures

5 I see it as a difficulty in general for the field.  
6 We are right now struggling with trying to come up with  
7 measures for impulsiveness and this poses great difficulty.  
8 I think it would not be a bad idea to consider in the future,  
9 as part of clinical trials where this issue is pertinent, tha  
10 some more elaborate forms of assessment, either of suicidal  
11 ideation or acts, maybe possibly expanding to acts of  
12 aggression of violence, be included.

13 DR. CASEY: Given that, what is your sense of an  
14 answer for question i?

15 DR. STANLEY: Again, like, I think, everyone here,  
16 I was greatly moved by the personal comments of the  
17 individuals who have experienced hard times, suicidal  
18 behavior and aggression and violence. I try to look at that  
19 experience that is reported individually and then go to the  
20 clinical trials, which, despite their drawbacks and whatever  
21 limitations there are, provide for me, as a scientist, the  
22 frame of reference that I feel most comfortable with in  
23 judging whether something is real or not above a certain  
24 probability.

Even within that context, as far as I could see,

1 there was no support to say that there is credible evidence of  
2 a causal link. In trying to put in context the anecdotal  
3 remarks, I look -- because as has been mentioned by a number  
4 of people here, they are, in some instances, very complicated  
5 cases -- so I try to look at their experience in light of the  
6 controlled trials that are in the nondepression sector. For  
7 the bulimia, the OCD, and for the obesity, again, I do not see  
8 any kind of induction of suicidal behavior, so I do not see  
9 that there is a causal link.

10 DR. LIN: I want to first say that I am generally in  
11 agreement with what has been said, especially what Dr.  
12 Lieberman mentioned earlier. I think the kind of information  
13 that we have been receiving and talking about belong to two  
14 areas. One belongs more in the area of hypothesis generation  
15 and the other area is more hypothesis testing. Both are  
16 important, but in making decisions, we have to rely more on  
17 the resource of hypothesis testing that has to come from the  
18 placebo-controlled double-blind studies. The evidence that we  
19 have looked at so far very clearly indicates that there is no  
20 evidence in terms of association between the drug and suicide  
21 risk.

22 However, the case reports are still valuable in the  
23 sense that even though they do not point to an increased  
24 suicidal risk in the population of more typically depressed  
25 patients tested in the studies that have been reported, maybe

1 the case reports and the results from the surveillance data  
2 can be looked at to see whether they point to any more  
3 specific hypotheses that could be tested in the future, such  
4 as maybe subgroups that may be at high risk that we do not  
5 know about.

6 DR. TAMMINGA: I would continue along the vein that  
7 Drs. Lieberman, Stanley, and Lin have been talking. I will  
8 try to articulate a "no" answer to question number i., in that  
9 Dr. Leber has actually called together a committee of science  
10 advisers, and unless you call for our resignation, as was  
11 suggested this morning, in fact, I think that the kind of  
12 advice you get from a group like us needs to be based on the  
13 numbers that have been presented. Clearly, from the data that  
14 have been presented, it would be hard to answer anything but  
15 "no" to question number i.

16 But , also, in listening to the personal reports that  
17 were given this morning, one would have to think of those  
18 personal reports as being either entirely coincidental to the  
19 drug treatment or perhaps some rare idiosyncratic reaction to  
20 the drug. As I was listening to the stories that were  
21 presented, it was hard to understand some commonality of  
22 response that would have made me think of a possible mechanism  
23 for a rare idiosyncratic response, because there were such  
24 differences in the stories that were presented.

25 It would seem to me that if some rare idiosyncratic

1 response to **fluoxetine** or to the other antidepressants is  
2 occurring, it would really take a much bigger data base than  
3 what we have to make a conclusion on that. So I would give a  
4 "no" answer to question number i.

5 DR. CASEY: **Are** there other committee members who  
6 want to address this? If you do not volunteer, I will ask you  
7 about question i.

8 DR. CASPER: I would want to join the committee  
9 members who have spoken by considering the data which have  
10 been presented and the data we have available right now on the  
11 populations which have been studied, on populations of  
12 depressed patients which have been studied. I do not think  
13 one could answer the first question but with a "no."

14 But I want to qualify my answer, because reviewing  
15 the literature and the reports we have received and listening  
16 to the heart-rending reports we have heard this morning, there  
17 are, I think, some common factors which might present  
18 themselves as risk factors.

19 In Dr. Teicher's report, what emerges is that  
20 patients were treated despite the fact that their depression  
21 did not improve. They continued treatment with **fluoxetine**.  
22 In some of the other reports we have received in the  
23 literature, the same has happened.

24 Now, this is not common in clinical practice and, I  
25 would venture, was very uncommon when tricyclic

1 antidepressants were introduced into psychiatric treatment.  
2 We were actually quite careful, and one would, knowing what we  
3 have heard again and again repeated today, knowing that  
4 depression is frequently and not uncommonly associated with  
5 suicidal thoughts, fantasies, ideas, which can emerge, which  
6 can disappear, which can reemerge, and cause sometimes  
7 suicidal acts -- if one knows this and one treats anyone with  
8 an antidepressant, one of course monitors the response. I  
9 have been concerned about the therapeutic optimism in trying  
10 to continue to treat patients who have not responded with a  
11 particular antidepressant.

12 So I would want to qualify my response in that under  
13 proper conditions of psychiatric treatment, and I would also  
14 want to mention this again in response to the reports that we  
15 have heard this morning, most of the men or women who were  
16 placed on fluoxetine I do not believe were really seen in  
17 treatment or monitored on a regular basis.

18 I think under those conditions an antidepressant  
19 might be associated with increasing suicidal ideation. I do  
20 not think we could at this point say whether it is causative,  
21 but we cannot rule out that the agent might not be involved in  
22 suicidal ideation, because the depression goes untreated.

23 DR. CASEY: Dr. Hellander?

24 DR. HELLANDER: I did not think I was going to get  
to comment, since I am not a voting member.

1 I am as hesitant to reach a conclusion on the basis  
2 of such preliminary evidence as anyone, and so I will not. I  
3 think the Lilly data are obviously very reassuring, although  
4 I am very concerned about the issues that we raised about the  
5 possibility of selection bias, that what they observed is not  
6 really what is happening. I think it is also true that it  
7 could be a rare side effect that would not be picked up in  
8 their clinical trials.

9 Also, I guess I am very disappointed today that we  
10 have not heard from the three people who have perhaps reported  
11 the most cases. We have not heard much from Teicher today, we  
12 have not heard from Worshing in Los Angeles about the  
13 association of akathisia with desperate thoughts, we have not  
14 heard from King and the association of treatment of OCD in  
15 children with fluoxetine, possibly with the emergence of some  
16 suicidal behavior.

17 I remain concerned that a small subgroup of people  
18 might respond badly to Prozac and other antidepressants and  
19 that we are perhaps missing them in looking only at the  
20 aggregate effect. Perhaps at this point it is so preliminary  
21 -- it has only been a year, I guess, or so since this effect  
22 has been suggested. The large data bases we have looked at  
23 have been, obviously, from the drug company itself. I guess  
24 I would like to see other data that would support that.

DR. TAMMINGA: I think that the committee would

1 appreciate, Dr. **Hellander**, your making some of the arguments  
2 of those people whom you just mentioned in lieu of their **bein**  
3 here.

4 DR. HELLANDER: Well, Teicher is here, and I would  
5 actually really appreciate it if he would have a few moments  
6 to talk, because I am very interested in his views and fully  
7 expected them to be more elucidated.

8 But the known side effects of Prozac are very  
9 different from the tricyclics. They are anxiety, insomnia,  
10 and agitation, some restlessness. In particular, Dr. Worshin  
11 in Los Angeles believes that in some patients, he has seen  
12 five patients with movement disorders -- he is actually a  
13 disorder movement specialist -- who develop akathisia on  
14 Prozac and, associated with this restlessness and terrible  
15 feeling that they had because of that, can develop some  
16 desperate thoughts. It was not like out of the blue they  
17 wanted to kill themselves; it was that they were so  
18 uncomfortable from the akathisia that they then became sort o  
19 desperate and became suicidal. With treatment of the  
20 underlying problem of akathisia, for example, with either  
21 dosage reduction of **fluoxetine** until the akathisia  
22 disappeared, or treatment with a beta-blocker, they did  
23 better. Or else taking them off of **Prozac** altogether their  
- 24 suicidal ideation disappeared.

That was his hypothesis. Not everybody agrees with

1 this. I have talked to other psychiatrists who treat a lot of  
2 schizophrenics who say they see neuroleptic-induced akathisia  
3 all the time and it is not particularly associated with  
4 desperate suicidal thoughts. So it is only a hypothesis and  
5 by no means confirmed. But that is what one person has  
6 observed and it is quite convinced of.

7 DR. CASEY: Could we save some of these for question  
8 ii, because I think we are expanding beyond --

9 DR. LEBER: Dr. Temple points out that we cannot get  
10 to question ii until we answer question i.

11 DR. CASEY: Watch me get to question ii.

12 (Laughter)

13 DR. ESCOBAR: My answer to question i. is clearly  
14 "no." But I believe there is a signal. A signal of what, I  
15 am not sure. It is not only the very moving testimonials we  
16 heard this morning but also the European data that Dr.  
17 Montgomery referred to, but also the concern I have about the  
18 lack of long-term controlled data we have in this country.

19 With that qualifying statement, I need to answer  
20 "no" to question i.

21 DR. LIEBERMAN: I was going to comment that although  
22 it seems that we are reaching a consensus in terms of general  
23 antidepressants and nonevidence to indicate increased risk for  
24 suicidal behavior in response to question i., there are  
25 lingering issues regarding **fluoxetine** that are being raised.

1 I think one of them has to do with not just the issue of  
2 suicidal behavior or self-aggressive behavior, but whether its  
3 side effects are different.

4           Clearly, it has a different side-effect profile, but  
5 in many respects that is a favorable aspect of the drug in  
6 terms of its utility. There may be, also, and this is  
7 something in relation to question ii. that might be  
8 considered, there may be some unfavorable aspects of its side-  
9 effect profile that relate to the major issue before Us of  
10 aggressive and suicidal behavior, but it sounds like we are  
11 sort "of moving off the general antidepressants and focusing  
12 more on the general clinical effects of fluoxetine.

13           DR. CASEY: I agree. Dr. Teicher?

14           DR. TEICHER: I would like to give a different tack  
15 on the issue and a different response. The question itself  
16 asks if there is credible evidence to support a conclusion  
17 that antidepressants cause the emergence. What we focused on,  
18 largely, is the scientific numerical data, which asks not does  
19 it cause it but is the incidence greater than the incidence or  
20 placebo? It is a different question.

21           I think that the data are reassuring that we have a  
22 situation where it is not worse than placebo in terms of the  
23 outcome measures that they have looked at 'and, in some  
24 instances -- in many instances -- it is better than placebo.  
25 But as Carol pointed out, it does not exclude the possibility

1 of rare idiosyncratic side effects, particularly in patients  
2 who would not have met their inclusion criteria for their  
3 clinical trials. That has certainly been my clinical  
4 experience, at least my observations suggest that some  
5 patients get much worse on the drug.

6 Now , if we are dealing with rare idiosyncratic  
7 responses, these are very hard to pick up in double-blind  
8 placebo-controlled studied, especially if we are dealing with  
9 incidence. It is hard enough to pick up, in double-blind  
10 placebo-controlled trials, efficacy of an antidepressant  
11 compared to placebo. Many trials fail to find it. When we  
12 are dealing with something which is **vanishingly** low and  
13 comparing it to a spontaneous rate, you are not necessarily  
14 going to find it. That does not exclude that possibility.

15 My way of thinking about it is to think about it in  
16 terms of what do antidepressants do and what do we know about  
17 suicide? I think there are a lot of different pieces of  
18 information that we need to consider. The first, the roll-  
19 back phenomenon has been mentioned, or the fact that some  
20 antidepressants have a very prominent energizing effect, and  
21 that if you have a patient who is suicidal but psychomotor  
22 retarded and inhibited in action and you give him this  
23 stimulating antidepressant, you may produce an uneven  
24 resolution of his depressive symptoms, and he may have, then,  
the energy to act on his suicidal thoughts.

1           So in those instances antidepressants can facilitate  
2 suicidal behavior, or enhance it. Again, they may be much  
3 more beneficial than harmful, but you have one clinical  
4 situation in which that can occur.

5           Secondly, you have the possibility that some  
6 antidepressants can produce a paradoxical worsening of  
7 depression, the phenomenon reported by Demlugi, where some  
8 patients on the medications simply become worse. They become  
9 much worse than you have ever seen them in the course of their  
10 treatment. You take them off the medication and they get  
11 better. That is the dechallenge aspect of it, which lends  
12 some credence to its being drug-induced.

13           If you then have a **rechallenge** and they get worse,  
14 again, you start to add some data that this is a real  
15 phenomenon. With the **Prozac** data, we have data on two  
16 patients with **rechallenge** who developed the phenomenon again.  
17 Overall, worldwide, I am aware of eight cases of **rechallenge**  
18 where they have had this effect a second time. Unfortunately  
19 they are not blind **rechallenge** and blind **rechallenge** would be  
20 much more compelling than open **rechallenge**. But that is  
21 something to be looked at.

22           So I think that some small percentage of patients  
23 can have a paradoxical worsening. I am not sure that **defin**  
- 24 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

1 their data, again, are quite reassuring.

2 Another mechanism that one has to think about that  
3 has not been brought up is the antidepressant-induced  
4 akathisia. If we look at the **neuroleptic** literature, a lot of  
5 associations have been made in the **neuroleptic** literature  
6 between the emergence of akathisia and suicide attempts or  
7 aggressive behavior. Most clinicians believe that, though I  
8 do not think it has been looked at carefully in double-blind  
9 placebo-controlled studies, but it is clinical lore.

10 **Akathisia** is a dangerous state and patients in a state of  
11 **akathisia** act in ways that are destructive and dangerous and  
12 they have to be really carefully monitored. It is a really  
13 dangerous side effect.

14 We know now that **tricyclic** antidepressants and  
15 selective serotonin uptake inhibitors can produce some degree  
16 of **akathisia**. Conceivably, that is a mechanism wherein at  
17 least some patients may be propelled into a state of suicidal  
18 behavior or aggressive behavior that they would not have been  
19 propelled into just given their natural illness. Again, it is  
20 not going to be picked up in these comparisons.

21 Another factor is that some elegant work over the  
22 last few years has really pointed to the importance of anxiety  
23 in suicidal behavior, the risks of panic and long-term outcome  
24 in suicide and short-term suicide risk, or just generalized  
anxiety. We know that some of these drugs can produce a

1 worsening or an exacerbation in anxiety, at least initially,  
2 and sometimes they can induce panic attacks. You add a panic  
3 attack to a patient who is already depressed and that may be  
4 the straw that broke the camel's back, so that in those cases  
5 you may have patients who go out and commit suicide who would  
6 not have committed suicide otherwise. That is another factor.

7 An additional factor that is important is drug-  
8 induced stage shifts. This is a controversial area in  
9 psychiatry, where they have looked for years as to whether  
10 drugs can precipitate episodes of mania, mixed mania and  
11 depression, or produce rapid cycling. The vast bulk of the  
12 literature suggests that antidepressant drugs as a class do  
13 this, that a substantial percentage of bipolar depressed  
14 patients will get switched into a mania or a mixed state or  
15 will cycle more rapidly.

161 We know that the mixed state, in particular, carries  
17 a high risk for suicide. It is one of the most dangerous  
18 states that a person can be in. Taking a bipolar depressed  
19 patient who may be psychomotor retarded, lethargic, not even  
20 thinking and concentrating and not particularly suicidal and  
21 putting him into a mixed manic and depressive state may  
22 markedly enhance his risk for committing suicide. That is  
23 another mechanism by which they may do this.

- 24 An additional mechanism: The early studies of  
25 suicide have pointed out that perhaps the most important

1 single symptom immediately associated with suicide is  
2 insomnia. Many patients take drug overdoses or make suicide  
3 attempts because they cannot get to sleep. The original  
4 report said do not underestimate the consequence of insomnia.  
5 The antidepressant drugs differ markedly in their effects on  
6 sleep. Some antidepressant drugs are sleep-promoting; other  
7 antidepressant drugs may produce insomnia as a side effect.  
8 If you take a depressed patient who is pretty close to the  
9 edge and you add to his symptom list insomnia, you may push  
10 him over the edge. So that is another way in which  
11 antidepressants can render a patient more suicidal.

12 Let me talk about what we have discussed. We have  
13 discussed suicidal obsessions. The reason why I believed, in  
14 our complicated cases, that we were dealing with a drug-  
15 emergent effect was not simply coincidence, not that they went  
16 on the drug and they developed suicidal ideation. By and  
17 large these were patients who were well known to us. We had  
18 been following them for about six years, on average. They had  
19 gone through innumerable other medication trials. We were  
20 very familiar with their illness and its manifestation, and  
21 the **symptomatology** that they developed during the time they  
22 were on **fluoxetine** was unlike anything they had experienced  
23 prior to or then following fluoxetine.

— 24 DR. CASEY: You are expanding onto item ii. more and  
25 more, and I would like to be sure that we stay focused to

1 question i., and I am soon going to ask for a vote of the  
2 committee. Do you have some more --

3 DR. TEICHER: I am trying not to discuss specific  
4 agents. I am trying to basically talk about --

5 DR. CASEY: I hear a lot about Prozac in your  
6 comments.

7 DR. TEICHER: Okay, but that is something I have  
8 been looking at. Basically, many of these things did not hav  
9 to do with Prozac. It is essentially enumerating mechanisms  
10 through which antidepressants can produce suicidal ideation.  
11 I think we need to hear these mechanisms, to think about them  
12 in order to really give this question fair consideration.

13 DR. LEBER: I have a point of information, because  
14 I think there is a fundamental difference between collecting  
15 information and demonstrating in a comparison between two  
16 groups under controlled conditions that the incidence of  
17 events is different. You, then, on the basis of how much  
18 variation, reach the conclusion that one does not seem to be  
19 as frequent as the other and, on the basis of some  
20 calculations, assume that it is not tenable under the  
21 assumption that they are both equivalent. That is how we do  
22 establish causality.

23 You suggest there is another road to the truth. I  
24 am not sure quite how you would do it, but it does not involve  
25 making comparisons. Instead, you have been raising issues of

rsm  
1 mechanism. If I can conceive of a mechanism, you seem to be  
2 saying, and that mechanism might -- you often slip and use the  
3 word "can" -- produce an event, therefore, it is plausible and  
4 possible, and I agree with you, it is.

5 But we are engaged in a public discussion where  
6 evidence is what is persuasive, and I ask, do you have the  
7 evidence that akathisia, one, induces suicidality, that sleep  
8 deprivation induces suicidality? You talk about not being  
9 able to test these phenomena in controlled trials, and yet  
10 your original report specified very clearly that 3.5 percent  
11 of the patients treated in your institution with fluoxetine  
12 experienced this phenomenon. Three-and-a-half percent, I  
13 might say, is an exceedingly high rate, which in controlled  
14 trials of the patients of the sort that would be at McLean  
15 would be easily detected.

16 I am trying to draw out the difference between  
17 speculation, which is good for hypothesis-generation, as Dr.  
18 Lin mentioned, and evidence that would persuade people in a  
19 disinterested way.

20 DR. TEICHER: I understand your point. Please  
21 understand mine. If you will look at broad categories, like  
22 change in a rating scale, and find no difference, it does not  
23 mean that all the patients on the drug who experienced it were  
24 placebo responders or that the drug was inactive or inert.

For a lot of this kind of information, what would be much mor

1 useful is blind **rechallenge** data. A test-retest paradigm  
2 would be more powerful in picking this up than the controlled  
3 trials.

4 Now , as far as controlled studies, I was going to  
5 cite the Rouen data to indicate that -- to go back to the  
6 Avery data, where, if you compare incidence on ECT versus  
7 adequate-dose **tricyclic** versus placebo, you find some  
8 interesting differences, that there is a much lower incidence  
9 of suicide attempts in patients who are treated with ECT  
10 versus adequate dose of **tricyclics**, or the available drugs at  
11 the time. There is a tenfold greater incidence of suicide  
12 attempts on **tricyclic** treatment. It is particularly  
13 noteworthy in patients who had no previous known suicide  
14 attempts. Those data are there as well.

15 As far as some data that have been bandied about  
16 showing no change in suicidal ideation, that is, the **Rosenbau**  
17 and Fauva data from my colleagues at Mass General, those data  
18 are interesting as well. Those data did not actually have  
19 power to pick up the difference between, say, a 1-percent  
20 incidence and a 3.5-percent incidence, which were preexisting  
21 literature values.

22 If you pool those data and compare all patients who  
23 received **fluoxetine** as part of their treatment regime versus  
24 all patients who did not receive **fluoxetine** as part of their  
25 treatment regime, you get a threefold difference in the

1 incidence of emergent suicidal ideation, and that difference  
2 is significant. Again, it is not double-blind placebo-  
3 controlled, but it was uninformed retrospective analysis.

4 So I think that there are some data. It is  
5 plausible and we can get into specific mechanisms and --

6 DR. LEBER: Again, maybe it would be useful if you  
7 would say precisely where these data that show an excess risk  
8 for fluoxetine actually are cited or published; in other  
9 words, referenced, because that would help us.

10 DR. TEICHER: I will be happy to show you. May I  
11 show "you a couple of slides?

12 DR. CASEY: I would rather not get into fluoxetine  
13 and --

14 DR. TEICHER: No, these are data that are published  
15 This is a reanalysis of the Fauve and Rosenbaum data.

16 DR. LEBER: I see, the survey. Right.

17 DR. CASEY: Let us stick with question number i. I  
18 would like to offer my opinion -- everyone else has offered a  
19 opinion -- and then call the question, form a question for us  
20 to vote on.

21 I do not find from the evidence today that there is  
22 credible evidence to support a conclusion that antidepressant  
23 drugs cause the emergence and/or the intensification of  
24 suicidality and/or other violent behaviors. Given that  
statement, I share the concerns that everyone else here has

1 raised, that the way we asked the question so far may not be  
2 able to allow us to detect people who are at risk for the very  
3 tragic experiences that we heard about this morning.

4 But given that, which then leads us to later  
5 questions, I do not believe there is credible evidence to date  
6 to support the idea that antidepressant drugs cause  
7 intensification of suicidality.

8 Dr. Temple has a comment. You cannot resist.

9 DR. TEMPLE: I cannot. It is a comment and a  
10 question. I have heard pretty much the uniform view that  
11 there is not such credible evidence, and that has been well  
12 expressed and the reasons have been given for it. I would  
13 like to make an assertion about that and see whether people  
14 agree that this is what they are saying.

15 The analysis of controlled trials is  
16 straightforward: You cannot detect an increased risk in  
17 those. That is fairly obvious and seems to rule out a very  
18 large risk.

19 But to reach the conclusion that there is not  
20 credible evidence, it seems to me one has to conclude that the  
21 descriptions of individual cases by Dr. Teicher and by the  
22 individuals who spoke this morning are at least compatible  
23 with the natural history of whatever disease they had. That  
24 is, you may not know that for sure, but at this point it is  
25 not persuasively shown that these events could not have been

1 spontaneous change.

2 I just want to be sure that that is what people --  
3 you may tell me that is the wrong question, feel free, but I  
4 think that is equivalent to saying that, and I would like to  
5 hear that explicitly, if that is what people mean.

6 DR. CASEY: My response to that is your explanation  
7 of not being able to distinguish from the natural course of  
8 the disease is one possibility, but another possibility is  
9 that we are not able to distinguish other causes as well from  
10 the natural course of the illness.

11 DR. TEMPLE: That is compatible.

12 DR. CASEY: It is compatible with, but not the sole  
13 explanation of.

14 DR. CLAGHORN: About what illness are we speaking?  
15 You know, in a sense, Dr. Teicher is telling us that he has a  
16 group of people that he has seen, on average, for six years,  
17 who have been nonresponders, who have multiple problems, who  
18 have possible physical problems as well, and he observed a  
19 phenomenon in those people that we seem not to find in a  
20 population we normally think of when we talk about the  
21 depressed population.

22 His observation may be quite valid. The question  
23 is, how would you go about evaluating it vis-a-vis it is  
24 almost as if he is talking about an utterly separate and  
25 minutely small group. It may be true that if you could

1 somehow devise tighter criteria for identifying this  
2 particular group of people you might find this with greater  
3 regularity, maybe 50-60-80 percent of such individuals would  
4 have such a response. That would be very, very valuable.

5 But I do not know that that is the way in which our  
6 question is posed right now. Our question right now is posed  
7 in terms of the universe of depressed patients as we  
8 ordinarily see them, who are really quite a bit different from  
9 this group of people. Would we expect this phenomenon to  
10 occur with any kind of regularity at all? That is one  
11 comment.

12 The other comment is just the very basic one that,  
13 my God, none of these drugs works on everybody. Some of these  
14 drugs, no matter which one you use, some people are not going  
15 to respond to. I mean, the fundamentals of working with a  
16 patient, listening to him, paying attention to what he says  
17 and responding appropriately to what he generates as  
18 information does not go away because of a statistical  
19 analysis. It is just another way of looking at the problem,  
20 which does not lend itself -- I mean, it is an experiment of  
21 one, it is always an N of one. You have to approach it in  
22 terms of making intelligent decisions about some one person.

23 I think there is a valuable lesson gleaned here  
24 about what not to do to certain individuals about aggressive  
25 dosing, escalations, and so forth, but it does not really

1 address question i., which is, in the universe of depressed  
2 patients as we normally think about them, does this  
3 information answer any questions for us?

4 DR. CASEY: I will ask the committee to vote on the  
5 following statement. It will be a true or false statement,  
6 since our usual efforts at voting on efficacy and safety of  
7 drugs is reshaped because of the nature of the problem: There  
8 is credible evidence to support a conclusion that  
9 antidepressant drugs cause the emergence and/or  
10 intensification of **suicidality** and/or other violent behaviors.

11 Those in favor of that statement, vote yes.

12 (No response)

13 Those opposed to that statement, no.

14 (There was a show of hands.)

15 And Dr. Dunner has left a proxy, which makes it  
16 unanimous at 10 to 0.

17 The next question is: Is there evidence to indicate  
18 that a particular drug or drug class poses a greater risk than  
19 others ?

20 DR. **LIEBERMAN**: I would like to begin by asking Dr.  
21 Teicher a couple of questions as a follow-up to his comments  
22 before. The mechanisms that you describe, I think, are very  
23 thoughtful and plausible in terms of a means by which the  
24 pharmacologic effects of drugs might lead to an end point of  
suicide or destructive behavior. Is it your notion that this

1 is a hypothesis that might apply to all antidepressant drugs,  
2 or specifically to **fluoxetine**?

3 DR. TEICHER: I do not know if you even go through  
4 all of them. I think that all antidepressant drugs carry **some**  
5 risks. For certain side effects **fluoxetine** has, perhaps, a  
6 higher risks; for other side effects, **fluoxetine** has lower  
7 risks. I think if you slash the pie, you will find that it  
8 will vary between class and nature of the antidepressant drug  
9 depending on the side effects that you look at.

10 DR. LIEBERMAN: With **fluoxetine** we have a limited  
11 experience that we can deal with in terms of when it began to  
12 be used in time. With the broad range of antidepressants, we  
13 have a much larger experience to look at. Still, within the  
14 limitations of the sensitivity of the reporting methodology  
15 and monitoring methodology, it would seem that if these  
16 various mechanisms were significantly prevalent, that there  
17 would be a greater amount of evidence associating  
18 antidepressant drugs with suicidal behavior to date.

19 Apart from the roll-back phenomenon, which is  
20 something that is not definitively proven as a *bona fide*  
21 entity but exists as a clinically observed phenomenon -- it  
22 has not been proven beyond doubt -- apart from sporadic  
23 reports in the literature, there are not large numbers of  
24 cases, let alone data from controlled trials which associate  
25 standard antidepressant drugs with suicidal behavior.

1 DR. TEICHER: That is a very good point. I think  
2 part of the problem, though, is we really have not carefully  
3 looked. I do not think it has been a major academic interest  
4 of many people to look at that. I do ask you to look at the  
5 Avery data. This is one of the few times it has been looked  
6 at. Those data are very interesting. In these patients who  
7 were treated with a variety of different treatments, ECT,  
8 conventional antidepressants, or neither ECT nor conventional  
9 antidepressants, if you look at suicide attempts in the  
10 hospital or during six months of follow-up, it was tenfold  
11 higher in the group that received antidepressant drugs  
12 compared to ECT.

13 If you look at the group of patients who made no  
14 suicide attempts prior to coming into the hospital, there was  
15 a higher incidence of suicide attempts in patients receiving  
16 adequate antidepressant treatment than in patients receiving  
17 neither ECT nor antidepressant. The Rouen data show, again,  
18 a higher incidence on drug compared to placebo. So these  
19 things may be out there; we really have not looked at it very  
20 carefully in these kinds of comparisons.

21 DR. LEBER: May I ask something? How were patients  
22 assigned to ECT versus those assigned to drug treatment?  
23 Isn't that a potential biasing issue, that there is a  
24 nonrandomized comparison?

DR. TEICHER: You bet.

1 DR. LEBER: So then, what can you conclude from th  
2 data?

3 DR. TEICHER: But how do you think it is nonrandom?  
4 Do you think that the healthier patients were assigned to ECT

5 DR. LEBER: Not at all. I am suggesting that you  
6 have a confounding --

7 DR. TEICHER: Okay, but if you assume that the  
8 sicker patients were perhaps at greater suicide risk, then wh  
9 would you expect to see a tenfold reduction in their suicidal  
10 incidence? They are just interesting data. It needs to be  
11 done "with random assignment, surely.

12 DR. CASEY: I think one of your earlier comments  
13 will surely be an outgrowth of today's meeting and all the  
14 other interest in this topic, is that there will be more  
15 research. At least I certainly hope so.

16 DR. MONTGOMERY: May I try and throw some light on  
17 this question in a class-by-class way? Take, first of all,  
18 the class of 5HT uptake inhibitors. We have one advantage  
19 over you in England, which is that we have four different 5HT  
20 uptake inhibitors available to us and we have substantial  
21 experience with one that was withdrawn, **zymeledine** [phonetic]  
22 and so there is a lot of experience in England.

23 One of the things that we have been privileged to b  
24 able to look at is the possible provocation or not of **suicide**  
25 thoughts and acts with other 5HT uptake inhibitors. This was

1 referred to in the presentations today and I just wanted to  
2 confirm that I have myself been able to look at those data.  
3 They are, to all intents and purposes, similar to the data  
4 that you saw today on **fluoxetine**. So from my perspective, it  
5 would seem that the 5HT uptake inhibitors as a class in these  
6 analyses on controlled double-blind trials against placebo  
7 show more or less exactly the same thing that we have seen  
8 here today. So, therefore, I would conclude that as a class  
9 the 5HT uptake inhibitors are not associated with the  
10 provocation of suicidal behavior or suicidal thoughts, taken  
11 from "the double-blind data.

12 DR. CASEY: Thank you. I am glad to hear there is  
13 only one advantage that England has over America.

14 (Laughter)

15 DR. MANN: I want to endorse the need for better  
16 data sets to operate from. But using those imperfect data  
17 sets that are available to us and playing with the numbers, it  
18 does appear that, looking across the **tricyclics** that are  
19 broken out in the poison centers and the toxicology data  
20 compared to the new antidepressants such as trazadone and  
21 **fluoxetine**, there really is not evidence, using IMS  
22 prescription rates, that one class of antidepressants is  
23 associated with more attempts than another class.

24 However, if you look within those data at the  
25 question of if a patient presents to an emergency room having

1 swallowed some pills, what is the probability of survival,  
2 then you certainly do not see a disadvantage for the patients  
3 who have taken the newer generation antidepressants; you see  
4 an advantage, which is statistically significant.

5           If anything, the drug that is hanging out there as  
6 the most unfortunate choice is desipramine, for reasons that  
7 I cannot understand pharmacologically. But if we take Dr.  
8 Teicher's approach to statistically significant data, we can  
9 predict with some degree of confidence that if you swallow  
10 drugs such as the **tricyclics**, that have significant  
11 **cardiotoxicity**, you are much more likely to kill yourself than  
12 if you swallow drugs that do not have the same cardiac  
13 toxicity, and that explanation would be consistent with the  
14 observation that, controlling for number of attempts, you are  
15 more likely to die if you have taken one of the more  
16 cardiotoxic classes of antidepressants than the other class.

17           This kind of puts a different slant on the  
18 discussion. It raises the question not only of the  
19 probability of feeling paradoxically more suicidal or making  
20 an actual suicide attempt; it also raises the question of if  
21 you are on antidepressants and you take it, what are your  
22 chances of survival?

23           DR. CASPER: I would like to do something which we  
24 are all used to more, perhaps, than answering questions  
25 categorically, namely, to generate hypotheses. I would like

1 to address question number ii. in a different way, because I  
2 believe we are talking today about **suicidality** or suicidal  
3 thoughts or acts as if they occur in a vacuum. I do not  
4 believe they occur alone; they occur in connection with other  
5 phenomena, with other experiences and feelings.

6] I think we have heard this morning, actually, in the  
7 patient reports, a number of events or experiences occurred  
8 prior to the suicide in these patients. So I would like to  
9 ask the question a slightly "different way, namely, do certain  
10 antidepressants perhaps increase the risk factors for  
11 **suicide?** Or risk factors for aggression, since we are  
12 talking about both these behaviors?

13 We all know **fluoxetine** has a very good side-effect  
14 profile. Generally, the side effects are fewer than with  
15 other antidepressant medications which are usually prescribed.'  
16 On the other hand, it has the side-effect profile which is not  
17 unlike that of a stimulant drug. What we have heard this  
18 morning is that one of the side effects is the occurrence of  
19 agitation, of anxiety, of panic attacks, and of insomnia.

20 If we listened to Dr. Fawcett's presentation about  
21 the risk factors in suicide, I think we need to keep those  
22 side effects in mind. He presented the data -- and I think he  
23 just left -- as increasing the risk for suicide. I do not  
24 want to leave the impression that I believe that we have data  
5 to support this hypothesis, but I think it is very worthwhile

1 to design a study looking, in a very small, probably,  
2 proportion of people who take Prozac and who develop these  
3 symptoms, at the profile of these symptoms, whether they  
4 develop agitation related to the depression, for instance. W  
5 know that sometimes a retarded depression can move into an  
6 agitated depression.

7 But what we have also heard this morning is some  
8 developed clear-cut panic attacks and those might be  
9 associated with suicide. My suggestion is that these studie  
10 need to be done.

11 I think my answer to number ii. would be that, give  
12 our current knowledge, I do not think we have the studieş  
13 available to say that a particular drug poses a greater risk,  
14 but I think we ought to be mindful that a particular drug  
15 poses or might create risk factors, which, in the end, might  
16 pose a greater risk for a subset of patients which might be  
17 minuscule, but is not minuscule, as we have heard this  
18 morning, for the families of those patients who have reported  
19 It might be a true phenomenon, but this has not been studied.

20 DR. LIN: Related to what has just been said, I  
21 would like to ask a question about the unit dose of Prozac.  
22 A number of people have mentioned that Prozac may cause  
23 akathisia and one of the ways that you cope with it is by  
24 reducing the dosage. Some reports have mentioned that  
25 patients on 20 mg of Prozac have developed akathisia or have

1 excessive anxiety symptoms.

2           Because the dosage that is on the market, the  
3 minimum, is 20 mg, it may discourage people from decreasing  
4 the dosage. I do not know whether this question is  
5 appropriate to bring up here for discussion, but it seems to  
6 me that if it is in a smaller dosage form, that may be helpfu  
7 for the clinicians to cope with that kind of problem.

8           DR. CASEY: I think that is somewhat of a different  
9 issue, but you are correct that it is an important area for  
10 discussion.

11           I would like to bring a rephrased question ii. to  
12 the committee and say there is evidence to indicate that a  
13 particular drug or drug class poses a greater risk for the  
14 emergence and/or intensification of suicidal thoughts and act  
15 and/or other violent behaviors.

16           Those in favor of that statement, please vote "yes.

17           (No response)

18           Those against that statement, vote "no."

19           (There was a show of hands)

20           It is unanimous.

21           One can abstain if he would like to abstain. **Those**  
22 who wish to abstain?

23           (No response)

24           Zero.

25           DR. SCHOOLER: The comment I wish to make is that

1 while I agree that the evidence does not indicate that any  
2 particular drug or drug class poses a greater risk, I am not  
3 convinced that all of the appropriate data and analyses have  
4 been done, and the same kind of issue that Dr. Casper raised  
5 that has been the theme throughout these earlier questions, I  
6 think that most of us feel like there is a fifth question that  
7 needs to be asked at the end, which is what would we like in  
8 addition to what we now have. Somehow, for me, the responses  
9 to this end up being always with that caveat, at least so far

10 DR. CASEY: Yes, I think that is a common theme that  
11 has come up today.

12 DR. TEICHER: Could I make a comment, please?

13 DR. CASEY: Can you make it a brief comment?

14 DR. TEICHER: I will make it very brief. I should  
15 have said something before, but I know it would not have  
16 changed the vote. But let me give you a completely different  
17 response. In terms of is there a class that may have a  
18 different effect, there was an hypothesis put forth by  
19 Burstein and Jackish that selective noradrenergic agents would  
20 have greater risk for this roll-back phenomenon by energizing  
21 patients more and suppressing serotonin, and Montgomery  
22 criticized the hypothesis very roundly and presented some good  
23 information.

24 But there have been data that have come up since  
25 then to suggest, one, in the one study where there is perhaps

1 differential data regarding placebo, that maprotiline is worse  
2 than placebo, that if you look at the coroners' data here,  
3 desipramine and nortriptyline are of higher incidence than the  
4 mixed amine inhibitors, and that if you take the Great Britain  
5 data from coroners and correct them by the toxicity of the  
6 data, the LD50 divided by the therapeutic dose, you find,  
7 also, that the noradrenergic drugs come out way on top.

8           So at least in terms of who winds up in the coroner  
9 with it in their blood stream, there may be some data actually  
10 pointing to noradrenergic agents which probably should be  
11 studied.

12           DR. CASEY: We certainly agree with the last  
13 comment.

14           DR. MONTGOMERY: May I make a request?

15           DR. CASEY: You should at least have a chance to  
16 respond, since your work was commented on.

17           DR. MONTGOMERY: I have published a paper which  
18 contradicts my previous stand. I now do believe that  
19 noradrenalin uptake inhibitors probably are the group that are  
20 likely to provoke suicide. What I would like this committee  
21 to ask for -- not today, because it is impossible -- is that  
22 the same analysis that has been done with the 5HT uptake  
23 inhibitors should also be requested for these other drugs to  
24 see if there are some data present in those companies to help  
25 to elucidate this.

1           It does not change my position, which is, I do not  
2 believe that there are sufficient data yet available from  
3 controlled trials to alter the position, but I think the  
4 hypothesis now stands and I think it is fair enough to ask  
5 questions specifically to it.

6           DR. CASEY: Thank you.

7           Given the situation as we have it, with the limited  
& data that we have, balanced by the personal reports in the  
9 first half of today, what advice can we give the agency as to  
10 what they should do? I do not mean which studies should be  
11 designed, because that really is more properly done in a  
12 conference that is set up specifically to do that and will  
13 take, probably, a few days to do. It is a very important  
14 question.

15           But given what we have, what do we recommend to the  
16 agency what they should do?

17           DR. HAMER: Are we on question iv. now? We sort of  
18 skipped iii., because --

19           DR. CASEY: No, iii. and iv. **belong** together. I  
20 propose to put iii. and iv. together and try to give some  
21 sense of direction from the committee's recommendations and  
22 advice as to what the agency should do. We have options all  
23 the way from nothing to recommending withdrawing the compound  
- 24 immediately, or something anywhere between those.

DR. LEBER: Change labeling is probably --

1 DR. CASEY: Well, change labeling is in the middle.

2 DR. REGIER: I think one of the questions that comes  
3 up, now that we have dealt with some of the scientific  
4 evidence, is the issue of good clinical practice, and is there  
5 anything that the FDA should do to assist with good clinical  
6 practice? As has been said, for none of these disorders do we  
7 have perfect response rates to any of these treatments.

8 I guess the question would be, if a physician is in  
9 Dr. Teicher's shoes and a patient comes in who has escalating  
10 suicidal ideation, regardless of his diagnosis, do you simply  
11 say t'o yourself there cannot be any causal link between the  
12 medication and these symptoms and, therefore, I will continue  
13 to push the medication higher and higher in order to finally  
14 break through this depression and get to a therapeutic  
15 response?

16 The way it has been phrased so far, the emergence of  
17 suicidal thoughts may, in fact, be a representation of a  
18 continuation of the illness. However, from a clinical  
19 standpoint, what it may mean is that the illness, then, "is not  
20 being appropriately affected by this particular treatment, and  
21 one would do well to cease at a given point and to withdraw  
22 the patient from a given medication.

23 The question, then, is, if we do not have a causal  
24 link to the emergence of either suicidal ideation or increased  
25 agitation or violent behavior, if that behavior does emerge in

1 the course of treatment, is there something in the PDR that  
2 should advise individuals to be cautious, that this response  
3 might benefit from a trial with a different medication or a  
4 different type of treatment?

5 I think that is the clinical question, whether or  
6 not, in fact, there is something that would be helpful to the  
7 practicing physicians that we might draw from the anecdotal  
8 experience and from the clinical experience that we have had  
9 today.

10 DR. HAMER: It perhaps is a little pompous of me as  
11 a statistician to comment on clinical practice of physicians  
12 but, on the other hand, since physicians have never hesitated  
13 to tell me what to do about my statistical analyses --

14 (Laughter)

15 -- it seems to me that, given the clinical practices  
16 of physicians with whom I have worked for many years, that if  
17 a patient comes to you and says, "I feel awful, I'm panicking,  
18 I'm going to kill myself, something terrible is going to  
19 happen," good clinical practice would be to listen to that and  
20 maybe take some action upon it.

21 It seems to me that that is sort of advice we have  
22 just been given by two people, at least, and that is entirely  
23 consistent with good normal clinical practice.

24 DR. MANN: Given the vote of the committee on the  
25 first two questions, in my personal view I think that it woul

1 be difficult to move from there to take any action in terms o  
2 labeling and so on, withdrawal of the drug or drugs, and  
3 certainly it would be difficult to, say, withdraw one drug as  
4 opposed to another, after having decided that there is no rea  
5 difference between one drug and another.

6 I think, however, there are a lot of clinicians out  
7 in the field who are wondering what to do and what to make of  
8 the situation. At the risk of reducing the forest of the  
9 Us., I think it is worth sending some information to the  
10 medical profession indicating where this committee arrived at  
11 in it's conclusions and to remind them of their responsibility  
12 as clinicians to do precisely as was just suggested, to listen  
13 very carefully to what their patients are telling them (as  
14 they are no doubt doing anyway) when they are treating them  
15 with antidepressants for depression, to monitor closely the  
16 fluctuations in the severity of the depression and the  
17 suicidal ideation, and to act as they would normally have  
18 done, size up the situation, change the dose, change the drug,  
19 change the patient's setting from an outpatient to an  
20 inpatient setting, as appropriate, and, in the meantime, we  
21 will try and develop better methods for finding out what is  
22 going on.

23 DR. CASEY: Would you change labeling or would you  
24 prefer to send out a "Dear Doctor" letter?

25 DR. MANN: I think a "Dear Doctor" letter seems

1 appropriate, since there are inclusions already in the  
2 labeling that address these very areas, and what we are doing  
3 is really placing those existing components of the current  
4 package inserts, we are reminding physicians of where they fi  
5 into the current picture.

6 DR. CASEY: There was recently sent a "Dear Doctor"  
7 letter. Should another one go?

8 DR. MANN: After the deliberations of this  
9 committee, that would be an appropriate action.

10 DR. LEBER: I want to point out a little bit of  
11 background. There has always been a tension between using  
12 labeling as a place to provide a comprehensive rich  
13 enumeration of facts about the drug and the use of the drug  
14 and the other side of the coin, which is exhorting physicians  
15 to good practice, turning labeling into a place to instruct  
16 physicians and practitioners in the arts of medicine. That i  
17 a very difficult road to travel, because in one breath you ar  
18 almost on the verge of telling people to be prudent, be wise,  
19 do the right thing, and yet you do not have the informational  
20 base on which to tell them what to do. You alert them to the  
21 difficulty of their situation, which anyone who has practiced  
22 medicine knows what is like. There is great difficulty with  
23 one of these patients, because they do not know what to do.

24 You tell them what they already know, but you have  
25 no concrete recommendations, no conditional probabilities,

1 nothing. You can postulate that it is akathisia, insomnia,  
2 the noradrenergic tone, the time of day, circadian rhythms,  
3 interactions with -- and yet you hesitate to do that, because  
4 you could be wrong.

5 So the question is, where do we want to be? How  
6 does the committee as a whole feel about this? I know that  
7 there will be a part of the community, no matter what you  
8 recommend, who is going to disagree with you. That is my bet

9 DR. CASEY: Dr. Laughren pointed out that we do not  
10 have to establish causality of something to have some issues  
11 raised in the labeling. Because of our first two votes we ar  
12 not prohibited from making suggestions regarding labeling.

13 From my point of view, I sense that my answer to Dr  
14 Stadel's presentation this morning is that, yes, there is a  
15 signal there. The problem is, what does the signal mean and  
16 how do we read it better than we have been able to read it so  
17 far? One answer is through more research. Another answer,  
18 another possibility, that will somewhat disagree with my  
19 professional colleagues this morning, is that I am not sure  
20 they have the evidence to convince us that if you change the  
21 labeling or increase the warnings that you really do scare  
22 people away from treatment. They presented it as if it is  
23 fact, and I am not sure that that fact is any more establish{  
24 than any other issue that was raised today.

I would not be so troubled by the possibility of

1 relabeling and possibly raising in the labeling the question  
2 that this issue is not yet fully answered to our satisfaction,  
3 that the data so far do not identify special patients at risk  
4 but good clinical medicine suggests that vigilance is in order  
5 and act. ons should follow vigilance, however the agency  
6 chooses to word that more specifically.

7 DR. TEMPLE: A very important consideration in what  
8 you do to therapy is whether you think that should be a  
9 general warning for antidepressants or for a particular drug.  
10 Which did you mean?

11 DR. CASEY: I would like to think about that for a  
12 minute, while someone else --

13 DR. TEMPLE: While you think about it, it clearly  
14 has the potential to influence therapy if you single out a  
15 particular drug for a comment of that kind, unless you mean to  
16 do so. It is okay to influence therapy, if that is what you  
17 were trying to do, but the presence of a warning -- dark print  
18 or otherwise -- on one member of a group and not on the other:  
19 carries a fairly clear implication that this is something to  
20 think about with one of the group and not the others. So one  
21 does need to address that.

22 DR. CASEY: I have had enough time to think. I  
23 think it is more likely to be a class issue than a specific  
24 drug issue, because I do not think we have adequate  
25 information on the other antidepressants besides Prozac, in

1 general, or the serotonin uptake inhibitors, specifically, but  
2 I can see the hands are raising quickly, and there are other  
3 opinions to express. I just wanted to start with that one.

4 DR. ESCOBAR: I agree that the signal is there and  
5 I agree with you -- I mean, I would not object to doing  
6 something to the label. In fact, the signal is there to such  
7 an extent that, as a clinician, if I were going to be facing  
8 tomorrow a number of patients who have some of these features,  
9 I would think twice before I did something. I think it is  
10 just fair to move that forward a warn the practitioners.

11 DR. TEMPLE: What are you warning them about? I do  
12 not understand how that fits with numbers i. and ii.

13 DR. CASEY: How can we raise the concern to our  
14 colleagues that there may be something there, after we have  
15 just said that we cannot find in the evidence that there is  
16 something there? I think the spirit to reflect is that the  
17 evidence so far does not give us clear evidence of an  
18 increased risk of suicidality but there is a concern that the  
19 issue has been raised -- you can state the issue has been  
20 raised, that there are not yet complete answers.

21 DR. TEMPLE: Is what you want to convey to people  
22 that time -- at least shortly after therapy is initiated is  
23 the time to be particularly careful, whether because people  
24 are not better yet or because of other phenomena, and that  
great attention should be paid to the patients, or something

1 of a general nature like that?

2 DR. CASEY: I do not think it is a time-specific  
3 issue, but it may be other risk-factor-related issues, a  
4 failure to respond, those kinds of things, after adequate dru  
5 exposure, whatever that is.

6 DR. LIEBERMAN: I think that we voted on questions  
7 i. and ii., indicating that no credible evidence existed to  
8 associate increase for suicidality in antidepressant drug use  
9 in general, and then in connection with **fluoxetine** in  
10 particular. Because of the limited amount of information wit  
11 **fluoxetine**, I, for one, felt a little less confident about th  
12 certainty of the decision with regard to question ii. than  
13 question i., but, nevertheless, on the weight of the evidence  
14 that is how we concluded.

15 In terms of what should be done, given this  
16 situation, I think that what remains of concern to me, and to  
17 the committee, I presume, is the fact that fluoxetine is stil  
18 relatively new in terms of our experience. We are still  
19 learning about what the full extent of its clinical propertie  
20 are, and there is this troubling number of cases that Dr.  
21 Teicher and others have described, and we heard described in  
22 vivid detail this morning, that make this a greater concern.

23 The question then becomes how can we respond to **tha**  
24 in a way which will be useful in the guidelines of the FDA  
mechanisms ? Dr. Mann raised the issue of a "Dear Doctor"

1 letter. One has gone out. What would another one do and what  
 2 should it state? I am not sure. I mean, I guess one thing  
 3 that could be done is to, at this point, dispel the  
 4 controversy to the extent that the committee's deliberation  
 5 can do that, by indicating what the outcome of their review  
 6 has been and, at the same time, also noting that despite the  
 7 fact that we feel there is evidence for increased risk, there  
 8 still is the potential, given the limited amount of  
 9 information and the existence of a series of case reports,  
 10 which warrant concern.

11 Beyond that, the other thought that came to my mind  
 12 was that it would clearly be of importance to have the  
 13 opportunity to verify any additional cases that may come to  
 14 light through the spontaneous reporting system or to the  
 15 pharmaceutical company subsequently in terms of obtaining  
 16 additional information to verify the association between  
 17 fluoxetine and the adverse behavioral reaction.

18 With clozapine I know that when the issue of  
 19 agranulocytosis is discussed then there has been an increased  
 20 effort to try and verify the legitimacy of cases that have  
 21 been reported. Whether something comparable might be done  
 22 here, I am not sure.

23 DR. CASEY: Dr. Lieberman, I am a little confused  
 24 about your recommendation for a "Dear Doctor" letter but not  
 25 a recommendation for a labeling change. I am not advocating

1 either, but if you feel strongly enough the need for alerting  
2 physicians to the possibility of a linkage in a "Dear Doctor"  
3 letter, why would you not propose something a little more  
4 permanent in nature like a labeling change?

5 DR. LIEBERMAN: I am not recommending a "Dear  
6 Doctor" letter. I was commenting on what Dr. Mann had raised  
7 because there was a question of what would the purpose and  
8 content of it be. What I wanted to state was the fact that  
9 although we felt that there is no credible evidence that there  
10 is, because of the limited experience, still, the potential  
11 for concern and continued surveillance, how could that be  
12 effected? The major way in which I was speculating it might  
13 be was through the spontaneous reporting system and seeing if  
14 there were ways of obtaining additional information beyond  
15 what goes into the data base ordinarily.

16 DR. LEBER: There is an important thing that I would  
17 like to point out, that Jeff is using the word "limited"  
18 information vis-a-vis fluoxetine. It is true that the  
19 duration of marketing of the drug is short compared to that of  
20 the tricyclics and the monoamine oxidase inhibitors, but that  
21 is not the only thing that deals with informational content.

22 In terms of the volume of subjects entered into  
23 rigorous controlled trial, actually there may be a relative  
24 excess of data on fluoxetine compared to the drugs that were  
25 developed in the 1960s and the 1970s. You have got to be

1 careful about that. I agree that we may not have all the  
2 evidence that you want, but you are sort of establishing as a  
3 fact that there is a relative paucity of information about  
4 **fluoxetine**, and I am not so sure that is true -- certainly in  
5 terms of experience and reports in the anecdotal literature  
6 -- but for **imipramine**, for example, just to pick on a drug  
7 that was recently marketed here, it had a long-standing  
8 history of very high risk of seizure that was never  
9 emphasized, yet it was well known, I believe, throughout the  
10 U.K.

11 There are things that are out there about those  
12 drugs that are not necessarily appreciated and never detected  
13 in the controlled trials, because they were not subjected to  
14 the same level or intensity of scrutiny. Where is this  
15 information going to come from to resolve the matter?

16 I become concerned at this point that we are sort of  
17 in the situation where we have heard only part of the  
18 evidence. You here have candled **fluoxetine**, it has been the  
19 focus of intensive speculation and interest, and then we have  
20 all these other areas where we have not systematically done  
21 anything with the same degree of intensity.

22 If you now move and make a statement, you will have  
23 effects. You may displace people from the use of **fluoxetine**  
24 to other drugs about which you know less, not more. That has  
25 consequences, and I would want the committee to face that

1 possibility -- at least address it (I am not telling you where  
2 to come out). But be aware that no action is unaccompanied by  
3 some reaction, I think, is an old physical principle.

4 DR. LIEBERMAN: Let me finish staking out my  
5 position, which is that, in terms of the labeling change, I do  
6 not think that is the appropriate action to take.

7 DR. CASEY: Thank you.

8 DR. MONTGOMERY: I wanted to make a small point.  
9 You have voted on these two issues and I was surprised by the  
10 unanimous nature of the vote. You totally agreed that there  
11 is no "class phenomenon, that the thing does not exist. It  
12 seems to me, therefore, very difficult to do a labeling change  
13 on the one set of data that you have got the best evidence  
14 from that you will get, that the 5HT uptake inhibitors have  
15 been subjected to very thorough examination on this specific  
16 issue.

17 The questions we have been looking at elsewhere than  
18 are much more indicative of some labeling change it would be  
19 much harder to get those data for, and it would seem to me  
20 that if you are going to go for labeling phenomena, you must  
21 do it for all antidepressants rather than to pick out the  
22 group where we have got very reasonable data that they are  
23 okay.

24 I would have thought myself that it is going to be  
25 very difficult to do labeling that does not undermine your tw

1 previous decisions. The only sort of labeling you could have  
2 would be advice to physicians.

3 In the U.K., our licensing authority would eschew  
4 this argument completely, because we do not advise physicians  
5 We simply license the drugs. We have to back away very much  
6 on how the drugs are going to be used by physicians, once the  
7 get them into their hands, and we know perfectly well that  
8 they use them in somewhat peculiar ways, in doses outside the  
9 recommended ranges, in conditions that we do not approve of,  
10 and that is their decision. But our licensing decision in th  
11 U.K. "would simply say it is for this indication.

12 We have in this indication some warning or not. We  
13 have examined the data today and the evidence is fairly clear  
14 cut that we have not got enough data in our hands to say that  
15 there is any credible evidence that antidepressants are  
16 associated with it or that there is a class phenomenon.

17 DR. STANLEY: If I could comment briefly, I agree  
18 with Dr. Montgomery on the point. It seems that once we have  
19 settled the issue of questions i. and ii., which, as I see it  
20 were based largely on a review of the controlled clinical  
21 trials, then you move to the question where you collapsed iii  
22 and iv. together and, as Tom mentioned, you can hold out the  
23 possibility, still, for a change. That seems to be based mor  
24 on the case vignettes that are either published in the  
25 literature or information that we heard here this morning in

1 this room.

2           The thing that impressed me, and I think it was  
3 mentioned by other panel members here, is the tremendous  
4 amount of heterogeneity of the individual cases that were,  
5 again, either published or presented here. I do not  
6 necessarily agree that there is a signal. I am not sure. But  
7 with such a heterogeneous clinical group, I do not know how  
8 you could go ahead and formulate any change in labeling. I do  
9 not know what direction you would take.

10           Just a note on the clinical cases that were reported  
11 here. As a nonpsychiatrist and nonbiostatistician, I am  
12 probably best qualified to comment on clinical care.

13           (Laughter)

14           I have to say that in many of the cases that I heard  
15 this morning, I was frankly very appalled by the lack of  
16 clinical care that some of the patients received, whether they  
17 were getting Prozac or anything. It just seemed to me a very  
18 bad level of care, somebody walking in with a rash all over  
19 his body and being sent home. Anyway --

20           DR. CASEY: I would agree with you about the last  
21 comment, some of the care people were receiving this morning.  
22 If we would put on the fronts of the PDR or on any other  
23 journal that we would be sure that would be read and heeded,  
24 we would say to the patients, "Get yourself a good doctor, "  
25 and we would say to the doctor, "Be a good doctor. " But I do

1 not think that will help.

2 It really is very important that people feel free to  
3 ask their physicians many questions and to be probing and not  
4 to be in the position where they feel they just must accept  
5 what they are told or that they must take what they are given  
6 without question.

7 DR. TAMMINGA: There are a number of us who are  
8 formulating positions different from our chair, but taking  
9 that risk, I would also -- it would be my opinion not to  
10 address the problems that we are discussing through a labeling  
11 change, but through some other mechanism, particularly since  
12 the field must be hypersensitive now and a labeling change  
13 might have even an exaggerated effect, given all of the  
14 publicity and questions that have been asked, particularly  
15 about fluoxetine.

16 Given the possibility that was generated in my mind  
17 this morning from listening to people outline their  
18 experiences with the drug, accepting the possibility that  
19 there might exist some rare idiosyncratic response to  
20 fluoxetine, what mechanisms does the FDA have already in place  
21 that would allow something like a periodic review, or does one  
22 just leave that to the field to come up with through articles  
23 like Dr. Teicher's article and things like that?

24 DR. LEBER: We have a continuous review process  
going on. As I said in my opening remarks, the fact that we

1 are having this meeting at this point in time does not mean we  
2 are suspending our surveillance operations or dropping  
3 negotiations with the sponsor. In fact, we will continue  
4 doing what we ordinarily do.

5 The question that is before you is -- there are two  
6 types of labeling changes. One labeling change is specific to  
7 fluoxetine. The other, as Dr. Temple pointed out, is a  
8 general labeling change for all antidepressant drug products  
9 that might provide more of the, I would say, educational  
10 exhortatory detailed response to what it means to be a good  
11 physician. There is a tension. There is. It is the do what  
12 is right, prima non nocere type thing, "think drug if things  
13 go wrong," all the other things.

14 What it cannot do, unfortunately, is tell you what  
15 to do when things go wrong. But it can certainly commiserate  
16 with you and urge you to think about it. I do not know how to  
17 write that. I hope I do not get the job.

18 DR. CLAGHORN: I think there is a feeling that most  
19 of us have, as everyone has talked about, the patients'  
20 descriptions, and so forth, that somehow we do not want,  
21 albeit we lack a level of evidence that gives us a sense of  
22 certitude and would move us to take some sort of drastic  
23 steps, to find some way to alert people who are not as attune  
24 to this kind of information as this group is.

I have scratched a very simple short paragraph whit

1 I intended as something that might be said about every  
2 antidepressant, whatever it was, that would go something like  
3 this . In a small number of patients, depressive symptoms hav  
4 worsened during therapy, including the emergence of suicidal  
5 thoughts and attempts. Surveillance throughout treatment is  
6 recommended.

7 It is a very generic kind of statement that says,  
8 hey, keep in mind that not everybody who gets these things  
9 gets better. Some people get worse, some people get a lot  
10 worse. Pay attention.

11 DR. LEBER: Would you go so far as to suggest that,  
12 in fact, the drug may be causally responsible?

13 DR. CLAGHORN: Oh, no, not at all.

14 DR. LEBER: **Any** drug? This is a generic statement.

15 DR. CLAGHORN: Absolutely not, and the statement  
16 does not make any assumptions as to what is going on. It  
17 simply says this phenomenon does occur: People get worse eve  
18 though you are treating them.

19 DR. LEBER: We almost have that in labeling now.  
20 Suicide, "the possibility of a suicide attempt" -- this is in  
21 the "Precautions" section -- "is inherent in depression and  
22 may persist until significant remission occurs. Close  
23 supervision of high-risk patients should accompany initial  
24 drug therapy. Prescriptions of" -- (fill in the blank) --  
"should be written for the smallest quantity of capsules

1 consistent with good patient management in order to reduce the  
2 risk of overdose. " Now , that is already generically in  
3 labeling.

4 DR. CLAGHORN: The only difference would be to  
5 include the statement that sometimes people actually get worse  
6 in the course of that therapy and may -- blah, blah -- but you  
7 are right.

8 DR. LEBER: This becomes a critical point. You do  
9 not want to suggest that the drug might be responsible,  
10 because that would lead to shifting, possibly, to another  
11 drug. So you might want to open the door on that or not open  
12 the door on that.

13 DR. CLAGHORN: I think we just say we do not have  
14 any evidence for that.

15 DR. LEBER: Well, you are raising the possibility  
16 that it might. If patients are worsening, it is either the  
17 disease -- what is the implication for the reader if the  
18 prescriber is faced with that point?

19 DR. CLAGHORN: I am being atheoretical --

20 DR. LEBER: But you are asking them to make an  
21 inference, and I want to see if the inference could be  
22 anything other than the consideration that possibly the drug  
23 did it.

24 DR. CLAGHORN: We do not believe the drug caused it

25 DR. CASEY: Yes, there is another inference, and

1 that is, this medicine is not helping this person. It does  
2 not necessarily mean the drug is doing it; it could mean it is  
3 failing to provide benefit.

4 DR. HAMER: And, also, his recommendation was for  
5 all antidepressants, not for a specific one.

6 DR. CASPER: I would like to support our chair's  
7 position and wonder whether really recommending a labeling  
8 change would be so inconsistent with saying there is no  
9 evidence right now that antidepressants or particular  
10 antidepressants is really related to the emergence of **suicide**  
11 **ideation**.

12 I think we need to consider whether the phenomenon  
13 we have heard about today is a real one and is one which needs  
14 to be studied. I have said I believe, from listening to what  
15 we have heard this morning, it needs to be studied further.  
16 I think there are two ways to do this. One is to design  
17 controlled studies and do the appropriate studies, which will  
18 probably take another five or 10 years before they are fully  
19 completed and analyzed.

20 Another would be to raise awareness, especially in  
21 our colleagues' minds, and give them the information in a very  
22 general way which is available to us, namely, the patients  
23 need to be -- and I would suggest, perhaps, in very general  
24 terms -- after the initiation of antidepressant drug  
25 treatment, the patients' symptoms ought to be closely

1 monitored, and perhaps say something about in the case of  
2 worsening of symptoms the patients need to be reevaluated.

3 I do not know whether another antidepressant drug  
4 would be the right step. I think the patient needs to be  
5 reevaluated if the patient does not get better. There might  
6 be another reason why the patient does not get better; the  
7 patient might have an organic brain syndrome. We do not know

8 I would speak in support of the labeling.

9 DR. HELLANDER: As far as the current labeling, I  
10 think one thing that is important is it really does not  
11 address the issue of people who are taking it for other  
12 reasons than depression. As we have heard today, a lot of  
13 people are taking it for weight loss, smoking cessation, mild  
14 mood disorders, eating disorders, everything under the sun.  
15 So if you only talk about the proper treatment of depression  
16 and closely monitor your patients and there might be some  
17 emergence of some suicidal symptoms related to their  
18 underlying diseases, well, then, you miss a third or so of  
19 patients who are currently on Prozac who might be susceptible  
20 to some adverse reaction of the drug.

21 Another thing I want to point out, and one of the  
22 reasons that we wrote for a labeling change, although we were  
23 ourselves very concerned about possibly people not undergoing  
24 treatment because they were afraid of what you are warning of  
25 or of restigmatizing depression, because so many people say,

1 whatever drug it is, "I was not told that there were possible  
2 side effects" -- I think today we heard that 10 or 15 times  
3 -- "My doctor told me this was a wonder drug, there are no  
4 side effects. "

5           Forget about suicidal ideation. They are not even  
6 told about anxiety and insomnia. You know, 10 to 15 percent  
7 of people on Prozac get these side effects. As we have also  
8 heard, these are possible factors that might increase the ris  
9 of suicide. It seems to me that there should be something in  
10 the label that would let people know at least that this  
11 committee still has some concerns and that they can find that  
12 for themselves, too, that they are not -- I am not saying thi  
13 as well as I wanted to.

14           If you sent out a "Dear Doctor" letter, I think one  
15 of the topics of it should also be that this meeting has not  
16 cleared Prozac or any other antidepressant and said we have n  
17 concerns about it, we are completely convinced nobody has a  
18 bad reaction to it. In fact, people have expressed that we  
19 are concerned about these reports, we do not quite know what  
20 to make of them, we have heard from the public, things are  
21 going on, we are not quite sure what is going on, we would  
22 like to know more.

23           I think what is going to happen is, you know, you  
24 are so unanimous on those two questions that there is a  
25 possibility that this will be conveyed as, well, you know,

1 everything is over, the controversy is resolved.

2 DR. LEBER: I have one concern, however, Dr.  
3 **Hellander**, that you also are putting your spin on what has  
4 gone on in this meeting to this point. It seems to me that i  
5 you were to read the record so far, all credible sources of  
6 evidence fail to indict. We have all said that the failure t  
7 have, if you will, compelling evidence of guilt does not in  
8 itself prove you guiltless.

9 On the other hand, people's lingering doubts do not  
10 translate into a specific indictment of **fluoxetine**. As a  
11 matter of fact, one of the controlled trials indicts  
12 **maprotiline**, if you want. The others are speculations.

13 One of the concerns that I think we have to address  
14 is what are you going to get into labeling? Who is going to  
15 send this "Dear Doctor" letter? Is it going to be Eli Lilly  
16 or all the manufacturers who market drugs? What is the topic  
17 going to be? What kind of advice are we going to give? What  
18 is the truth?

19 One of the things that I would hope this committee  
20 could decide is one simple set of dichotomies: Should there  
21 be a labeling change, yay or nay, and if you recommend a  
22 labeling change, will it be specific to **fluoxetine**, yes or no  
23 and if not, should it be general? I think at least give us  
24 that much direction.

How people will interpret the dicta from this

1 meeting is going to be a function of what they probably  
2 believe, to begin with, where they want to go, and the usual  
3 things given to how people read these kinds of transcripts.  
4 But I think the record of votes at this point really suggests  
5 nobody found anything. They simply are acknowledging the  
6 possibility that something may be there, but that is true of  
7 everything. Something may be there for every drug out there,  
8 and that is what my concern is. It is sort of a no-win  
9 situation for Prozac, because it has been in the public eye  
10 and people have accused it and, therefore, it may be guilty.  
11 That "is certainly true, or it may be, but there is no  
12 compelling body of evidence. We do not know what to do.

13 I would like you now to give us some specific  
14 recommendations on how to deal with this.

15 DR. LAUGHREN: Several committee members have  
16 expressed concern about a physician who tells a patient at the  
17 outset of treatment that this drug is without any side  
18 effects. It is not clear what one does to improve the  
19 behavior of a physician like that through a labeling change.

20 DR. SCHOOLER: I think that what we are hearing in  
21 the conversation now is a sense of malaise, possibly induced  
22 by the time of day, but I think more likely induced by the  
23 fact that we are not completely comfortable, and the question  
24 is how to deal with that discomfort. Some of the discomfort,  
25 which has been expressed with great articulation, is, I think

1 that people are concerned about the quality of medical  
2 practice that they have heard related here.

3 One would like to believe that these are the  
4 extreme, extreme cases and that the reason these cases have  
5 been as dreadful and as unfortunate as we have heard has been  
6 in some measure due to the fact that the quality of the  
7 practice was as unusual as the quality of the outcomes appear  
8 to be when we relate these outcomes to the kinds of general,  
9 more scientifically based, perhaps, data that we have heard.

10 My concern is that the kinds of issues that have  
11 been "raised as concerns are not going to be redressed by  
12 labeling, because they really are concerns that have more to  
13 do with do a better job, pay more attention, listen to the  
14 patient, if someone does not improve after four or five weeks  
15 think about why that might be, and so forth.

16 The only answer that I can find for myself is one  
17 that I think Dr. Casper raised, which is, we really do need to  
18 obtain more data. In fact, we probably have more data about  
19 fluoxetine, as Dr. Leber suggested, than about most other  
20 drugs. But we really do need to know more about these drugs  
21 generally in studies that focus fairly specifically on issues  
22 of suicidality and suicidal thought.

23 At one level, you have to think that it is a fairly  
24 sorry state where we are picking one item from the Hamilton  
25 Depression Scale and one item from the Symptom Checklist 90a

1 indicating what we are going to find out about **suicidality**,  
2 and that the item from the Hamilton Depression Scale is one  
3 with which I think many of us might quarrel with the labeling  
4 of the anchor points, much less other issues.

5           It seems to me that it is not clear that the  
6 concerns we are expressing can be resolved by labeling,  
7 although they are very real concerns.

8           DR. CASEY: Would you recommend a change of  
9 labeling?

10           DR. SCHOOLER: No.

11           DR. MANN: A couple of quick comments. The first is  
12 another argument in favor of the "Dear Doctor" letter and tha  
13 is that following this meeting I would much rather see the  
14 conclusions drawn here summarized by the FDA and distributed  
15 to the American medical profession rather than by the various  
16 drug companies. I think that is a very critical point. It  
17 allows the agency to place its more impartial view on the  
18 table in front of medical practitioners before the drug  
19 company representatives get to them with their own version of  
20 what happened here. That is point number one.

21           Point number two relates to the question of the  
22 discomfort that the committee has felt about the data  
23 availability. There are **32,000** to **33,000** suicides reported i  
24 this country every year. That means in two years more people  
25 die from suicide than died in the Vietnam war. That is a

1 major source of information that could be tapped by this  
2 committee and other related committees.

3 For example, I think it would be valuable for us to  
4 know which of these patients was taking what specific  
5 antidepressant and the next time a committee like this has to  
6 convene, those kinds of data will be available.

7 DR. CASEY: I would propose that we address our  
8 malaise with a few specific questions, as Dr. Leber has asked  
9 for. I will ask the committee to vote, first, on the issue o:  
10 should there be a labeling change in general.

11 We will take it in two questions. First, the  
12 general question, and then the second question, whether it  
13 should be specific to a compound or class.

14 The first question is, should there be a labeling  
15 change? Those in favor, vote "yes."

16 (There was a show of hands)

17 Three.

18 Those against?

19 (There was a show of hands.)

20 Six.

21 Abstaining?

22 (No response)

23 None.

24 The next issue, I think, is specific only to those  
three who voted "yes" on the first question.

1 PARTICIPANT: A minority vote.

2 DR. LEBER: That is fine. That is getting their  
3 opinions.

4 DR. CASEY: For those who think a labeling change  
5 should be considered, should it be for the class of drugs?  
6 Those in favor of a class of drugs, vote "yes."

7 (There was a show of hands)

8 Three out of three.

9 Those "no?"

10 (No response)

11 Good . It is zero.

12 DR. LEBER: But you still have to ask how many want  
13 it specifically.

14 DR. CASEY: Is there anybody on the committee who  
15 feels specific labeling to a particular compound should be  
16 addressed?

17 (No response)

18 No.

19 DR. SCHOOLER: The one other comment I would like t  
20 make is that is that I think Dr. Mann's suggestion that the  
21 deliberations of this committee be reflected in a  
22 communication that goes to the field of physician providers  
23 would be very, very valuable.

- 2' DR. LEBER: The mechanism and the content may not be  
so easily identified.

1 DR. CASEY: What would you say in it?

2 DR. SCHOOLER: What we said here today, which has  
3 been so well recorded because --

4 DR. LEBER: Welcome to the committee, Nina, how  
5 would you like to join a subcommittee?

6 (Laughter)

7 DR. SCHOOLER: Which has been so well recorded by  
8 the fact that we have spoken directly into the microphones.

9 DR. LAUGHREN: Before you take a vote on something  
10 like a "Dear Doctor" letter, I would like to hear a little bit  
11 more "about what you would want to go in it and what you would  
12 want it to achieve, keeping in mind that it is a one-shot  
13 thing and it does not really have much of a lasting impact.

14 DR. CASPER: Maybe I could help Dr. Schooler. What  
15 has been in our minds is to raise this particular question  
16 which we have raised today, and to raise this in other  
17 physicians' minds, namely, are antidepressant drugs -- have  
18 they been associated with adverse events beyond those  
19 described during treatment? Just to raise the question as a  
20 question, not as a fact.

21 DR. LAUGHREN: If you have enough suspicion about  
22 that possibility and you feel strongly that physicians ought  
23 to be informed about that, why would you not put it in  
24 labeling?

25 DR. CASPER: Oh, I would put it in labeling.

1 DR. LAUGHREN: Okay. Well, I guess this is  
2 addressed to the people who have suggested a "Dear Doctor"  
3 letter and do not want a labeling change.

4 DR. SCHOOLER: I will try to defend that a bit. It  
5 seemed to me that Dr. Mann made the case very persuasively  
6 I am sorry that he had to leave, because I hoped that he would  
7 also want to speak to this. The major concern that I had in  
8 not being in favor of labeling change was the two votes that  
9 we took and I came to believe the decisions that we made  
10 suggested that there was not credible evidence, but one of the  
11 issue's that was my reservation throughout that process was  
12 that I felt we were working with half a deck in terms of data  
13 that the best data we had were regarding fluoxetine and we had  
14 very, very few data regarding other drugs.

15 So saying that we are not comfortable with the  
16 amount of data that we have, which is a very comfortable  
17 position for me as a nonphysician, I do not have to make  
18 decisions that may be life-and-death decisions for patients,  
19 it seems to me that physicians who do have to make such  
20 decisions ought to be alerted about that.

21 DR. LEBER: I think the conclusion of the committee  
22 today is not proven in the sense of the Scottish jury's  
23 verdict. It is not the same as not guilty. The problem is  
24 that, having reached that conclusion, you now want to convey  
25 something of utility and value to the practitioner who knows

1 he is in trouble because the patient is not responding, not  
2 doing well, and behaving atypically. Given our uncertainty,  
3 given the lack of knowledge, just what do you say? How do yo  
4 give advice in a situation that is inherently a dyadic one  
5 between the practitioner and the patient? You do not know th  
6 facts, you do not have a generic principle: What is it you  
7 want to say? Beware, you may be wrong? Beware, you may be  
8 raising the dose when you should be dropping it? Beware that  
9 things may be going wrong and you perhaps should seek  
10 consultation with those more experienced than you?

11 I mean, there are a lot of possibilities. Beware,  
12 hospitalize the patient, this is a signal. That is the  
13 problem for us. How do you translate the good intention into  
14 something that we could practically do? For the record, we d  
15 not issue "Dear Doctor" letters, ordinarily. We probably  
16 could write "talk" papers, but even then, as Dr. Temple says,  
17 the content of them is what becomes so difficult. Maybe it i  
18 worth a couple of minutes trying to find out how, in the  
19 context of what I have just said -- what do you want us to  
20 say?

2 DR. LIN: I would not be opposed to the idea of  
2 sending out a letter. I think perhaps it could serve two  
2 different purposes. First of all, it would serve to  
- 2 communicate what has been talked about here that in some way  
would be reassuring to the clinicians in terms of the general

1 conclusion that we have reached today.

2 At the same time, I think after doing that we can  
3 also have a paragraph saying that while there is no evidence,  
4 we should continue to monitor the possibility of maybe a very  
5 small group of patients may have paradoxical reactions, even  
6 though there is no evidence at all. I think that would be a  
7 reasonable approach to take.

8 DR. TEMPLE: That is difficult advice for us to  
9 follow. The first part, that is, reassuring people on the  
10 basis of the results here, becomes perilously close to Lilly'  
11 job, 'and they can take care of that.

12 The second part of it fills me with a sense of  
13 contradiction. If we did not think -- we could put something  
14 or urge Lilly to put something in the labeling, even if it is  
15 not proof positive. We could do that. But the committee has  
16 for the most part, said do not do that. To then, instead of  
17 putting it in labeling, where it becomes part of promotion an  
18 part of the environment in which the drug will be given and  
19 just put it in a "Dear Doctor" letter, a one-shot thing, so i  
20 passes quickly, does not make sense. If it is worth doing,  
21 then we could do it. But if it is not worth doing, we do not  
22 really balm our conscience very much by just kind of passing  
23 it quickly.

24 DR. TEICHER: I guess the one point I was going to  
25 make, Dr. Casey, is that the average clinician, when he

1 encounters a patient having a side effect on medication,  
2 frequently refers to the package labeling or the PDR to look  
3 and see is this a reported side effect. If it is a reported  
4 side effect, he may discontinue the drug or change treatments  
5 in some way. If it is not a reported side effect, he may say  
6 no, the medication cannot be causing it, stay on the  
7 medication, it is something else.

8 DR. TEMPLE: They are in labeling now. If that is  
9 what one --

10 DR. TEICHER: No, no, I understand that. But what  
11 is going to happen, based on the results of the committee  
12 vote, which is a very honest vote that I am happy with, people  
13 are going to say it is free of all blame, it is free of all  
14 risk, and I think for the committee to communicate in some way  
15 that there is at least a small measure of uncertainty and  
16 there is a small desire to see more data is useful to  
17 communicate to clinicians. It is not absolute, it is not  
18 black and white, and it is still in the process of further  
19 evaluation.

20 DR. CASEY: To Drs. Leber and Temple, I think this  
21 is an issue that some of us feel more affectively than the  
22 kind of thing that you can palpate. We are struggling with  
23 giving you language, because we are not yet sure how to say it  
24 ourselves.

DR. LEBER: The likelihood is that we will probably,

1 as is customary, write a talk paper at some point on behalf of  
2 the agency which will contain our distillation of the advice  
3 given here today. It will probably say what is obvious from  
4 the votes, and that people -- reasonably -- remain concerned  
5 about the possibility that there are areas of information that  
6 we need that we do not have and we will pursue things as we  
7 ordinarily do.

8 Some people will think, of course, that all this  
9 accomplishes is once again saying we are not acting when we  
10 should be acting, but I think we would probably want to  
11 emphasize -- I want to make sure I have this right, that we  
12 are not urged to act by this committee. I think that is a  
13 very important bottom line on the other side. You did not  
14 tell us to go out and do something because failure to do  
15 something would precipitate a major -- you know, it is  
16 unconscionable or bad for the public health.

17 DR. TEMPLE: There were several people who thought  
18 that some sort of labeling perhaps might be useful. Any time  
19 there is a divided committee, we can consider both parts. If  
20 people want to write in to us quickly -- soon, that is -- the  
21 particular words, we can certainly consider them.

22 DR. CASEY: From the committee.

23 DR. TEMPLE: From the committee.

- 24 (Laughter)

25 The possibility of some kind of labeling change does

1 not have to be ruled out. There was enough discussion so tha  
2 obviously people could have gone one way or the other, but  
3 still it is, obviously, very difficult to know what to put in

4 DR. HAMER: I wanted to say, as we listened to the  
5 stories this morning, many of which were really heartbreaking  
6 and, in my pompous, **nonphysician** manner, would certainly have  
7 to say sounded like bad medical care, I think what many of us  
8 were feeling was that we would like somehow to give advice to  
9 improve that medical care. That is probably not something  
10 that the FDA can do in a "Dear Doctor" letter or anything lik  
11 that "to tell people, "Pay attention to your patients. If the  
12 patient appears to be having a terrible time, do something  
13 different. "

14 Maybe that is what people would like to see done an  
15 there is just no way for the FDA to do that.

16 DR. MONTGOMERY: I wanted to say my reaction to thi  
17 morning's presentations. I thought they were terrible  
18 individual testaments to the evil nature of depressive  
19 illness, that depression is something which people assume is  
20 easy to treat, they assume that if they do not have it  
21 treated, it will go away of its own accord. It is a very  
22 nasty condition, and what I took from this morning was a  
23 description by individuals that they had expected that, havin  
24 started on medication, that it would automatically resolve an  
25 it did not.

1           It seems to me that one of the things that came out  
2 this morning quite clearly was that there was a need to inform  
3 patients about the terrible nature of depressive illness  
4 itself, rather than trying to ascribe blame to a drug or  
5 something else. It seems to me that that is what the  
6 testament was really saying to us. They were seeking largely  
7 to blame a drug, but they were actually describing a very  
8 nasty illness, and that is something which I think we should  
9 pay attention to.

10           DR. CASEY: I would agree. In summary, depression  
11 is common, it has morbidity, it is dangerous, it has  
12 mortality, it is torturing, it is often unrecognized, and  
13 often untreated or poorly treated. Given that, you are  
14 correct in urging that treatment of depression be improved.  
15 There have to be other ways in this country to do that besides  
16 through labeling and through the FDA, and some of those  
17 efforts are going on.

18           I appreciate your international perspective in  
19 coming as an "outsider" to listen to what we were wrestling  
20 with and bringing your advice.

21           We are getting close to closing. Unless someone has  
22 the burning urge to make additional comments, I would like to,  
23 first, thank the visiting members of the committee for their  
24 efforts, thank the committee members, thank Mr. Bernstein for  
all his efforts in making this meeting run smoothly -- he has

1 done a very good job -- thank all the people who came this  
2 morning to present, thank the people from Lilly, who have  
3 spent a lot of time and effort to bring new information to  
4 us . I now bring the meeting to a close.

5 DR. LEBER: Before you do, we have one other person  
6 to thank. Tom Laughren and I, on behalf of the Division and  
7 the agency, want to say something about you. This is your  
8 swan song and this is your last time to serve as chair of thi  
9 committee. I think each of us who has had the privilege of  
10 serving with you knows what it is to have a good chairman.  
11 You have done a fantastic job, you have been fair, you have  
12 been straight on, you have done the right thing, and you have  
13 kept us out of trouble, and I want to thank you for it all.

14 (Applause)

15 DR. CASEY: Thank you very much. I have been with  
16 the committee for four-and-a-half years and it has really  
17 truly been both a personal and professional very positive  
18 experience. It has been very rewarding to work with both the  
19 agency and all my committee members over the years. Thank yo  
20 very much.

21 We are adjourned.

22 (Whereupon, at 5:40 p.m., the meeting was  
23 concluded. )

24

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 *em*