

Dr. Breggin's note: The FDA was fraudulent in its Black Box explanation that suicidality was found in the pediatric patients but not in the adults, because the adult studies were not comparable to the pediatric studies and were flawed beyond redemption. The adult studies were not even monitored or verified by the FDA, nor required to follow specific evaluation procedures. Why would the FDA trust the drug companies to do a more honest job evaluating the adult suicides on their own than they did when the companies originally hid all the data on child suicides? (see pp. 13-14 of this FDA hearing).

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FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION RESEARCH (CDER)
- - -
PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE



- - -
TUESDAY, DECEMBER 13, 2006
8:00 A.M. to 5:30 P.M.

- - -
HILTON HOTEL
THE MARYLAND BALLROOM
8727 COLESVILLE ROAD
SILVER SPRING, MARYLAND

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Patient Representative
Center for Drug Evaluation & Research
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ANDREW C. LEON, PH.D.
Expertise: Biostatistics
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19 Center for Drug Evaluation and Research
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21 MARK LEVENSON, M.D.
22 Center for Drug Evaluation and Research
23 Medical Reviewer

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1 P-R-O-C-E-E-D-I-N-G-S (8:00 A.M.)

2

3 CALL TO ORDER AND OPENING REMARKS

4 DR. PINE: My name is Daniel Pine, and I

5 am the acting chair of the Psychopharmacologic

6 Drugs Advisory Committee. I would like to begin by

7 calling today's meeting to order.

8 As many of you know, we are gathered here

9 today as a Committee to discuss the results of an

10 ongoing meta-analysis of data on suicidality

11 emerging from antidepressant trials.

12 Historically, this has been an issue that

13 has been examined by many organizations including

14 the FDA in great detail over the last five or so

15 years.

16 Today, the specific purpose is to look at

17 newly available data that focuses on results

18 compiled by the FDA in trials among adults where

19 all the previous meetings we have spent time
20 talking about data in children.

21 A few housekeeping orders, number one, we
22 have an incredibly full schedule. We have many,

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1 many speakers for the open public hearing. Because
2 of that I'm going to try to move things along and
3 keep us very much to a tight schedule exactly
4 outlined on your schedules that you have in front
5 of you.

6 I'm going to ask that all the speakers
7 remember to use the microphones by turning them on
8 by pressing the button so that you can speak into
9 the record when you make your comments and then to
10 turn it off when you are finished.

11 In terms of other introductory remarks, I
12 would like to introduce you to the other members of
13 the Committee and the other people who will be
14 speaking before us to go around and introduce
15 themselves.

16 INTRODUCTION OF COMMITTEE

17 DR. PINE: Once again, as I said, I am
18 Daniel Pine. I am a child psychiatrist from the
19 National Institute of Mental Health Intramural
20 Research Program.

21 Tom.

22 DR. LAUGHREN: Tom Laughren. I'm the

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1 director of the Division of Psychiatry Products at
2 FDA.

3 DR. JONES: I am Lisa Jones. I am a
4 medical officer on the Safety Team with the
5 Division of Neurology and Psychiatry at the FDA.

6 DR. STONE: Marc Stone. I am a medical
7 reviewer on the Safety Team in the Division of
8 Neurology and Psychiatry.

9 DR. LEVENSON: Mark Levenson. I am a
10 statistical safety reviewer in CDER.

11 MS. GRIFFITH: I am Gail Griffith. I am
12 a writer and I am also a family advocate and a
13 lifelong sufferer of major depressive disorder.

14 DR. ARMENTEROS: Jorge Armenteros, child
15 adolescent and adult psychiatrist.

16 DR. GOODMAN: Wayne Goodman. I am a
17 professor and chairman at the University of Florida
18 in Gainesville. I am a past member and chair of
19 PDAC. My term as chair ended in June 2006, and I
20 am delighted to be invited back as a consultant.

21 DR. REESE: Cicely Reese, Committee
22 designated federal official.

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1 DR. LEON: I am Andrew Leon. I am
2 professor of biostatistics at Weill Cornell Medical
3 College.

4 DR. SLATTERY: I am Marcia Slattery. I
5 am the head of Child and Adolescent Psychiatry at
6 the University of Wisconsin.

7 DR. SCHULTZ: I am Susan Schultz. I am a
8 geriatric psychiatrist at the University of Iowa.

9 MS. BRONSTEIN: I am Jean Bronstein, a
10 retired nurse from Stanford University Hospital and
11 the community representative.

12 DR. POLLOCK: I am Bruce Pollock. I am a
13 geriatric psychiatrist at the University of Toronto
14 and the University of Pittsburgh.

15 DR. ROBINSON: I am Delbert Robinson. I
16 am a psychiatrist at the Zucker Hillside Hospital
17 and the Albert Einstein College of Medicine.

18 DR. MEHTA: I am Dilip Mehta. I am a
19 retired industry physician. I am the nonvoting
20 industry representative on the Committee.

21 DR. PINE: Thank you. I would like to
22 remind the Committee that in the spirit of the

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1 Federal Advisory Committee Act and the Sunshine
2 Amendment any discussion about today's topics
3 should take place only in the public forum of this
4 meeting. Specifically, they should not occur
5 during lunch, during breaks, or in private
6 discussions.

7 I will also ask in the service of
8 assisting the Committee that the audience and the
9 press refrain from asking questions to the
10 Committee during breaks, but wait until the meeting
11 has adjourned, until the end of the day.

12 In terms of the next item of business,
13 Cicely.

14 CONFLICT OF INTEREST STATEMENT

15 DR. REESE: I will be reading the
16 "Conflict of Interest Statement." The following
17 announcement addresses the issue of conflict of
18 interest and is made part of the record to preclude
19 even the appearance of such at this meeting.

20 The Food and Drug Administration is
21 convening today's meeting of the
22 Psychopharmacologic Drugs Advisory Committee under

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1 the authority of the Federal Advisory Committee Act
2 of 1972.

3 The Committee will discuss the results of
4 the FDA ongoing meta-analysis of suicidality data
5 from adult antidepressant trials. This meeting is
6 a particular matter involving specific parties.

7 Based on the agenda for today's meeting
8 and all financial interests reported by the
9 committee members and consultants in accordance
10 with 18 U.S.C. 208(b)(3), full waivers have been
11 granted to the following participants:

12 Dr. Andrew Leon, for his role as a member
13 for other data safety monitoring boards for an
14 affected firm. He receives between \$10,001 and
15 \$50,000 per years.

16 Ms. Jean Bronstein, for her ownership of
17 stock and a bond in an affected firm in which the

18 value falls between \$50,001 and \$100,000, and her
19 husband's, her spouse's, ownership of stock in an
20 affected firm in which the value falls between
21 \$5,001 and \$25,000.

22 Dr. Bruce Pollock has been granted a

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1 limited waiver for his activities on an advisory
2 board and speakers bureau for an affected firm in
3 which he receives less than \$10,001 per year and
4 for his teaching for an institution established by
5 an affected firm. He receives less than \$5,001 per
6 year. Dr. Pollock will be permitted to participate
7 in the Committee's deliberations. He will,
8 however, be excluded from voting.

9 Waiver documents are available at the
10 FDA's docket webpage. Specific instructions as to
11 how to access the webpage are available outside
12 today's meeting room at the FDA information table.

13 In addition, copies of all the waivers
14 can be obtained by submitting a written copy to the
15 Agency's Freedom of Information Office, Room 12A-30
16 of the Parklawn Building.

17 With respect to the FDA's invited
18 industry representative, we would like to disclose
19 that Dr. Dilip Mehta is serving as the nonvoting
20 industry representative acting on behalf of
21 regulated industry and is retired from Pfizer.

22 In the event that the discussions involve

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1 any other products or firms not already on the
2 agenda for which FDA participants have a financial
3 interest, the participants involvement and their
4 exclusion will be noted for the record.

5 With respect to all other participants,
6 we ask in the interest of fairness that they
7 address any current or previous financial
8 involvement with any firm whose produce upon which
9 they may wish to comment.

10 DR. PINE: Thanks, Cicely.

11 Okay. The way that the next 90 minutes
12 are going to go is that we are going to begin the
13 meeting by hearing from the FDA, and there really
14 will be three parts to this.

15 We will begin with Tom Laughren will give
16 us 15 minutes of background introductory remarks
17 and give us an overview of the key issues, after
18 that we will have three database presentations
19 again from the FDA, and then we will have time for
20 some brief discussion. After that 90 minutes, we
21 will take a break and then we will move to the open
22 public hearing.

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1 There will be some time for questions,
2 but I would like to ask that we try to restrict the
3 questions to the materials that are presented.

4 The hope is that we are going to spend a
5 good chunk of the afternoon in more open

6 discussions and open questions. All the
7 representatives from the FDA will be here.

8 With that I would like to introduce
9 Tom Laughren who is going to begin with fifteen
10 minutes of introductory remarks.

11 FDA INTRODUCTORY REMARKS & OVERVIEW OF ISSUES

12 (PowerPoint™ presentation in progress.)

13 DR. LAUGHREN: We are considering new
14 information on the occurrence of suicidality during
15 treatment of adult patients with antidepressants.

16 This is actually a followup to a meeting
17 that was held on antidepressants and suicidality in
18 pediatric patients in September 2004. The focus of
19 that meeting was on a finding of an increased risk
20 of suicidal thinking and behavior in pediatric
21 patients taking antidepressants.

22 We are going to be using the term

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1 "suicidality" to refer to the combined endpoint of
2 suicidal thinking and behavior throughout this
3 session.

4 Now, subsequent to that meeting in 2004,
5 we decided to expand this exploration for
6 suicidality into the adult population. We have now
7 completed that analysis, and I will say it has been
8 a major effort involving 372 placebo-controlled
9 trials of antidepressants in almost 100,000
10 patients.

11 Now, the occurrence of suicidality in the
12 context of treating patients with depression and
13 other psychiatric illnesses has actually been a
14 concern and a topic of debate for a long time.

15 In fact, in terms of antidepressant
16 labeling, the recent introduction of the black box
17 carried the standard language that you see in this
18 slide under precautions which essentially alerted
19 clinicians to closely monitor patients during
20 initial drug therapy out of concern for the
21 possible emergence of suicidality.

22 Now, this standard statement did not, of

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1 course, explicitly warn of the possibility that
2 antidepressants treatment may actually have a
3 causal role in the emergence of suicidality, but it
4 did allow for that possible interpretation.

5 Now, in fact, as early as medical school,
6 most physicians learn of this concern. In fact, it
7 has been a part of medical lore for a very long
8 time that antidepressants may have an early
9 activating effect that may give depressed patients
10 the energy to follow through on suicidal impulses
11 before the mood improvement associated with the
12 antidepressants treatment has a chance to take
13 effect.

14 Now, this statement that is on this slide
15 here is one that was taken from a textbook of
16 psychiatry that was published over 40 years ago.

17 It is referring to a period of time during which
18 tricyclic antidepressants were the antidepressants
19 available for psychiatrists. Basically, the
20 statement says, "With beginning convalescence," and
21 again this is referring to a period of time after
22 initiating treatment with a tricyclic, "the risk of

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1 suicide once more becomes serious as retardation
2 fades."

3 Now, the mechanism that is suggested in
4 this quote to explain an increase in suicidality
5 early in antidepressant treatment is that one of
6 several mechanisms have been proposed to explain
7 the clinical observation that some patients being
8 treated with antidepressants, particularly early in
9 treatment, may have an increase in suicidality.

10 Proposing a mechanism, however, is quite
11 a different matter from demonstrating empirically
12 that there is a causal association between
13 antidepressant use and the induction of
14 suicidality.

15 The pediatric data that we presented at
16 the September 2004 Advisory Committee meeting I
17 believe represented the first systematic
18 demonstration of a causal link.

19 The finding in the pediatric data in a
20 sense confirmed a view that was already widely
21 prevalent in clinical lore, whatever the mechanism.

22 Now, despite this fairly widely held

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1 view, the use of antidepressant use has increased
2 in recent decades rather than decreased. Now, of
3 course there has been some change in antidepressant
4 prescribing over the past few years, and there will
5 be some discussion of that later in the meeting.

6 Over the prior two decades,
7 antidepressant use had dramatically increased.
8 Again, I think that fact suggests that as a group
9 clinicians have placed more weight on the
10 longer-term benefits of antidepressants than on
11 their concerns about possible early risks of
12 increased suicidality.

13 The dual findings of an early increase in
14 the risk of suicidality but also a longer-term
15 benefit with antidepressants treatment would not
16 necessarily be inconsistent. It is possible for a
17 drug to have opposite effects over time even within
18 the same domain.

19 Now, the debate on this question of
20 antidepressants and suicidality with regard to the
21 adult population intensified in 1990. At this time
22 Martin Teicher, a psychiatrist at Harvard Medical

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1 School, along with several of his colleagues
2 published a paper on the experience of six adult
3 patients that were suicidal as a result of being
4 treated with Prozac®, "fluoxetine."

5 Now, this paper and the ensuing
6 discussion led Lilly, the manufacturer of Prozac,
7 to conduct new analyses of their clinical trial
8 data for Prozac to explore for the emergence of
9 suicidality.

10 This issue was brought to the
11 Psychopharmacologic Committee in September of 2004.
12 Over the next several years, additional data were
13 accumulated as applications for newer
14 antidepressants were submitted and reviewed, and
15 several groups have in recent years conducted
16 pooled analyses for adult data on completed or
17 attempted suicides from these programs in order to
18 continue to explore for a signal of risk.

19 Now, actually these searches were
20 motivated by two concerns, two competing concerns.
21 One concern that was very prevalent in the nineties
22 was a concern that actually placebo assignment

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1 placed patients at increased risk of suicide and
2 the ethics of conducting placebo-controlled
3 clinical in depression was being challenged.

4 At the same time there was the other side
5 of the argument that the concern was about
6 induction of suicidality by virtue of taking an
7 antidepressant.

8 Arif Khan in 2000 published a paper based
9 on adult data that that he obtained under Freedom
10 of Information from FDA reviewers of attempted
11 suicides from adult data available to his group,
12 and he reached the same conclusion. That was the
13 Storosum, et al., paper of 2001.

14 Now, today we are going to be presenting
15 the updated results from completed suicides from
16 our current database in adults. Even before this
17 analysis, we had looked at completed suicides in
18 adult antidepressant trials and reported on these
19 results. The earlier analysis was focused on nine
20 antidepressant drugs over a total of 251 randomized
21 placebo-controlled trials.

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1 We reached a similar conclusion to
2 others, that there did not appear to be an
3 increased risk of completed suicides associated
4 with assignment to either active drug or placebo in
5 adults with major depression or various anxiety
6 disorders. These results were published in Hammad,
7 et al., in 2006.

8 Now, based on the findings of a signal of
9 increased risk of suicidality in association with
10 the short-term of antidepressants in pediatric
11 patients, the September 2004 Advisory Committees
12 recommended that FDA add a box warning to
13 antidepressant labeling and require a medication
14 guide to alert patients' families and caregivers of
15 this risk. Both of these changes were implemented
early in 2005.

16 The new warning language warns of the
17 risk of suicidality in pediatric patients and
18 advises that prescribers balance this risk with
19 clinical need in deciding on the use of an
20 antidepressant in this population.

21 The risk is characterized in terms of
22 risk difference. In other words, what we were

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1 seeing is an average risk of 4 percent for this
2 outcome suicidality in drug-treated patients
3 compared to 2 percent in placebo-treated patients
4 during the initial few months of treatment.

5 Labeling also notes that there were no
6 completed suicides among those studies.
7 Prescribers are advised to observe patients closely
8 for clinical worsening for the emergence of
9 suicidality or for unusual changes in behavior.

10 Families and caregivers are also advised
11 for the need of close observation of their family
12 members who are taking antidepressants and to
13 communicate any changes to the prescriber.

14 Now, just as we were getting underway
15 with our analysis of the adult suicidality data,
16 there was an issue of "BMJ," February 17, 2005,
17 that included three papers that are pertinent to
18 this question of adult antidepressant use in
19 suicidality. Since these papers are so relevant to
20 the discussion today, I'm going to mention them
21 briefly, and we will come back to these papers
22 later on in our presentations.

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1 The first paper, Ferguson, et al., 2005,
2 was a systematic review that was focused on data
3 available from published reports of controlled
4 trials of antidepressants in adults being treated
5 for depression and various other indications.

6 What they found was a twofold increase in
7 the risk of suicide attempts in users of SSRIs
8 compared to placebo or other interventions, but no
9 difference when you compare SSRIs to tricyclic
10 antidepressant use. There was no difference,
11 however, in completed suicides across these trials.

12 There were serious limitations to this
13 review, most important probably being a lack of any
14 safety information on, roughly, 58 percent of the
15 patients who were eligible for that analysis.

16 The second paper, Gunnell, et al., 2005,
17 was also a systematic review. This focused on data
18 that was available to the MHRA and summaries that
19 they published on their website. MHRA is FDA's
20 counterpart in the U.K.

21 They focused on SSRIs. Again, they
22 looked at self-harm and they also looked suicidal

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1 thoughts. What they found was that the odds ratio
2 for SSRIs to placebo was greater than one for self-
3 harm but less than one for suicidal ideation and

4 neither finding was statistically significant.
5 Again, there was no difference across the treatment
6 groups for completed suicide.

7 The third paper, Martinez, et al., was a
8 nested case control study in the General Practice
9 Research Database in the U.K. This is a large
10 cohort, a practice cohort, where patients are
11 followed closely and systematic data and systematic
12 data are collected.

13 It examines self-harm behavior and
14 suicide in adult and pediatric patients with
15 depression who were treated with either an SSRI or
16 a tricyclic. Overall, what they found was no
17 difference in the risk between those two groups.
18 However, there was a suggestion of an increased
19 self-harm behavior in patients aged 18 and younger
20 for SSRIs compared to tricyclics.

21 Now, clearly there was overlap in the
22 studies included in the meta-analysis that we are

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1 going to be presenting today for adult
2 antidepressant trials and those trials that were
3 looked at in the two systematic reviews, the
4 Ferguson review and the Gunnell, et al., review.

5 Now, unlike the authors of these separate
6 systematic reviews, we did have access to patient
7 and trial level data, and that allowed us to do
8 certain analysis that the other authors could not
9 do.

10 I think this an important difference, and
11 we will comment later on some of the differences
12 from our analysis compared to these other
13 systematic reviews.

14 The plan for today, first of all, we are
15 going to present the findings from our
16 meta-analysis of the adult suicidality data. We
17 will provide our interpretation of these data.

18 Finally, we are going to briefly outline
19 our plans for labeling modifications based on these
20 new findings. We have not posed any specific
21 questions for a vote, but we are asking you to
22 discuss our findings in detail and our proposed

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1 changes to labeling and give us your feedback.

2 Thank you.

3 DR. PINE: Thank you, Dr. Laughren.

4 Any questions or clarifications?

5 (No response.)

6 DR. PINE: Okay. For the next speaker, I
7 would like to introduce Dr. Lisa Jones who is going
8 to give a data overview of the data on
9 antidepressants and suicidality in adults.

10 Lisa.

11 FDA PRESENTATION

12 ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:

13 DATA OVERVIEW

14 DR. JONES: Thank you.

15 (PowerPoint presentation in progress.)

16 DR. JONES: I would like to present to
17 the Committee this morning an overview of the data
18 that was the basis for the FDA's adult suicidality
19 analysis. An overview of both the data collection
20 process and what the final data set was composed
21 of.

22 Unless otherwise specified, persons in
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1 the presentations this morning will be referring to
2 these eleven drugs, composed of the six selective
3 serotonin reuptake inhibitors, "SSRIs," and
4 five non-SSRIs.

5 I'm showing here that drugs which were a
6 combination of an antidepressant and another drug
7 such as Symbyax®, a fluoxetine/olanzepine
8 combination, were not included in the final
9 analysis.

10 The data used in this analysis was taken
11 from randomized, controlled trials that had been
12 performed by the sponsors of the eleven
13 antidepressant drugs from the previous slide.

14 For some times perspective on the data
15 collection, the FDA sent four data request letters
16 to the sponsor from December 2004 to August 2005.
17 The resulting data sets were received back by the
18 FDA from September 2005 to September 2006.

19 The total of four letters or four
20 requests letters were sent to the sponsors in order
21 to address the various issues which arose during
22 the earlier review of the data sets.

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1 The FDA data request letter contained
2 fairly detailed guidance to the sponsors on what
3 trials should be included in the data set for each
4 drug.

5 Specifically, the letter stated that the
6 trial should be randomized, placebo-controlled
7 trials only, that the trial could be for any
8 indication or of any length, but you have at least
9 20 subjects per treatment arm.

10 Prior to the submission of the final data
11 set, the sponsors submitted a list of the trials
12 they intended to include and exclude, and the FDA
13 provided feedback on the composition of the final
14 data sets.

15 The previous slide noted that trials for
16 any indication could be submitted and we did indeed
17 receive trials from a wide variety of indications.
18 These indications were first divided into two broad
19 groups: those for major depressive disorder or
20 "MDD," and those which were not for major
21 depressive disorder.

22 The non-MDD trials were further divided
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1 into four subgroups: other depressive disorders,
2 other psychiatric disorders, behavioral disorders,

3 and other disorders.
4 The placement of a particular indication
5 into one of these categories was reached by a
6 consensus of the review team. Also, I should note
7 that the MDD and non-MDD data sets were submitted
8 separately by the sponsors.

9 This slide lists the various depressive,
10 dysphoric and dysthymic disorders that were
11 included under the indications within the "other
12 depressive disorders" subgroup.

13 This slide lists the indications
14 indicated in the "other psychiatric disorders"
15 subgroup: ADHD, adjustment disorder, Alzheimer's
16 disease, bulimia, obsessive-compulsive disorder,
17 the negative symptoms of schizophrenia, and various
18 panic and anxiety disorders.

19 Under "behavioral disorders" were studies
20 of alcoholism, insomnia, weight and obesity issues,
21 and smoking cessation.

22 Finally, under the "other disorders" were
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1 fibromyalgia, incontinence, sexual dysfunction, and
2 various pain-related indications.

3 For all the drugs combined, data from a
4 total of 404 trials were submitted to the FDA.
5 Only 372 trials were included in the final data set
6 for the analysis, however, 32 trials were excluded,
7 23 for having less than 20 subjects per treatment
8 arms, and there were 3 in which there was
9 inadequate subject data available.

10 In addition, there were also six trials
11 submitted in duplicate because both the treatment
12 arm and the active control arm utilized one of the
13 eleven drugs being studied. The same trial was,
14 therefore, submitted in the data sets for each of
15 the two drugs. These trials were included in the
16 final data set only once to prevent the double
17 counting of these subjects.

18 The previous slides have described the
19 collection of the denominator data for the
20 analysis, and the next few slides will describe the
21 collection of the numerator or event data. TO

22 identify potentially suicide-related adverse

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1 events, sponsors were asked to search their
2 preferred terms, their verbatim terms, and the
3 comment sections of the trials for various suicide-
4 related text strings, some of which are shown in
5 this slide: the accident attempt, burn, cut, and
6 gun.

7 The search was limited to the
8 double-blind period of the studies. Subjects with
9 events predating baseline were not exclude. Events
10 were counted if they recurred during the trial.

11 For example, if a subject had a history
12 of suicidal ideation prior to enrollment in the
13 trial and then reported suicidal ideation within

14 the trial, this would be counted as an event of
15 suicidal ideation.

16 Adjudication of the possibly suicide-
17 related adverse events generated by the text string
18 search was performed according to the Columbia-
19 Classification Algorithm of Suicide Assessment or
20 "CASA."

21 Due to the large number of subjects in
22 the adult analysis, almost 100,000 patients, the

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1 adjudication process was left as the responsibility
2 of the sponsors and was not overseen or otherwise
3 verified by the FDA. This is in contrast to the
4 pediatric suicidality analysis in which the FDA was
5 actively involved in the adjudication.

6 A number of the sponsors chose to comply
7 with the request to use the Columbia-Classification
8 Algorithm by actually having the suicidologists at
9 Columbia perform the adjudication.

10 For those who chose not to outsource the
11 adjudication to Columbia, there is some evidence
12 that the Columbia algorithm can be applied
13 consistently by different groups including the
14 FDA's experience during the pediatric suicidality
15 analysis in which independent groups at the FDA and
16 at Columbia reached similar results when
17 adjudicating the same potential events.

18 Reports identified for the text strings
19 which were clearly not suicide-related such as
20 epigastric pain from the text string gas were
21 excluded.

22 Events were classified into one of the

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1 following categories, completed suicide, suicide
2 attempt, preparatory acts, suicidal ideation,
3 self-injurious behavior, intent unknown, and not
4 enough information, fatal, and nonfatal.

5 The numbers on the right-hand of the
6 slide represent a ranking of severity with one, a
7 completed suicide, being the most severe event. An
8 important aspect of the event data is that
9 information on only the most severe event was
10 submitted to the FDA.

11 For example, if a subject reported
12 suicidal ideation, preparatory acts, and a suicide
13 attempt during a trial, the data set would only
14 contain information on the suicide attempt.

15 Finally, these two slides summarize the
16 variables contained within the drug data sets. In
17 addition to trial and subject identifiers, the data
18 set contained information on trial characteristics
19 such as setting; inpatient or outpatient; the
20 location, North American or not; on subject
21 demographics, age, gender, race; and information on
22 treatment including on active control treatment, if

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1 one was present.

2 There were variables on disease severity
3 including whether the subject had a history of
4 prior suicidal attempt or ideation as well as
5 baseline and final scores on whichever disease
6 severity scale was used; outcome-related
7 information on event; the time to event; or time on
8 study drug, if no event occurred; and, finally, on
9 deaths by any cause which occurred within 90 days
10 after the intended treatment.

11 Thank you.

12 DR. PINE: Thank you, Dr. Jones.

13 Unless there is a burning question, I
14 think I'm going to hold clarification questions
15 until after the next presentation which naturally
16 segues from the presentation we just had.

17 Not seeing any of those, I will introduce
18 Dr. Mark Levenson who is going to present the
19 results from the analysis using the methods just
20 discussed by Dr. Jones on antidepressants and
21 suicidality in adults.

22 ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:

0036

1 STATISTICAL SAFETY REVIEWER EVALUATION

2 DR. LEVENSON: Hello, I'm Mark Levenson.
3 My Colleague Chris Holland and I are statistical
4 safety reviewers in CDER. Our presentation today
5 is on the statistical evaluation of the adult
6 suicidality data.

7 (PowerPoint presentation in progress.)

8 DR. LEVENSON: The presentation is
9 divided into four parts. I'm briefly going to
10 describe the objectives of our analysis, and then
11 I'm going to go into the specifics of your
12 statistical analysis and plan which includes the
13 definition of the population, the endpoint, and the
14 statistical methods; then I will present the
15 results, which include the primary and secondary
16 results, extensive sensitivity analysis to the
17 primary results, and some subgroup analysis; and,
18 finally, I will summarize the presentation.

19 Briefly, the primary objective is to
20 estimate the effect of antidepressant drugs versus
21 placebo on suicidality in adults in double-blind,
22 randomized, placebo-controlled clinical trials.

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1 As a secondary objective, we are going to
2 explore the effect of various subgroups defined by
3 subject-level and trial-level characteristics.

4 Now going on on the analysis plan, as
5 Dr. Jones just described, the medical team divided
6 the submitted trials into five indication groups.

7 I will just review them here: major
8 depressive disorder and four non-MDD indications,
9 other depressive disorders, other psychiatric
10 disorders, behavioral disorders, and other
11 disorders.

12 The primary analysis population, which we

13 will refer to as psychiatric indications include
14 all subjects from trials in these first three
15 indication groups: major depressive disorder, other
16 depressive disorders, other psychiatric disorders.

17 As the secondary analysis populations, we
18 consider each of the five indication groups
19 separately. Our primary endpoint which we refer to
20 as suicidal behavior and ideation consists of the
21 first four event codes that Dr. Jones just
22 described: completed suicide, suicide attempt,

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1 preparatory acts, and suicide ideation.

2 For secondary endpoints, we look at
3 suicidal behavior, which consist of the first event
4 codes, and we look at suicide ideation only, which
5 is the fourth event code.

6 I would like to emphasize that the only
7 emphasis is that subjects who had an event code in
8 these first three categories may have also had
9 ideation because, as Dr. Jones described, only the
10 most severe event was submitted for each subject.
11 The emphasis here is for ideation there was no
12 record of anything more severe, but for behavior
13 they may well have ideation as well.

14 The primary analysis method is referred
15 to as an exact method for a common odds ratio. It
16 is a stratified method. This allows the background
17 rates of different trials to vary. It doesn't
18 insist that every trial has the same rate of
19 suicidality.

20 It is very well suited to handle low
21 event counts, which is the case in our current
22 data, and small trial sizes, which is not

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1 necessarily the case in the trials that we see, but
2 when we start looking at some subgroups it may be
3 the case.

4 The method assumes that there is a common
5 odds ratio across all trials. That, roughly, means
6 for each trial the ratio of the treatment group
7 events to the placebo group events is constant.

8 It does not make use of trials that have
9 no events. Because of the low event rates we will
10 see, when I start presenting the data, there was a
11 significant number of trials that did not have any
12 event, and this method does not make use of them.

13 To examine the robustness of the primary
14 analysis method, we looked at trying alternate
15 methods and sensitivity analysis. We examined
16 deviations along several fronts.

17 The first set of methods we looked at are
18 traditional model-based methods often used in meta-
19 analysis including Mantel-Haenszel odds ratio
20 methods with and without continuity corrections.

21 It has been pointed out that continuity corrections
22 may bias the results in the present setting.

0040

1 We looked at logistic regression, both
2 unconditional and conditional versions. The
3 conditional framework is designed to improve the
4 statistical properties of the estimate.

5 We looked at methods that are referred to
6 as random-effect methods. These methods allow the
7 treatment effect to vary by trial. You recall the
8 primary analysis method insisted that the treatment
9 effect, the odds ratio, is common across all the
10 trials.

11 These methods allow this treatment effect
12 to vary by trial. Again, it's referred to as
13 random-effect methods in contrast to the primary
14 analysis method and these methods which are
15 referred to as fixed-effect methods.

16 The two methods we applied in this
17 category are generalized linear mixed model and
18 DerSimonian-Laird method often used in
19 meta-analysis.

20 As I pointed out a slide a two ago, many
21 of the trials did not have any events, and so for
22 all the methods I described do not make use of those

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1 trials.

2 We applied one method that does make use
3 of all trials including trials that do not have
4 events, and that is the Mantel-Haenszel risk
5 difference method.

6 Finally, we employed Bayesian methods in
7 the sensitivity analysis. These methods encompass
8 both fixed- and random-effect models and allow for
9 other hierarchies as drugged effects to be
10 incorporated. They do make use of trials with no
11 event.

12 The particular models that we employ were
13 used in a paper by Kaizer, et al., in 2006, applied
14 to the pediatric data presented to the Committee in
15 2004.

16 For the subgroups, we looked at both
17 subject level and trial level characteristics
18 including: age group; gender; race; drug type, SSRI
19 versus non-SSRI; the location of the trial,
20 North America versus other locations; the setting,
21 inpatient, inpatient and outpatient combined versus
22 outpatient only.

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1 Now the results, first, looking at trial and
2 subject summaries, as Dr. Jones pointed out there
3 was a total of 372 trials that were submitted that
4 were used in the analysis. The largest class of
5 trials fell in the major depressive disorder
6 indication group, followed by the other psychiatric
7 disorders.

8 Overall, in the primary indication group,
9 in the primary analysis population, which consists
10 of subjects in these first three indication groups,
11 there were 295 trials. Looking at the location of

12 the 295 trials, about three-quarters of them or 219
13 were located in North America.

14 Looking at the duration of these trials,
15 all but a small percentage were 18 weeks or less.
16 Only a small percentage was greater than 18 weeks.
17 The bulk of the trials fell into the 5- to 12-week
18 category. The mean duration of the trials was
19 about 10 weeks and the median duration was about 8
20 weeks.

21 When we looked at subject
22 characteristics, comparing differences between the
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1 test drug subjects and the placebo subjects, there
2 were no noticeable differences for age, gender,
3 race, baseline history of suicide attempts,
4 baseline history of suicide ideation, and treatment
5 exposure. Because there were no significant
6 differences in treatment exposure, we chose
7 subject, not subject years, as a unit of analysis.

8 Here we look at a tally of all the events
9 broken down by treatment group: placebo, test
10 drugs, active control. There were eight completed
11 suicides overall among the treatment group. The
12 largest class of events was suicide ideation, with
13 358 events, followed by suicide attempt.

14 Over here you also see the total sample
15 size for each of the trial arms. You see that the
16 test drugs had more subjects overall than the
17 placebo arm.

18 Looking at unadjusted events, a number of
19 events per subjects over the five indication
20 classes and looking at the placebo arm, you see
21 that the three indication classes that make up the
22 primary analysis population have, roughly, similar
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1 unadjusted rates.
2 Unadjusted rates for the other indication
3 classes are notably lower. For the three
4 indication classes, the unadjusted rates for the
5 placebo are higher than those for the test drugs.

6 Summarizing across the entire psychiatric
7 indication group for the primary endpoint of
8 suicide behavior and ideation, the overall
9 unadjusted rate for placebo was .72 percent, for
10 the test drug it was .62 percent.

11 One hundred and seventy-four of the two
12 hundred and ninety-five trials, or roughly about 60
13 percent of the trials, had events. Forty percent
14 of the trials did not have events, and that is
15 probably not unusual given these low event rates
16 that many trials would not have events.

17 Now we look at the adjusted rates based
18 on the primary analysis method. We are going to be
19 looking at a fair amount of plots like these that
20 refer to forest plots. Here we are plotting the
21 odds ratio for the eleven test drugs overall for
22 the primary endpoint of suicide behavior and

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1 ideation and psychiatric indications.
2 The key value here to look at is the
3 value of one. A value less than one would imply
4 that the test drugs are associated with lower rates
5 of suicidality than the placebo.

6 Now we are going to look at a very
7 similar plot but broken up by indication class, the
8 five indication classes. You can see among the
9 three indication classes that make up the primary
10 analysis population, they have roughly similar
11 estimates.

12 Looking at the secondary endpoints of
13 suicidal behavior and suicide ideation only, the
14 intervals for these odds ratio estimates overlap.
15 The estimate for ideation is lower than that of
16 behavior.

17 Moving on to the results of the
18 sensitivity analysis, first, look at the risk
19 difference. This is a very similar plot to the
20 odds ratio plot, but rather than plot odds ratios
21 we are looking at risk differences.

22 The chief advantage of this approach in
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1 the sensitivity analysis is it makes use of all the
2 trials including the 40 percent of the trials that
3 did not have events. It also may have more readily
4 interpretable estimates.

5 What should be noted from this plot is
6 that -- well, let me first point out that zero here
7 is the key value. Like in the odds ratio a value
8 of one is the key value, the key value here is
9 zero. A value less than zero would imply that the
10 test drugs are associated with lower rates of
11 suicidality than the placebo.

12 If you compare this plot to the odds
13 ratio plot, the patterns are very similar and the
14 overall estimate is negative similar to the odds
15 ratio being less than one and it slightly overlaps
16 the key value of zero. This supports the odds
17 ratio estimate.

18 This is probably the most statistical
19 slide of the presentation. It includes all the
20 sensitivity methods we applied that I described
21 earlier in the presentation.

22 The first thing to note is that generally
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1 all the sensitivity methods that produce odds
2 ratios give very similar results. Mantel-Haenszel,
3 Mantel-Haenszel with continuity correction, you can
4 see that the estimate is slightly lower, which is
5 to be expected by our understanding of the
6 continuity correction.

7 The DerSimonian-Laird method was one of
8 the random-effect methods. Had there been trial
9 heterogeneity, had the odds ratios varied by trial,
10 we might see that this interval is wider than the

11 above intervals and perhaps the estimate is
12 different. That is not the case, so that lends
13 evidence that we don't have significant differences
14 among the trials in the odds ratios.

15 We had the logistic model and the
16 conditional logistic. The generalized linear mixed
17 model, again that is a random effects model and we
18 don't see any differences there compared to the
19 other estimates.

20 Then, we have three versions of the
21 Bayesian model: a fixed effect, a random effect,
22 and hierarchical model. Again, there are not very

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1 many differences. One small difference is
2 hierarchical model appears to have a lower
3 estimate.

4 Looking at subgroups, the key subgroup we
5 are going to look at is the age subgroup. For the
6 adult population, we looked at four age groups: the
7 youngest 18 to 24, followed by 25 to 30, 31 to 64,
8 and greater than 65. This is for the primary
9 endpoint of suicidal behavior and ideation. We are
10 showing unadjusted rates there in the psychiatric
11 indication group.

12 One thing to point out, these are
13 unadjusted rates. The lowest age group, the
14 placebo has a lower rate than the test drug. For
15 the oldest age group, the reverse is true, the
16 placebo has a higher rate than the test drug.

17 Now we will look at the adjusted rate.
18 On this slide, I have added one additional group,
19 the pediatric data. This was the data presented to
20 an Advisory Committee in 2004, and it has been
21 reanalyzed using the present method, the present
22 analysis, but the results are qualitatively very

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1 similar to what they were when they were previously
2 presented.

3 The interval does not overlap one. It is
4 significantly greater than one, which was the
5 previous conclusion.

6 Overall, the significant finding here is
7 this clear trend in the odds ratios from the lower
8 age groups to the higher age groups. The lowest
9 age group in the adult population, the estimate is
10 greater than one, implying that the test drugs
11 might be associated with higher rates of
12 suicidality than the placebo. However, the
13 interval does overlap one, so this is not a
14 statistically significant result.

15 By the time we get to the oldest age
16 group, the estimate is on the lower side of one and
17 the interval falls below one. This is a more
18 significant finding, a more significant result
19 here.

20 We also look at this in terms of risk
21 differences. This is the same plot. Again, this

22 makes use of all the subjects. The only thing that
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1 I am going to point out here is that the pattern is
2 very similar to the odds ratio.

3 I am going to look more closely at the
4 risk difference estimates which have an
5 interpretation, which I will talk about on the next
6 slide.

7 The risk differences can be interpreted
8 as additional subjects with the suicidal behavior
9 and ideation events, and I am going to express them
10 per thousand subjects.

11 Using the estimates on the previous
12 slide, in the pediatric data we might expect for
13 every thousand subjects put on the test drug versus
14 placebo, we might see fourteen additional subjects
15 with events. That estimate has a 95 percent
16 confidence interval that goes from 6 subjects to 22
17 subjects.

18 The youngest adult age group, the
19 estimate is four additional subjects, but that
20 confidence interval goes negative. This negative
21 would imply we might see one less patient in the
22 test drug versus the placebo until we get up to the

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1 oldest age group where the estimate is six less
2 patients and the whole interval falls below zero.

3 One last slide on the age groups. Here
4 looking specifically at the youngest adult age
5 group, the 18 to 24, we look at the secondary
6 endpoints of suicidal behavior and suicide ideation
7 only.

8 We see the same trend we saw in the
9 overall adult, that the ideation estimate is lower
10 than that of behavior, but the intervals overlap.

11 For the other subgroups, I won't present
12 them now, but I will point out there were no
13 noticeable differences between the genders; between
14 the race; between the location of the trial; the
15 setting of care, inpatient versus outpatient; and
16 the drug class. There is no noticeable difference
17 between the SSRI drug classes versus the non-SSRI
18 drug classes.

19 Finally, that brings me to the summary.
20 For the primary analysis population endpoint, the
21 overall odds ratio was .84. Again, that estimate
22 would imply that the test drugs associated with

0052
1 lower rates of events than the placebos, but that
2 confidence interval overlaps one, so it is not a
3 statistically significant result.

4 There is a clear pattern in the estimates
5 with increasing age. The lower age groups are
6 associated with higher rate relative to the placebo
7 of suicidality versus the older age groups.

8 The subgroups that I just mentioned do
9 not have notable effects. Finally, we applied the

10 primary analysis method. We performed sensitivity
11 analysis that test the robustness of the methods of
12 various departures, and we found all the results
13 very consistent.

14 Thank you. That concludes the
15 presentation.

16 DR. PINE: Thanks, Dr. Levenson.

17 We actually do have a couple of minutes
18 for any clarifying questions either for Dr. Jones
19 or for Dr. Levenson. Again, I would like to try to
20 keep it to the material that has been presented,
21 any questions about or any clarifications.

22 Yes, Dr. Pollock.

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1 QUESTIONS

2 DR. POLLOCK: Could you give us some idea
3 of the numbers of those over the age of 65 and what
4 the range was in these trials?

5 DR. LEVENSON: Okay. What was the range?

6 DR. POLLOCK: The age range.

7 DR. LEVENSON: Yes, let me get to that.
8 Okay, here is the percentage within the four age
9 groups. The greater than 65 was a very small age
10 group and also the youngest age group is smaller.

11 DR. PINE: To clarify, that would be
12 8 percent of the 27,000 to get the numbers; is that
13 right?

14 DR. LEVENSON: Eight percent of the
15 placebo, yes, right.

16 DR. PINE: Roughly, 200 subjects.

17 Yes, Dr. Goodman.

18 DR. GOODMAN: I was glad to see that you
19 reanalyzed the pediatric data using the methodology
20 that was utilized for the adult data. Did any
21 differences emerge in the findings with the two
22 analytic approaches?

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1 DR. LEVENSON: No. There were kind of
2 several steps removed from the pediatric to the
3 adult. In the pediatric, the primary measure was
4 risk ratio, and we are using odds ratio.

5 As you move step by step, adding more of
6 the differences, it gradually moved from I think a
7 point estimate of the risk ratio which is 1.88 or
8 something to this 2.2.

9 In all cases, the intervals were above
10 one, so it wasn't very qualitatively different. I
11 think the differences were readily interpretable.

12 DR. PINE: I'm going to take a question
13 from Dr. Leon and then maybe one more question, if
14 somebody else has one.

15 DR. LEON: Do you have a slide that shows
16 the number of suicide events for the youngest age
17 groups? Were there any deaths in the youngest, 18
18 to 24?

19 DR. LEVENSON: No, I don't have a slide.
20 We might have that in the briefing pack. We might

21 be able to get to you about it when we look in the
22 briefing package.

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1 Marc, do you have any information on
2 that?

3 DR. STONE: I think we will check. In
4 terms of the completed suicides, there may have
5 been one in the 18 to 24, but most of them were not
6 in that group.

7 DR. PINE: Any other final questions?
8 Yes, Dr. Robinson.

9 DR. ROBINSON: You mentioned in the
10 presentation that some of the manufacturers did
11 their own assessments and some of them used the
12 Columbia group. Do you know sort of what was the
13 breakdown in terms of the percentage of subjects
14 that were assessed "independently" by Columbia?

15 MS. JONES: I also will need to double
16 check that, but I believe it was, roughly, four to
17 five who had the adjudications done by Columbia.
18 Dr. Kelly Posner is here and she actually could
19 give a better answer to that.

20 DR. PINE: If you could step to the
21 microphone, Dr. Posner.

22 DR. POSNER: Six or seven of the nine,

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1 and again they all used the same system. We just
2 applied it in those six or seven.

3 DR. PINE: Okay. I would like to thank
4 Dr. Jones and Dr. Levenson. Then, for the last
5 presentation, I would like to introduce
6 Dr. Marc Stone from the FDA who is going to
7 describe further analyses, looking at the
8 association between antidepressant treatment and
9 suicidality in adults, and then once again we will
10 have about 10 minutes for open discussion about
11 this first set of presentations before taking a
12 break.

13 ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:

14 MEDICAL REVIEWER EVALUATION

15 (PowerPoint presentation in progress.)

16 DR. STONE: Good morning. I think Lisa
17 and Mark did a good job of showing you the sources
18 and methods that we used in this analysis and the
19 basic findings. I'm going to add a little bit of
20 exploration and interpretation.

21 I took a slightly different approach than
22 Mark did. I wanted to include the active control

0057

1 arms because it gives us more patients to look at.
2 It also allows us to consider tricyclates and other
3 older antidepressants, which because they were not
4 the primary drug provided by the sponsors, were
5 always if they were included, they were only
6 included as active controls.

7 Also, you will get slightly different
8 estimate because I used conditional or

9 fixed-effects logistic regression, which was one of
10 the methods that Mark showed in his sensitivity
11 analysis.

12 I think we have shown that the results
13 are pretty robust no matter what method you use. I
14 used this method because it's very flexible. It
15 makes it easy to consider active controls without
16 doubling up on the number of placebo subjects,
17 which is a problem when you use something like the
18 exact method. Also, it allows you to look at
19 covariants and particularly to look at covariants
20 as continuous variables.

21 Going to studies of adults, these are the
22 similar figures including the active controls to

0058

1 what Mark just showed you. We had a lower than one
2 odds ratio for suicidal behavior ideation that
3 moves slightly over one so it's not considered
4 statistically significant.

5 If you don't consider suicidal ideation
6 and just consider suicidal behavior, you have an
7 odds ratio that is very close to one with fairly
8 narrow confidence intervals saying that there is
9 unlikely to be an overall difference between drug
10 and placebo in suicidal behavior.

11 I thought at some point we ought to at
12 least include the estimate for completed suicide
13 which you can see is higher than one but with very
14 large confidence intervals who have only got eight
15 events among a hundred thousand subjects. That
16 basically tells you that it is statistically
17 meaningless. You really can't consider it to be
18 any different than chance.

19 If you look at the grouping by
20 indications, again these are the breakdowns that we
21 made. As Mark said, we concentrated on these
22 three, the psychiatric disorders. He didn't

0059

1 explain why we were less keen on looking at these
2 additional indications. I will try to show you
3 why.

4 If you look at the number of events by
5 indication, you can see if you look at the
6 psychiatric indications, the ratio of attempts to
7 ideation is about two or three to one.

8 Ideation, the relationships between
9 ideation and suicide attempts are fairly high. If
10 you have suicidal ideation, you are at fairly high
11 risk for suicide attempts in this population.

12 However, if you look at the other groups,
13 first of all, you don't have many events. You only
14 have nineteen events, and only one of them is a
15 suicide attempt, so your ratio is eight to one or
16 eighteen to one. Suicidal ideation probably means
17 something different in these people who don't have
18 psychiatric problems.

19 If you look at the incidents, which is

20 how often these events occur, you can see again
21 that they are most common in major depression,
22 which is certainly not at all surprising. However,
0060

1 the other psychiatric disorders it is a little
2 less, roughly, half as much. It is the same order
3 of magnitude. It is not radically different.

4 On the other hand, if you look here, the
5 rates of occurrence are probably about a tenth of
6 what you see in major depression for ideation.
7 Again, we are dealing with a rather different
8 population.

9 Finally, when you look at the estimates
10 for suicidal behavior ideation, you get a pretty
11 similar result for the psychiatric disorders for
12 odds ratios. These look higher.

13 It's not statistically different because
14 you've got very few events, a relatively small
15 population. The difference here could easily be
16 due to chance, but it could easily not be.

17 The problem is that if you look at the
18 overall estimate, it is going to be driven by the
19 psychiatric disorders because there are many more
20 subjects with events. It's basically going to hide
21 what's going on in these other disorders.

22 We think it would be kind of a mistake to
0061

1 generalize outside of the psychiatric disorders
2 because we simply do not have enough events and we
3 have at least some indication that things could be
4 a little bit different outside of people without
5 psychiatric disorders.

6 Plus, of course there is a much lower
7 underlying rate of suicidality, so any effect of
8 the drug is likely to be far less in any condition,
9 whether the effect of the drug is good or ill.

10 If you look at psychiatric disorders
11 only, these are the results you get. Again, you
12 have a bit more statistical power. If you look at
13 suicidal behavior ideation, you get a P value right
14 at .5. I think if you take that out a couple of
15 decimal places, it goes a little bit over one.

16 Again, if you look at suicidal behavior
17 alone, close to one, fairly narrow confidence
18 intervals, no statistical evidence of an increase
19 in the adult population for suicidal behavior with
20 treatment with antidepressants.

21 What about drug class? Like you said, I
22 was able to include some of these older drugs by
0062

1 looking at active controls. We tried to break them
2 into some classification.

3 Things get a little noisy if you look at
4 it drug by drug, but we would hope that if there
5 were some functional differences that you would see
6 them looking at drug class.

7 We made the classification to see if

8 there were any differences, and I don't think there
9 are. Again, you get very similar results across
10 drug classes. Similarly, looking at just suicidal
11 behavior, if anything it gets closer.

12 The big issue, age. Here you can see, to
13 answer Dr. Pollock's question, this is a breakdown
14 of subjects by age and events. Sometimes it is
15 easier to look at the raw numbers. You get a
16 better idea looking at the raw numbers than you can
17 do with the fancy statistics.

18 The thing I would point out here is that
19 you've got similar numbers of subjects under 25 and
20 subjects over 65 and about 10 times as many in the
21 25 to 64 range. Similar here (pointing), and a
22 tenfold difference here.

0063

1 You can compare. In the placebo group
2 you've got similar numbers -- 21, 21, 21, 24 --
3 with a similar number of subjects. It is, roughly,
4 the same.

5 By this, by 10, maybe it is a little bit
6 lower in the middle group. If you look at drug,
7 and again divide this by 10, you've got like 64,
8 24, 12. There is a gradient going on here by age.

9 When you do the fancy statistics, that is
10 indeed what you find, that higher risk in adults
11 under age 25, a lower overall risk of behavior
12 ideation in the middle range, and then among older
13 adults it's even more reduced for suicidal ideation
14 or behavior.

15 If you plot it here, you can see the
16 differences with the confidence band. As I pointed
17 out, using conditional logistic regression, you can
18 plot age as a continuous variable. that is what
19 you see here, just to give you some sense of how
20 that gradient works graphically.

21 When you look at suicidal behavior, you
22 will get an even more dramatic result. Again,

0064

1 similar numbers tenfold, so you get like 8, 3, and
2 7, and here you get 32, 7, and 1. Thirty-two to
3 one even though you have a similar number of
4 subjects. Quite an impressive gradient.

5 With age, again when you do the
6 statistics, statistically a significant increase
7 under age 25. Right at one for 25 to 64 for
8 suicidal behavior when you don't consider ideation,
9 when you just look at behaviors. Then, very much
10 reduced in the age 65 and over class. Once again,
11 you have the same plot and the same curve.

12 If you try to think about this with the
13 pediatric studies, and this is the published
14 version of what was presented here at this
15 Committee two years in the "Archives of General
16 Psychiatry" this year.

17 Look at 24 trials, 4,500 subjects, a much
18 smaller group than what we looked at here. In

19 fact, we had about twice as many subjects in the
20 young adult range as we have in the pediatric
21 range.

22 Again, this is a translation of the risk
0065

1 ratios and the odds ratios. The reasons the risk
2 ratios are higher than you saw in the published
3 papers is because of the continuity corrections,
4 which tended to lower the results because you had
5 so many trials with zero events in at least one of
6 the arms, and that probably biased results.

7 We have recalculated them without the
8 continuing corrections, and you can see that you
9 get the range 2.22 for an odds ratio, clearly
10 statistically significant.

11 What is also interesting is without the
12 continuity correction suicidal behavior was not
13 statistically significant. However, if you take
14 the continuity correction out, you do find that you
15 have a statistically significant elevation in
16 suicidal behavior in the pediatric group.

17 If you wanted to narrow it down to the
18 SSRIs, there is a statistically significant
19 increase as well. When you compare it to what we
20 have found in the adults, and I broke the pediatric
21 group into two age ranges within the pediatric
22 studies, you get again a very interesting looking

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1 gradient.

2 You can say some of these results are too
3 small to be statistically significant, but it is
4 the gradient that is what makes things interesting.

5 Similarly, if you just look at suicidal
6 behavior, you get an even steeper gradient. The
7 SSRIs in major depression, once again a gradient,
8 perhaps again a little less steep, but certainly
9 what appears to be a definite gradient with age.

10 Once again, if you combine all the data
11 and you look at age as a continuous variable to
12 look at the gradient, you can see with both
13 behavior and ideation or behavior alone, that it is
14 a steeper gradient with behavior alone.

15 Once again, looking at all the data
16 including the pediatric studies, subjects under age
17 25, adults and children, adults 25 to 64, adults
18 over 65, the gradient here. This time I added some
19 confidence intervals for this line just to show
20 that there is a lot of uncertainty about exactly
21 where the line crosses the range of one, because it
22 is not all that clear.

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1 You should take this line as much more of
2 an impressionistic feeling rather than something
3 with great statistical precision. That is even
4 more true if you look at suicidal behavior where
5 you've got very wide odds ratios, but again, this
6 essential gradient is still quite clear.

7 If you look at the data as a whole, since
8 we think we are looking at the same phenomenon in
9 adults under age 25 as we saw in children, I think
10 it makes sense to combine all subjects under age
11 25.

12 If you look at it by indication group,
13 major depression, other psychiatric disorders both
14 have elevated significant odds ratios at around
15 two.

16 This other depression group is a much
17 smaller group. It is kind of a hodgepodge of
18 indications that we have excluded just to keep this
19 major depression pure, so we wouldn't expect to see
20 much in this group by itself. The odds ratio isn't
21 high but very, very wide confidence intervals. Of
22 course overall, a odds ratio of 1.94, and that's

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1 highly significant.

2 If you look at suicidal behavior, you see
3 something pretty similar. Again, the odds are a
4 bit higher, particularly in the other psychiatric
5 group, but wide confidence intervals. You are
6 dealing with fewer events here.

7 The other depression bops around, now
8 it's in a similar range as the other indication
9 groups, but again, very wide confidence intervals,
10 and overall a pretty clear result.

11 If you break things down by drug class,
12 again all subjects under age 25, it's pretty
13 similar maybe, maybe something a little bit higher
14 in the SNRIs, similarly if you just look at
15 suicidal behavior.

16 Now, Tom mentioned the meta-analyses
17 that were published in the "British Medical
18 Journal." What I tried to do here is to duplicate
19 their methods to the data that we have and see if
20 there were any meaningful differences.

21 The first one I looked at was the Gunnell
22 study. This was based on summary data by drug not

0069

1 by trial, which is problematic. It was given by
2 sponsors to the MHRA, the British medicines and
3 healthcare device regulatory agency.

4 It just looked at six SSRI drugs. They
5 said they had 477 trials, 52,000 subjects. It is
6 important to point out that the suicidality events
7 were not reviewed or subjected to standard
8 criteria.

9 It could easily include events that may
10 have occurred after people were taken off the drug
11 or even the trial was completed but it was still
12 reported as a subsequent adverse event.

13 Of course, whether something is called a
14 "suicide attempt" or a "completed suicide" or
15 "accidental death" was not closely perused. Here,
16 if you compare what Gunnell published with what we
17 have, it seems to have a much larger number of

18 trials but no more subjects, in fact slightly fewer
19 subjects.

20 This may be because they include a lot of
21 very small trials. They excluded trials with
22 twenty or more subjects. Also, notice that there

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1 were quite a few more events. These are completed
2 suicides reported. Because they didn't go through
3 the adjudication processes, it's not surprising
4 that you do see a good deal more events.

5 If we limit ourselves just to SSRIs
6 without fluoxetine and without the nondepression
7 indications for citalopram -- this is because the
8 data that Gunnell got for fluoxetine did not
9 separate completed suicides from suicide attempts,
10 so they decided not to analyze it.

11 What is interesting is that despite all
12 of these differences we get almost the same odds
13 ratio. Similarly, if you look at nonfatal
14 self-harm -- again more trials, fewer subjects,
15 more events reported, but again, clearly identify
16 odds ratios.

17 I think this shows that there aren't
18 significant biases out there in the reporting of
19 these events, whether you look at the events very
20 carefully and closely and are very strict about
21 what you include or if you are very liberal about
22 what you include, you seem to get very similar

0071

1 results.

2 Finally, looking at suicidal thoughts.
3 When up here (pointing, in this case, we do have
4 more events reported. This I think is because you
5 are unlikely to have suicidal thoughts reported for
6 subjects who have already finished a trial, an
7 event involving self-harm, or certainly a completed
8 suicide because it is likely to get back to the
9 sponsor and be reported as an adverse event.

10 Suicidal thoughts, you have to pretty
11 much have the patient in front of you and talk to
12 him. Here, it is interesting that we have similar
13 rates, and once again virtually identical odds
14 ratios.

15 The second study by Fergusson looked at
16 trials reported in the public domain either through
17 published papers or what was in the Cochrane
18 Registry. It used the Cochrane methodology, but
19 once again because it was based on what was
20 reported in papers, the suicidality events were not
21 reviewed or subject to standard criteria.

22 In this case, if you look at SSRIs and

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1 placebos, we have more trials because we have lots
2 of unpublished trials and Fergusson was limited to
3 published trials.

4 Their trials tended to be smaller as we
5 have about fifty percent more trials but four times

6 as many subjects. However, the thing to look at
7 that is interesting about Fergusson is that if you
8 look at the ratio of fatal to nonfatal events here
9 for SSRIs, 4 fatal events, 23 nonfatal suicide
10 attempts, if you looked at his data on SSRIs and
11 tricyclics, 5 and 29, a similar ratio, here in the
12 placebo group, 4 and 31, then you have 5 to 10
13 times as many nonfatal suicide attempts as failed
14 suicide attempts.

15 Of course, you look at our data and the
16 ratio is even higher, sixty to two, thirty-one to
17 two, zero, zero, five, seven. However, over here
18 in the controls in his study, he has three fatal
19 events and only six nonfatal events, and that is
20 pretty odd.

21 Looking at all the data that we've seen
22 before, nonfatal suicide attempts should be a lot

0073

1 more common than fatal suicide attempts. You would
2 have to suspect that maybe some events are missing
3 here.

4 Then, here looking at the comparisons of
5 SSRIs and tricyclics, you notice there are more
6 trials here because he included trials -- we only
7 included trials that also had a placebo-control arm
8 -- but he included all direct comparisons of SSRIs
9 and tricyclics. He ends up with more subjects and
10 more events.

11 If you look at the odds ratios, he does
12 have a higher odds ratio for suicide attempts, but
13 I think that is because we are missing nonfatal
14 suicide attempts in the placebo group. This is a
15 number that I would have some doubts about.

16 When we did the analysis, we came up with
17 1.31, not statistically significant. Looking at
18 SSRIs and tricyclics where we don't seem to have
19 that problem, we came up with very similar results
20 once again.

21 I think as we have said already, the
22 observed relationship between antidepressant drug

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1 treatment and the incidence of reported suicidality
2 events in clinical trials is strongly related to
3 age.

4 When suicidal behavior and ideation are
5 considered together, the risk associated with drug
6 treatment relative to placebo is elevated in
7 subjects under age 25, reduced in subjects age
8 25 to 64, and further reduced in subjects age
9 65 and older.

10 However, when we take ideation out of the
11 picture, when suicidal behavior alone is
12 considered, the risk associated with drug treatment
13 relative to placebo is elevated in subjects under
14 age 25, neutral in subjects age 25 to 64, and
15 reduced in subjects age 65 and older.

16 I think it is also important to note that

17 the observed relationship between suicidality, age,
18 and antidepressant treatment appears not only in
19 major depressive disorder but in all subjects with
20 psychiatric diagnoses.

21 I think what this implies is that there
22 is something different about the psychopharmacology
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1 of suicide, that it's different than the
2 psychopharmacology of depression, that they are two
3 separate phenomenon.

4 I think the observations are most
5 consistent with two general facts, one that
6 promotes suicidality and one that prevents it. In
7 older subjects, the preventative effect tends to
8 predominate, while in younger subjects the opposite
9 is true.

10 In a simpler explanation that denies the
11 preventative effect and assumes only a promoting
12 effect, does not explain the protective effect that
13 is seen in older subjects.

14 I also wanted to comment, briefly, on the
15 idea that what we are seeing may be due to
16 reporting effects. Could antidepressant treatment
17 simply cause more events to be reported? Could
18 treatment allow subjects, particularly younger
19 subjects, to simply become more articulate and open
20 about their thoughts and actions?

21 I think this data does not support that
22 idea very well because the drug effect appears to
0076

1 be at least as great on suicidal behavior as on
2 suicidal thoughts, both in promoting it and
3 protecting against these phenomenon.

4 Suicidal behavior is potentially directly
5 observable. A lot of suicide attempts end up in
6 the hospital and seeking other kinds of medical
7 attention.

8 For a reporting effect to credibly
9 explain the results, drug treatment must have a
10 substantially greater effect on reporting of
11 suicidal behavior than on the reporting of suicidal
12 thoughts.

13 That seems a little odd, that if you are
14 going to make people more open in reporting these
15 things, why would you be more talking about
16 behavior and not talking about suicidal thoughts?

17 Either that or almost all of the suicidal
18 behavior that we have seen here with self-reported
19 rather than observed by others, that there were
20 very suicide attempts that were so dramatic that it
21 resulted in people being found, ending up in the
22 hospital, or otherwise being known by other people.
0077

1 Then, you also have to say that the
2 reporting effects must be strongly age-related so
3 that this increased articulation is not just
4 something you would see in kids or young people,

5 but that middle-aged people have more trouble
6 reporting than older people. I think that would
7 take a lot of very ingenious explanation.
8 Finally, I think for further
9 investigation that there may be some differences
10 between drugs and drug classes, and that is
11 discussed in the review document. It could well be
12 a chance finding. I don't think it's anything to
13 get excited out.

14 However, it would be interesting to
15 confirm them, and if you could confirm them, to
16 look for an explanation because that might lead to
17 some indication as to why we're seeing this
18 age-related phenomenon, what it is about
19 antidepressants drugs that can promote or prevent
20 suicidality.

21 DR. PINE: Okay. Thank you, Dr. Stone.
22 I would actually like to thank all of the

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1 speakers for really keeping directly within our
2 time limits and for giving us the most pertinent
3 facts that we can really think about throughout the
4 rest of the day.

5 I also want to thank the panel for
6 withholding all but the most important questions.
7 We are left with about twenty minutes or fifteen
8 minutes to discuss these issues, so I would like
9 everybody to think about their questions. Cicely
10 has a quick announcement before we open it up for
11 questions.

12 DR. REESE: I would just like to make a
13 last call for the open public hearing sign-in. If
14 there is anyone in the audience who has not yet
15 signed in who preregistered, please step outside
16 the room and sign in.

17 Thank you.

18 DR. PINE: I will open it up now for any
19 questions.

20 Yes, Dr. Leon.

21 QUESTIONS

22 DR. LEON: When we evaluate the safety

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1 data, the risk benefit ration really provides
2 valuable information as we saw in the pediatric
3 data. I mean, that was really very revealing.

4 I saw in the briefing document that
5 overall the pooled response rates were about
6 50 percent for active and maybe 40 percent for
7 placebo. I saw that in one of the documents.

8 Can you tell me out of the three hundred
9 or so trials, the psychiatric indication trials,
10 how many of those were positive trials?

11 DR. STONE: No. We didn't break that down by
12 trials. We didn't sit down and say "Look at each
13 trial. Which one is statistically significant?"

14 Again, this was a response variable that
15 was just reported by the sponsor. We didn't

16 validate them. We assume that's what they
17 considered a response for their NDA submission, but
18 that wasn't necessarily the case. We didn't audit
19 that. We just wanted a general kind of qualitative
20 sense of what was going on.

21 So, no, but I think a 50 percent response
22 rate versus a 40 percent response rate implies that

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1 there are a fairly large number of negative trials.

2 DR. LAUGHREN: Marc, we did look by age
3 strata as well. Did you prepare a slide for that
4 or--?

5 DR. STONE: No.

6 DR. LAUGHREN: You didn't. Can you just
7 say what the results are?

8 DR. STONE: Yes. To summarize that, if
9 you look at response by age, the odds ratio for
10 response for the middle age range, 25 to 65, was
11 about 1.5, and it's slightly lower at the other two
12 ends. You've got about a 1.3 or so.

13 DR. LAUGHREN: Actually, for less than 25
14 the odds ratio, this is looking at whatever
15 response measure the sponsor used, is 1.54 and the
16 confidence interval is 1.34 to 1.76, so
17 statistically significant. For 25 to 64, it is
18 1.84 with a confidence intervals of 1.77 to 1.93.
19 For over 65, it is 1.39 with a confidence interval,
20 again statistically significant, 1.24 to 1.57.

21 DR. PINE: Just so everybody is clear on
22 this last point, because numbers got thrown around

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1 fairly quickly, I think this is a very important
2 point. Dr. Leon raised the issue that one of the
3 issues that was very important in the pediatric
4 trials was not only that there was a clear signal,
5 as we said, in terms of the association between
6 active treatment and suicidal thoughts or behavior,
7 but there was also a lot of questions about the
8 degree to which efficacy had been demonstrated.

9 I think most people felt that efficacy
10 had not been demonstrated. What we just heard,
11 very quickly, and you will correct me if I'm wrong,
12 is that to the extent that we have the data and
13 that we have analyzed it, there is evidence of
14 efficacy in all the age groups that were examined
15 here from a statistical, if not a clinical
16 significance standpoint?

17 DR. LAUGHREN: Given the very limited
18 glimpse we have of efficacy, again this is just one
19 fairly crude measure, but it does suggest that
20 across all of these different age spectra you do
21 see evidence of efficacy.

22 DR. PINE: Dr. Goodman?

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1 DR. GOODMAN: I want to stay with this
2 point to make sure I understand. It sounds like
3 there is a gradient, though, in terms of efficacy,

4 at least to the degree that there is less efficacy
5 in the very young population. The oldest
6 population you said there is less efficacy. It's
7 not a straight line. I understand that.

8 How much could the lack of efficacy
9 explain the signal we're seeing in the under 25
10 range? I think I know the answer. This is a very
11 important point like Dr. Pine said, and I want to
12 make sure it's been clarified.

13 DR. STONE: Well, I think, getting into
14 some of the discussion, because we looked at
15 responders versus nonresponders and the suicidality
16 rates going on there.

17 If you look at the under 25, and I just
18 want to be very clear that this efficacy data is
19 just for the adults, because we don't have any of
20 the efficacy data for the pediatric study.
21 However, if you look at the number of suicidality
22 events among responders and nonresponders, the

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1 ratio is similar whether it is placebo or drug.

2 Where you see the difference is in the
3 people that don't have events. There is a shift in
4 the population so that what the drugs appear to do
5 in the under 25 population is take people that are
6 not suicide prone and turn them into responders.

7 There is less suggestion of an effect of
8 a reduction in suicidality or an increase in
9 suicidality as being affected by the drug. For
10 example, if suicidality were truly associated with
11 response, you might see five times as many events
12 in the responders as in the nonresponders for
13 people on drugs and a much lower ratio, maybe two
14 to one, in the placebo group.

15 You don't see that. What you see is the
16 ratio shift. I have a copy of the review right
17 here? Yes. I think the way they described it,
18 specific words, you are separating subjects who
19 have an inherently lower propensity for suicidal
20 behavior from those with proclivities by the
21 treatment effect, by treatment response.

22 DR. PINE: I am going to summarize this

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1 and then I'm going to ask Dr. Temple to comment and
2 then maybe we will move on to other issues and come
3 back to this.

4 My take on the question of efficacy is
5 that to the extent that there is evidence of
6 variability and efficacy in the adult data, it does
7 not follow the pattern for the suicidal thoughts
8 and ideation.

9 In other words, there we saw very clear
10 linear decrease or a linear decrease in terms of
11 the efficacy data, if we make anything of it, there
12 is an inverted use.

13 Dr. Temple.

14 DR. TEMPLE: The results you have just

15 been talking about here are pooled over this vast
16 number of people. I have no idea if you did that
17 for the pediatric populations, you would probably
18 see a favorable result, too, that's really
19 different.

20 It is also worth remembering that over
21 the years, and very consistently, half of all
22 reasonably sized adult depression studies failed to
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1 show a statistically significant difference.

2 There is a big difference between pooling
3 the massive results and showing even modest benefit
4 in that and the individual trial-by-trial results.

5 The other observation I just wanted to
6 make -- I know everybody knows this, too -- that we
7 are talking about treatment of acute depression,
8 which has a very high failure rate in every age
9 group we have looked at, obviously worse in the
10 youngest people.

11 That is in contrast with maintenance
12 studies, which very infrequently fail and which in
13 some sense may have more to do with outcome than
14 when you are looking at the overall effect in the
15 community of what happens. It seems worth just
16 making that distinction.

17 DR. PINE: I actually want to call
18 attention to that point. Because I've been here at
19 maybe four meetings with you, and you have made
20 that point at every single meeting.

21 DR. TEMPLE: Oh.

22 DR. PINE: No, it's good because I don't
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1 think the point has been realized by the fact that
2 you keep making it but other people don't make it.

3 Namely, the point is that the efficacy
4 data in the studies of adult depression that the
5 FDA have reviewed are much stronger, the efficacy
6 data are much stronger, in the discontinuation
7 designs than in the acute parallel group randomized
8 control designs. That again is a point that I have
9 heard you make, and I think it is important that
10 other people acknowledge it and hear it.

11 DR. TEMPLE: Of course, you can't, or at
12 least we don't think you can, do very long-term
13 comparisons of treatment and no treatment in people
14 who are recurrent depression. Most people wouldn't
15 let you leave them untreated, so it is very hard to
16 get the answer you really want.

17 DR. PINE: Dr. Goodman.

18 DR. GOODMAN: I had a question about the
19 other behavioral category. I understand the
20 limitations of that data set and that you are
21 starting with a small denominator and you don't
22 have that many events. That said, did you examine
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1 the relationship by age in the same fashion, and
2 was there any pattern in terms of the so-called

3 "suicidality signal" and the behavioral conditions
4 by age?

5 DR. STONE: I don't think so because it
6 was so small. On the other hand, if we had the
7 data with us, we could probably run it during the
8 break.

9 DR. GOODMAN: The reason I ask it is
10 because it helps us in terms of conceptualizing the
11 mechanism that might be behind this phenomenon.
12 When we first examined this, I think some of us
13 were surprised in the pediatric population that it
14 wasn't confined to depression.

15 If it is confined to psychiatric
16 disorders but does not occur in other behavioral
17 disorders, that tells us something different in
18 terms of its mechanism of action in terms of trying
19 to conceptualize the adverse event.

20 DR. STONE: Well, I would point out that
21 the point estimates for the odds ratios are higher.
22 They are about 1.5 for the entire adult population.

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1 Any estimate you are going to get is likely to be
2 elevated, again, with wide confidence intervals.

3 If you've got 6 with under 25 and 2 at 25
4 to 64 and one at 65 and older, I'm not sure that
5 one would be any more convincing than what we have
6 now.

7 However, at least because we are seeing
8 that higher rate, there is a kernel of a suggestion
9 in the data, but I don't think we can take it any
10 farther than that.

11 DR. PINE: Dr. Laughren.

12 DR. LAUGHREN: Just a point, there are a
13 total of 19 events for the other behavior
14 disorders. It is hard to know what you are going
15 to be able to do with that.

16 DR. PINE: Ms. Bronstein.

17 MS. BRONSTEIN: Yes. My question is a
18 very basic question about design and research.
19 When we heard public testimony about the pediatric
20 population, we heard a lot about activation
21 syndrome or whatever you want to call it.

22 As I looked at what was included and what

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1 was excluded, this is what I'm wondering whether I
2 interpreted it correctly. All patients coming off
3 the drug were excluded after one day; is that
4 correct?

5 We don't have any notion of what happens
6 to folks out a little bit if there was some kind of
7 activation syndrome? Am I interpreting that
8 correctly?

9 DR. STONE: Yes. The phenomenon we
10 decided to focus on was what happens to people when
11 they are on the drug or shortly after they stop the
12 drug. If you look at some of the other studies,
13 for example, those meta-analyses, they did not make

14 those kind of exclusions, and we got very similar
15 results.

16 The one thing we did do as kind of a kind
17 of quality control was we asked the sponsors to
18 supply us with information on all deaths that
19 occurred on subjects within 90 days of the intended
20 end of the treatment period.

21 We knew that it would be tricky to try to
22 adjudicate anything that was less clear than a

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1 death and trying to say whether that was a suicide
2 or something else was also probably tricky, so we
3 just asked them to collect deaths.
4 There were relatively few. We ended up with
5 nothing we could interpret, but it didn't seem like
6 there was any great disparity.

7 DR. PINE: I actually have a question
8 about this, and then maybe Dr. Laughren can
9 respond. My recollection, but it might be flawed
10 about the same issue that Ms. Bronstein is bringing
11 up, is when we first started to look at the data in
12 pediatrics, there was some concern that we might
13 miss a signal if we only focused on the data within
14 the trial, and therefore there was great interest
15 in also looking after the trial.

16 I think, again the way I remember the
17 events, we were all somewhat surprised to see the
18 signal. I wondered the degree to which that really
19 shaped your thoughts about not looking in as much
20 depth in the week after the trial?

21 DR. LAUGHREN: The reason we chose to
22 focus only on what's happening during the

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1 double-blind trial plus one day is that was the
2 only part of these trials that we could be
3 confident about. If you look across these trials,
4 there is enormous variability in what happens to
5 patients after the nominal endpoint of the trial.

6 In some cases, patients are tapered and
7 then slowly withdrawn; in some cases, it's cold
8 turkey; and, in some cases, they go to another
9 drug. It is so variable that we just didn't have
10 confidence.

11 The question is a very reasonable one.
12 If what you are asking is, is withdrawal a
13 potential stimulant for increased suicidality, it
14 is a very reasonable question. We don't have the
15 answer to that based on this data. It is something
16 that should be looked at, but it is a separate
17 question.

18 DR. TEMPLE: I mean, the focus here is on
19 what Tom presented initially, the idea that
20 relieving depression enables you or something like
21 that. That is determined from the period while you
22 are on the drug. The withdrawal question is a very

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1 interesting one, but, for reasons Tom said, hard to

2 get at when you don't have a controlled setting.
3 DR. PINE: Dr. Armenteros.
4 DR. ARMENTEROS: Yes, I understand this
5 is a large data set. Do we have an idea as to how
6 frequently were older medications being used
7 concomitantly, for example, benzodiazepines or
8 things of that sort that may perhaps modulate a
9 little bit what is going on?

10 DR. STONE: No, we didn't ask for that to
11 be reported. It would just make the database too
12 large and to unwieldy.

13 DR. PINE: Dr. Slattery?

14 DR. SLATTERY: I am wondering if there
15 were differences in severity of illness, you
16 implied that you had looked at both inpatient and
17 outpatient treatment studies, and whether the
18 numbers of inpatient versus outpatient studies
19 differed significantly between the different age
20 groups and whether that had any impact on outcome?

21 DR. LEVENSON: The only thing I have to
22 say to address that is we didn't see a difference

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1 in the inpatient versus the outpatient setting and
2 only a small minority of the trials were inpatient,
3 so there is not a lot of information there.

4 DR. PINE: We are going to take three
5 more questions before the break. Again, there will
6 be a lot of other time for discussion. We are
7 going to take in this order a question from
8 Dr. Mehta, a question from Dr. Leon, then a
9 question from Dr. Goodman, and then we will take a
10 break.

11 Dr. Mehta.

12 DR. MEHTA: I have a question one of the
13 Marks. Were you able to look at the data in terms
14 of suicidality during the first three weeks of
15 study compared to the remaining seven or eight
16 weeks of average treatment? Because most of the
17 time efficacy of an antidepressant doesn't kick
18 until about three weeks.

19 DR. LEVENSON: We had some information
20 there, but, no, at this point we haven't looked at
21 it.

22 DR. PINE: Dr. Leon.

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1 DR. LEON: The briefing document mentions
2 the problem of ascertainment bias in this, I mean,
3 in these post hoc analyses of the large data set.
4 There was a varying degree of scrutiny of a
5 collection of the data across the trials.

6 I wonder, though, if you did analyses of
7 the Ham-D suicide item that was used in the
8 pediatric analysis and that might be more
9 systematically collected across the trials?

10 DR. STONE: We asked for it. It was
11 reported in various differing ways, some different
12 subscales, different groups. I tried to look at

13 it. It didn't seem to show us anything.

14 DR. PINE: That was the conclusion from
15 the pediatric studies as well, that it really
16 didn't reveal anything in the face of positive
17 events.

18 Okay. With that, I would actually like
19 to once again thank the speakers and thank the
20 Committee. I think, knock on wood, hoping not to
21 jinx us, we are off to a very good start.

22 We are going to take a fifteen-minute
0095

1 break, and we are going to start promptly at
2 10 o'clock. Thank you again. We will see you in
3 fifteen minutes.

4 (Recess taken.)

5 OPEN PUBLIC HEARING

6 DR. PINE: We are going to begin the
7 public hearing. If I could ask everybody to either
8 move outside, if you would like to continue your
9 conversations or take your seat if you would like
10 to be here for the public hearing.

11 I just also want to warn everybody that
12 we are going to be going without a break from now
13 until 1:30, and we are only going to have a half an
14 hour break for lunch. For the next three and a
15 half hours, there will not be any breaks.

16 For this section, again, if I could ask
17 people standing to please either find a seat or
18 move into the hall for their conversations. For
19 this section of the meeting what we are going to do
20 is we are going to devote considerable time for
21 public testimony. I have to say that from the past
22 meetings, this has been one of the most powerful

0096
1 parts of the meeting.

2 We always face a great conflict in terms
3 of trying to balance issues of being fair to
4 everybody who has very important things to say on
5 the one hand, but on the other hand limiting this
6 section of the program to the point where it is
7 weighed appropriately, given our desire to balance
8 issues of science and issues of public health
9 concern.

10 Due to those issues, the way that we are
11 going to proceed is that each speaker will have
12 three minutes when they come to the podium. You
13 can see that there is a podium in the middle of our
14 table. We have a timer who is the official keeper
15 of the three minutes.

16 Igor, if you can, raise your hand.

17 (Igor complies.)

18 DR. PINE: As you can see, when you are a
19 speaker, Igor is the official keeper of your time.
20 When you get to the podium, your time will begin.
21 You will have a 30-second warning that will appear
22 on the podium when the light turns yellow, and then

0097

1 when that 30-second period is up, the microphone
2 will go off.

3 Now, in the past when we have done this,
4 people have shown very sincere courtesy to the
5 other speakers in keeping their comments to the
6 three minutes.

7 I would just ask again, so that everybody
8 has a fair chance to speak to the Committee, if
9 everybody would do that in this instance as well.

10 In terms of the first speaker, the first
11 speaker is Kim Porto.

12 MS. PORTO: I am a little vertically
13 challenged here. Good morning ladies and
14 gentlemen. My name is Kimberly Porto. I have
15 asked my parents Barbara Bedina and Raymond Bedina,
16 and my sister Cara Bedina behind me to join me here
17 at the podium.

18 On October 9, 2003, my brother Raymond E.
19 Bedina died of Lexapro®-induced suicide after
20 taking Lexapro for only nine days. Ray was just 32
21 years old when he passed.

22 Those who knew Ray remember his loving,

0098

1 giving personality, his great sense of humor, his
2 warm smile that would take you in and hug you, and
3 his insistence that his friends and his family were
4 more important than anything else.

5 Ray was the kind of brother, son, and
6 friend you felt lucky and proud to have. He was
7 successful at everything he tried. He excelled at
8 his career and he excelled at life.

9 Ray was prescribed Lexapro by his primary
10 care physician for fatigue associated with anxiety.
11 He had no history of depression or any other mental
12 illness.

13 At the time he was prescribed Lexapro Ray
14 was feeling stressed about work, but only because
15 the current demands of his job were not allowing
16 him to spend as much time with his family and
17 friends as he would like.

18 He was becoming concerned that he hadn't
19 had the opportunity to settle down and start a
20 family as many of his close friends had at that
21 point in time.

22 Within a couple of days of starting

0099

1 Lexapro, Ray began to experience very unpleasant
2 side-effects. When his coworkers and friends
3 noticed that he was not himself and not feeling
4 well and asked him what was wrong, he told them
5 that he had recently began taking a new medication
6 called Lexapro and that he felt that it was making
7 him feel ill.

8 Within five days on Lexapro, I noticed my
9 brother pacing back and forth through my house,
10 uneasy, agitated, and anxious. His hands were
11 shaking. We knew something was wrong. Only in

12 retrospect do we now understand that what he was
13 experiencing was an adverse reaction to the drug
14 Lexapro.

15 The next day Ray told a friend that he
16 thought the Lexapro was making him feel weird, and
17 he had very strange thoughts running through his
18 mind.

19 Within seven days of taking Lexapro, Ray
20 was thinking about suicide. He expressed thoughts
21 about hurting himself. Two days later, he went to
22 a hotel alone. He never said goodbye to anyone.

0100

1 My sweet, loving brother who had always
2 sought peace and expressed strong views against
3 suicide and violence ended his life by cutting
4 himself with a knife and poisoning himself with
5 pills.

6 Ray died alone. I am sure that he was
7 also very scared and very sick. My brother never
8 should have suffered and died that way.

9 Over the past fifteen years, too many
10 tragedies like this have destroyed too many lives.
11 Too many families, like ours, are broken and
12 struggling every day with the pain and anguish of
13 losing a loved one in this horrific manner.

14 My brother and his doctor deserved to
15 know the truth about the suicide risk associated
16 with Lexapro. Had Ray and his doctor been warned
17 that Lexapro can cause the emergency of akathisia
18 and suicide, Ray would be here with us today, and
19 my family wouldn't have paid the ultimate price for
20 your failure to warn.

21 The American people have a right to know
22 that SSRIs can cause suicide, and that holds true

0101

1 regardless of whether you are age 5 or 75. We have
2 a right to make informed decisions.

3 DR. PINE: Thank you.

4 Before we have the next speaker, I would
5 like to read the following from the FDA.

6 "Both the Food and Drug Administration,
7 the `FDA,' and the public believe in a transparent
8 process for information gathering and decision
9 making.

10 "To ensure such transparency at this open
11 public hearing session of the Advisory Committee,
12 the FDA believes it is important to understand the
13 context of an individual's presentation.

14 "For this reason, the FDA encourages you,
15 the open public hearing speaker, at the beginning
16 of your written or oral statement to advise the
17 Committee of any financial relationship that you
18 may have with any company or any group that is
19 likely to be impacted by the topic of this meeting.

20 "For example, the financial information
21 may include a company's or a group's payment of
22 your travel, lodging, or other expenses in

0102

1 connection with your attendance at this meeting.
2 Likewise, the FDA encourages you at the beginning
3 of your statement to advise the Committee if you do
4 not have any such financial relationships.

5 "If you choose not to address this issue
6 of financial relationships at the beginning of your
7 statement, it will not preclude you from speaking."

8 For the next speaker, Mr. Chris Coffin.

9 MR. COFFIN: Good morning. My name is
10 Chris Coffin. I am with Pendley, Baudin & Coffin,
11 in Plaquemine, Louisiana. I am an attorney, and I
12 am also a registered nurse.

13 As an attorney, I am here on behalf of my
14 clients and other people, like those you will hear
15 from today, who have suffered a tremendous loss of
16 loved ones because of antidepressant-induced
17 suicide.

18 As a nurse, I am here on behalf of all
19 healthcare providers who truly have their patients'
20 best interests at heart like some of you, I'm sure,
21 on this panel.

22 A couple of issues that I would like to

0103

1 cover: number one, I hope that you all recognize
2 the major importance of the decisions that you are
3 being asked to make regarding labeling and warnings
4 with antidepressant drugs.

5 They truly are life-and-death decisions.
6 You are going to hear much testimony about those
7 issues today. I hope you pay very close attention
8 to the testimony that will be given.

9 You should know that the data that you
10 have been provided by the pharmaceutical
11 manufacturers doesn't tell the whole story. I
12 think we have recognized that in some of the early
13 discussions. Dr. Leon specifically asked about the
14 risk/benefit analysis, and what do we know about
15 efficacy in these trials.

16 There is a lot more information that the
17 FDA has not been provided. Fortunately, there is
18 an avenue in the United States for individuals to
19 get this information, often through litigation.

20 I would encourage you all to use your
21 powers of subpoena to go and get additional
22 information from the pharmaceutical companies so

0104

1 some of the questions such as the one that Dr. Leon
2 asked earlier can be answered.

3 The issues surrounding antidepressants
4 and suicide have obviously been looked at for many
5 years dating back to the late eighties and early
6 nineties. As many of you might know, the PDAC in
7 1991 looked at these issues and decided to take no
8 action.

9 Other countries in the world have taken
10 action and have moved much quicker than the

11 United States. Fortunately, the PDAC in 2004 did
12 decide to take some large steps and add black box
13 warnings for children. Unfortunately, the same has
14 not yet happened for adults.

15 I would like to see that this Committee
16 takes this very seriously, looks further into the
17 information, and considers the number of lives that
18 can be saved by adding black box warnings for all
19 age groups, from children up until the elderly.

20 Let's learn from our history. Don't let
21 time pass, and don't let more lives be lost. Make
22 a serious inquiry into the data that is available

0105

1 that the pharmaceutical companies have. Lastly,
2 with that data, make sure we educate our healthcare
3 providers. They definitely need it.

4 Thank you.

5 DR. PINE: Thank you.

6 Our next speaker is Ms. Ellen Hanson.

7 MS. HANSON: Hi. My name is Ellen Hanson
8 and I am also a registered nurse, a mother of five
9 children, and at the age of 42 I became a widow.
10 My husband was 43.

11 First of all, I want to point out that
12 statistics and studies will never reflect the true
13 number of people directly affected by SSRI
14 suicidality in real life.

15 There are friends and coworkers, mothers
16 and fathers, husbands and wives, brothers and
17 sisters, and children whose lives are permanently
18 and irrevocably damaged and changed.

19 My husband, Scott Hanson, died on May 10,
20 2004. His daughter Tiffany was 18 years old; our
21 son Scott was 4; and our triplets, Kathleen, Sean
22 and Heather were 18 months old.

0106

1 Our son has neuroblastoma, cancer of the
2 sympathetic nervous system. On May 10 at
3 6:00 a.m., my husband, a union carpenter, got up
4 for work, put on his clothes and work boots, and
5 even had hardware in his pockets for work. He
6 kissed me good morning. I never saw my husband
7 again alive.

8 Scott was prescribed Paxil® because he
9 was having difficulty adjusting to our having
10 triplets. He had no history of being suicidal.
11 His Paxil dosage had been doubled about three weeks
12 before his death.

13 While on Paxil, I had noticed that he
14 would become easily agitated. After a night of
15 insomnia, he would be lethargic during the day. He
16 had terrible night sweats, which he was told was
17 due to the Paxil. No one ever said anything about
18 the risk of suicidality.

19 Prior to my husband's death, we went to
20 his company's annual party and participated in a
21 Walk for Pediatric Cancer. The day before his

22 death was Mother's Day. There was no hint that he
0107

1 would become suicidal.

2 After Scott left the room that morning on
3 May 10, I assumed he had gone to work. When I got
4 up later in the day, I noticed his car in the
5 driveway. I looked around and couldn't find him.
6 Meanwhile, I had to take care of the children.

7 I called his work and he wasn't there. I
8 had my sister and friend come over to help me with
9 the kids so I could look for Scott. I drove to the
10 beach to see if by some chance he had gone
11 fishing.

12 I didn't find him. I began to worry that
13 he might have had a heart attack or a stroke or
14 fallen in the woods or in the pond or our property.

15 I looked further and further on our land
16 and eventually I found my husband hanging from a
17 tree. I had to reach out and touch his hand to see
18 if this was even real.

19 I cut him down with a rope and I cut the
20 rope off his neck. I held him in my arms until the
21 police came. I didn't want them to take him away.

22 He was my husband and my best friend. He
0108

1 could always make me laugh. He was a son, a
2 brother, and an uncle. Most importantly, he was
3 Tiffany's daddy and to my four small children he
4 was papa.

5 I felt strongly that what happened to
6 Scott was related to his taking Paxil. It was
7 completely impulsive and bizarre. I know he didn't
8 want to be dead. Even two years later, I feel like
9 his death was an accident, a medical accident.

10 I didn't know that Paxil could cause
11 someone to become suicidal until the policemen who
12 arrived on the scene said, "Oh, no, not another
13 one" when I told them that he was taking Paxil. I
14 was not informed. It is a vitally important issue.

15 DR. PINE: Thank you.

16 The next speaker is Ms. Julie Totten.

17 MS. TOTTEN: My name is Julie Totten, and
18 I am the president and founder of Families for
19 Depression Awareness. We are a national nonprofit
20 organization that helps families recognize and cope
21 with depressive disorders. I would like to make
22 three points.

0109

1 First, untreated or poorly treated
2 depression leads to suicide as it has in my family.
3 People do need medical treatment, and they may need
4 antidepressants.

5 Second, family members like me need to be
6 actively involved in diagnosing, helping diagnose,
7 and monitor treatment.

8 Third, monitoring treatment is really the
9 issue here. Tools like our "Depression Wellness

10 Guide," which we have tested and developed for the
11 past two years in response to the first FDA
12 advisory need to be made available to people to
13 help them monitor their treatment.

14 I lost my brother, Mark, to suicide
15 sixteen years ago and he was never diagnosed. He
16 was extremely depressed. He exercised, ate right,
17 even meditated. He needed medical treatment, and
18 he never got it.

19 After my brother died, I helped my father
20 get diagnosed with depression and he has done well
21 on antidepressants. I experienced the terrible
22 tragedy of suicide with my brother with no

0110

1 treatment, and then I have witnessed success with
2 my father.

3 My story shows how important family
4 members like myself who don't have depression but
5 can help get their loved ones diagnosed and treated
6 are.

7 After the FDA put out the first advisory
8 in 2004 to monitor treatment, we at Families for
9 Depression Awareness very enthusiastically agreed
10 with you.

11 But, when we looked around, we didn't
12 find any tools to help families monitor their
13 depression treatment. We found little help, so we
14 developed this "Depression Wellness Guide."

15 We tested the guide with hundreds of
16 families across the country and it helped them
17 monitor, and it helped them monitor their treatment
18 and get well.

19 As one participant said, "I was blown
20 away by the positive effect of the guide. It made
21 all the difference in my recovery, and I was able
22 to recognize certain feelings and trigger points

0111

1 when I could barely see a ray of hope."

2 The question is, What do families do
3 right now when you tell them they have to monitor
4 treatment? It's usually nothing because they don't
5 have any tools. It is like giving them a
6 destination with no map to get there. Please tell
7 people in your advisory where to go for helpful
8 resources to monitor their treatment like "The
9 Wellness Guide."

10 In summary, please consider that
11 depression is a treatable medical condition and
12 medications do help as I have seen, like other
13 families, with my own eyes. Get family members
14 like myself involved so they can help when people
15 are depressed and not functioning well.

16 Let the public know that monitoring is
17 really the issue and give them links to resources
18 like our "Wellness Guide" so they can know what to
19 do.

20 Thank you.

21 DR. PINE: Thank you.
22 The next speaker is Ms. Suzanne Gonzalez.

0112

1 MS. GONZALEZ: Good morning. I would
2 rather be anywhere than here. There is supposed to
3 be a picture of my husband up there with my son.
4 My husband was 40 years old. We tried
5 for 10 years for another child. This (indicating)
6 is my daughter Elaina. Four pills into Paxil, he
7 woke up, within an hour he shot himself in the
8 head. He did this less than 10 feet from where my
9 son was sleeping.

10 If I would have done our usual routine,
11 this little boy would have found his father facing
12 ours with a bullet wound to his head.

13 You people have known about this for
14 15 years or more. I hold you all responsible for
15 his death, and I always will. I wasn't prepared
16 for this speech. I wasn't prepared for his
17 suicide.

18 I just keep asking myself, or I did in
19 the beginning, what was my husband thinking? I
20 hear these stories of people just taking the pills
21 and going crazy.

22 How crazy did you make him that morning

0113

1 that he would get up, not think, and do this to
2 himself? You have ruined my life, my daughter's
3 life, my son's life. How in the hell do I tell a
4 kid that his father committed suicide?

5 How dare him. The bullet was a .357. It
6 could have ricocheted and done something to this
7 boy. Worst yet, my husband could have killed us.
8 She (pointing) wasn't home. What if she would have
9 come home and found all of us dead?

10 There are so many stories out there. I
11 read about this stuff every damn day and cannot
12 believe that you people sit on this and do
13 nothing.

14 You have made everybody a wreck. These
15 people have to come here before Christmas. They've
16 got kids. They've got families. Ho, ho, ho, to
17 you.

18 (Applause.)

19 MS. GONZALEZ: I don't know. I wake up
20 every morning and I say to myself, "Oh, my God,
21 he's dead. He is fricking dead."

22 Do you wake up and think, "How many

0114

1 people are going to die today because I'm not doing
2 nothing?"

3 You're not doing nothing. I was worried
4 about coming here. Who in the hell are you? Who
5 are the pharmacy people? It may appear like I'm
6 upset and I'm not conducting myself in a proper
7 way. I don't give a damn.

8 I used to be a hell of a nice person. I

9 used to be outgoing, friendly. I took care of my
10 family. And this has to happen to us? This is not
11 fair.

12 DR. PINE: Thank you.

13 MS. GONZALEZ: Yeah. Thank you for
14 nothing.

15 (Applause.)

16 DR. PINE: The next speaker is Dr. John
17 Mann.

18 DR. MANN: Good morning. My name is John
19 Mann and I am professor of psychiatry at Columbia
20 University and director of research at the New York
21 State Psychiatric Institute. I am here
22 representing the American Foundation for Suicide

0115
1 Prevention as its immediate past president.

2 The Foundation's members include leading
3 experts on prevention of suicide and thousands who
4 have struggled through the horrors of losing a
5 family member to suicide and are committed to the
6 prevention of suicide.

7 The majority of suicides in the
8 United States are the lonely outcome of untreated
9 depression. Suicide prevention studies in Sweden,
10 Japan, Germany, and one conducted by the Foundation
11 in Hungary have shown that improving the skills of
12 doctors in terms of diagnosis of depression and
13 more use of antidepressants results in major
14 declines in suicide rates.

15 These positive results likely explain why
16 the regions of the United States that have the
17 highest prescription rates for SSRI antidepressants
18 have the lowest suicide rates at all ages including
19 children and young adolescents.

20 Based on the relationship between
21 antidepressant prescription rates and suicide rates
22 in the U.S., Dr. Robert Gibbs and I have estimated

0116
1 that the black box warning introduced by the FDA in
2 early 2004, which caused a decline in prescription
3 rates in children and adolescents of about 22
4 percent, would result in over 200 more suicides in
5 those under 19 years of age.

6 There has, indeed, been such a decrease
7 in antidepressant prescriptions and such an
8 increase in suicides in this age group. In 2004,
9 we now know that there were 115 more suicides in
10 15- to 19-year-olds and 213 more suicides in 20- to
11 24-year-olds.

12 Introducing the black box warning in 2004
13 has led directly, in our opinion, to this decline
14 in antidepressant prescription rates in young
15 people and the increase in suicide rates.

16 The decline in prescription rates has
17 continued in 2005 and 2006, almost certainly
18 resulting in even more of an increase in youth and
19 young adult suicides.

20 I recommend that the Committee reverse
21 its previous recommendation of a black box warning
22 and instead have text reminding doctors of the need
0117

1 for careful monitoring of depressed, suicidal
2 patients on antidepressants. We can more good by
3 encouraging treatment for all depressed children
4 and adults.

5 DR. PINE: Thank you.

6 The next speaker is Allen Jones.

7 MR. JONES: Hi. My name is Allen Jones.
8 Unlike the prior speaking, I will announce my drug
9 company connections. I have none.

10 I wish I weren't here today. I wish I
11 could be at home going about my business confident
12 that the FDA would do its job for the American
13 people. I don't have any such belief.

14 Few Americans today believe the FDA can
15 be trusted to do its job. Conflict of interest is
16 no longer the FDA's dirty, little secret.
17 Conflicts of interest have been widely reported.
18 They are well known.

19 Conflicts of interest have tarnished the
20 image of the FDA and, more importantly, have
21 damaged the FDA's willingness and ability to place
22 public safety interests ahead of drug industry
0118

1 profit. Conflicts of interest have resulted in
2 many of the tragedies you are hearing about today.

3 Conflict of interest is no longer an FDA
4 secret, but there are still mysteries at the FDA
5 like why are these conflicts allowed to continue
6 Why is the FDA still seating advisory panels
7 comprised largely of people with financial ties to
8 the drug industry?

9 Why hasn't the FDA not even disclosed the
10 names of the drug companies these panel members
11 work for? And why, for heaven's sake, in all of
12 American can't we find a consumer representative
13 who doesn't own stock in two drug companies?

14 (Applause.)

15 MR. JONES: Does the FDA serve the drug
16 industry or the American people? This panel will
17 answer that question today. The ironclad political
18 protection of the drug industry is beginning to
19 crumble.

20 The American public is becoming informed
21 and outraged regarding the negative influence that
22 drug industry marketing and mistakes have had on
0119

1 our health and economy.

2 The American people and our
3 representatives are beginning to act. Doctors,
4 pharmacists, and researchers are beginning to be
5 held accountable for their misdeeds.

6 Courageous states' attorneys general,
7 federal prosecutors, and plaintiffs' attorneys are

8 honing in on the devastation that drug industry
9 money has wrought on the government entities,
10 employees, and institutions that are supposed to
11 protect us. They are learning the role that
12 conflict of interest plays in this corruption of
13 our safeguards.

14 Most recently, last month in
15 Pennsylvania, the former chief pharmacist and head
16 of the state psychiatric formulary committee was
17 indicted on felony and misdemeanor charges for his
18 conflicts of interest with drug companies.

19 Last week, a researcher for the National
20 Institutes of Health was arraigned on and pled
21 guilty to similar felony charges. I hope, I pray,
22 and I believe we are going to see a lot more of

0120

1 that sort of thing.

2 Change within the FDA has begun slowly
3 but not from the top. It began with the courageous
4 examples of Dr. David Graham and Stephen Neeson.
5 Others like them will emerge. Maybe one will
6 today.

7 In closing, I will speak a simple truth.
8 The love affair between the pharmaceutical industry
9 and our government institutions has to end. It is
10 time to remove the moneychangers from the temple.
11 Please begin today. Protect the American people.

12 (Applause.)

13 MR. JONES: Issue rational warnings about
14 the known dangers of these drugs.

15 Thank you.

16 (Applause.)

17 DR. PINE: Thank you.

18 The next speaker is Nick Korzie.

19 MR. KORZIE: Hey. What's going on folks?
20 I'm Nick Korzie. I'm 16 years old. I was on the
21 drugs myself for at least two years. I OD'd on the
22 drugs and I was taken off those, ProzacR is the

0121

1 drug that I OD'd on, and put on two other SSRIs
2 with two other antipsychotic and a seizure
3 medication.

4 I am not psychotic. I don't have
5 seizures. I was just depressed. It is sick that I
6 was put on medications that I didn't even need. I
7 took a gun to school. Luckily, I didn't shoot
8 myself; I missed.

9 I got locked up. As soon as I got out, I
10 realized in the court hearings it wasn't my fault.
11 I made bad decisions because I wasn't thinking
12 clearly.

13 Then, I started talking to people,
14 adults, and hearing through the papers that other
15 people were going through the same things I was. I
16 started realizing that I need to help other people
17 because they have helped me.

18 I met all these wonderful people and

19 talked to them about the same things that I went
20 through. Not only was I having nightmares, other
21 people were having nightmares. It wasn't just me.
22 I found that out.

0122

1 I'm here today to tell you that it's not
2 our fault that we are getting in trouble. It's not
3 our fault that we are suicidal. It's not our
4 fault. If you would just take care of us and take
5 care of what you're supposed to, protecting the
6 people. We are the people.

7 Your excuses that the drugs don't work or
8 the suicidal ideations are there before we take the
9 drugs, that doesn't make sense. Instead of upping
10 our dosages, why not just take us off the
11 medications? Obviously, if they are not working,
12 then there is no point to them. Protect the
13 people, protect me. Either give warnings or get
14 rid of the drugs.

15 Thank you.

16 (Applause.)

17 DR. PINE: Thank you.

18 The next speaker is Christopher
19 Kratochvil.

20 MR. KRATOCHVIL: Good morning. My name
21 is Chris Kratochvil, and I am a child and
22 adolescent psychiatrist at the University of

0123

1 Nebraska Medical Center in Omaha, Nebraska. I have
2 conducted research in mood disorders funded by the
3 National Institute of Mental Health as well as
4 pharmaceutical companies.

5 I paid for my own travel to participate
6 in this hearing and am speaking today on behalf of
7 the American Academy of Child and Adolescent
8 Psychiatry.

9 This morning I would like to make three
10 points based upon the pediatric antidepressant
11 experiences which may be useful to consider in
12 today's deliberations.

13 Antidepressants are effective in the
14 treatment of pediatric depression. Antidepressant
15 use has been correlated with a decrease in youth
16 suicides. The pediatric black box label was
17 correlated with a significant decline in the use of
18 antidepressants in children and adolescents.

19 First, as one of the principal
20 investigators in the NIMH-funded Treatment for
21 Adolescents with Depression Study, we demonstrated
22 that fluoxetine, both alone and in combination with

0124

1 cognitive behavioral therapy, was safe and
2 effective for the treatment of adolescent
3 depression.

4 Medication was important in improving the
5 impairing symptoms of these youths while cognitive
6 behavioral therapy alone was no more effective than

7 placebo.

8 Second, as demonstrated by Gibbins,
9 et al., in November 2006, "American Journal of
10 Psychiatry," SSRI prescriptions have been
11 associated with lower suicide rates in children.

12 While no direct causation can be
13 determined, this data is certainly congruent with
14 previous data demonstrating declining suicide rates
15 correlated with increases in antidepressant
16 prescriptions.

17 Third, several pharmacoepidemiological
18 studies have identified declining pediatric
19 prescriptions for antidepressants since the 2004
20 pediatric antidepressant hearings and the release
21 of the pediatric black box label.

22 For example, recent data presented by

0125

1 Thompson, et al., demonstrated a 19.6 decline in
2 new pediatric antidepressant prescriptions from one
3 year prior to, to one year following the black
4 box.

5 This decline was due in part to
6 physicians who stopped treating depressed patients
7 as well as referrals to specialists with excessive
8 waiting periods due to a significant workforce
9 shortage leaving many children and adolescents with
10 depression with limited access to care.

11 It is obviously crucial to thoroughly
12 assess the risk of any intervention, but potential
13 benefits and risks of not treating must be
14 considered as well.

15 My concern is that heightened anxieties
16 will result in diminished appropriate use of these
17 effective treatments, leading to unnecessary
18 suffering, impairment, and possible loss of life.

19 I ask the Committee to take these
20 concerns into account when deliberating potential
21 recommendations for the treatment of our patients
22 suffering from depression.

0126

1 DR. PINE: Thank you.

2 The next speaker is Darrel Reiger.

3 DR. REGIER: Good morning. I am
4 Darrel Regier representing the American Psychiatric
5 Association where I am director of research. No
6 pharmaceutical or other outside funds were used in
7 conjunction with my testimony to this Committee.

8 In preparing the recent FDA report, both
9 the clinical and statistical groups observed that
10 the trials reviewed were not designed to address
11 the suicide risk objectives, and thus suffer from
12 significant limitations of post hoc analysis.

13 Rather than relying on such limited
14 evidence, the FDA should base major public policy
15 recommendations on prospective clinical trials that
16 have directly and systematically assessed both
17 effectiveness and risks.

18 Hence, any leap to extending current
19 black box labels would be poorly based and,
20 secondly, the current dysfunctional monitoring
21 recommendations that are not supported by evidence
22 should be replaced.

0127

1 The current policy has led to black box
2 advisories, plummeting treatment rates, and
3 undocumented advice on how to monitor any patient
4 placed on antidepressant medications.

5 The current analysis shows that adults
6 collectively showed no increased suicide risk,
7 although there was some variation by age including
8 a strongly protective effect of the medications on
9 persons 65 years and older.

10 An overreaction to these partial data,
11 arguably, could lead to calls for launching a
12 mandatory treatment campaign for any adult over age
13 65 who has depression.

14 However, such a poorly researched suicide
15 immunization campaign might prevent some deaths,
16 but might also have other unanticipated
17 consequences such as the ones that we have had from
18 the earlier recommendations.

19 If the FDA proves to have overreacted to
20 the first round of pediatric data in 2004, the
21 substantial reduction in prescription medications
22 for this at-risk population may be seen as

0128

1 precipitating the recent CDC-documented increase in
2 completed suicides in the adolescent population
3 after a sustained decrease of over a decade.

4 Also, the sudden imposition of the
5 seven visits in twelve weeks protocol as part of
6 the labeling language for the 2004 hearings has no
7 empirical basis.

8 However, measurement-based treatment
9 approaches have recently been demonstrated in the
10 NIMH Star*D Study. Likewise, the PHQ-9 has been
11 tested and used by the American Academy of Family
12 Physicians, the American College of Physicians, and
13 the APA to monitor depression treatment response
14 and risks including suicidal ideation.

15 Monitoring should be tailored to the
16 severity to the severity and treatment needs of the
17 patient by telephone followup or at each
18 face-to-face visit.

19 We recently have heard from primary care
20 practices that some physicians are refusing to
21 initiate treatment for depression because they
22 couldn't guarantee seven visits in twelve weeks.

0129

1 Again, as the FDA considers labeling
2 changes, we would suggest that you move toward a
3 more evidence-based monitoring recommendation that
4 avoids creating the much greater risk of disruptive
5 lives and suicide that are associated with

6 untreated depression.

7 Thank you.

8 DR. PINE: Thank you.

9 The next speaker is Moira Dolan.

10 DR. DOLAN: Hello. My name is Dr. Moira
11 Dolan, executive director of Medical Accountability
12 Network. We are a nonprofit accepting donations
13 from individuals only and have no support from
14 commercial interests or from other groups. Our
15 purpose is to make medicine accountable based on
16 full informed consent.

17 Here are some of our grave concerns with
18 the adult suicidality studies that were discussed
19 this morning. Inexplicably, the drug makers only
20 had to report one event per subject.

21 Incredibly, events occurring within the
22 tapering period were not included. Events more

0130

1 than one day after the last double-blind treatment
2 period were not included, and this is in spite of
3 drug half lives from five hours to over a week.

4 The attempted compensation for
5 informative censoring was wholly inadequate.
6 Again, inexplicably the FDA made no attempt to
7 adjudicate the drug makers' reports of what
8 consisted of "suicidality."

9 Even with these handicaps, however, the
10 data did show an increased incidence of suicidality
11 in 18- to 24-year-olds. Remarkable increased
12 suicidality was found in the evidence supplied by
13 the makers of Celexa®; Cymbalta®; BuSpar®; and, to
14 a lesser extent, Luvox®.

15 There is no biological explanation for
16 such a drug effect on adolescence and young adults
17 and yet not on people over age 25. In fact, there
18 is no precedent for any adverse drug event warning
19 to be given for children but not for adults when it
20 doesn't specifically relate to growth or
21 maturation.

22 Obviously, more studies need to be done.

0131

1 This time with data collection that is designed to
2 give some answers. However, to have this data in
3 hand and yet to continue to refrain from
4 undertaking an urgent, broadly disseminated
5 information campaign with immediate and plainly
6 worded warnings -- warnings against the possibility
7 of tragic, unnecessary deaths by drug-induced
8 suicide -- well, this is nothing less than a gross
9 abdication of the patient protection
10 responsibilities of the FDA.

11 The concerns of the Medical
12 Accountability Network are that physicians and
13 pharmacists have legal and ethical obligations. We
14 have to provide patients with adequate information
15 so that they can give informed consent for any
16 given treatment.

17 When you settle for more study in the
18 absence of urgent consumer protective action,
19 frankly physicians and pharmacists are forced to
20 ignore the FDA. Unlike the FDA, those of us on the
21 front lines cannot ignore the fact that we are
22 faced with people's lives.

0132

1 Look at your ethics codes, ladies and
2 gentlemen of the Committee, and recall that we are
3 talking life and death here, then take a look in
4 the mirror. Let that bear on your actions as
5 Advisory Committee members.

6 Thank you.

7 (Applause.)

8 DR. PINE: Thank you.

9 The next speaker is Deborah Gruder.

10 MR. GRUDER: My name is Ashir Gruder and
11 I am 23 years old. In 2004, my father Scott was
12 given sample packs of Paxil CR™ and told to call
13 back in about three weeks. He killed himself
14 13 days later.

15 One hundred years ago, Congress created
16 the FDA in response to the numerous health hazards
17 present in the American marketplace. Its job was
18 to protect the American people. It is now a
19 century later and the dangers are far greater than
20 they have ever been.

21 Multinational drug companies let their
22 seemingly endless R&D expenditures justify valuing

0133

1 profits over the sanctity of human life. This
2 shortsightedness has led to the emergence of a vast
3 new array of dangers to the health of the American
4 people.

5 It is too late for you to protect my
6 father. He is dead, and nothing we do today will
7 bring him back. You do have the opportunity to
8 save countless other lives.

9 It took a public outcry for the
10 government to act in 1906. Well, let this serve as
11 our outcry. The people need a champion. I implore
12 you please stand up for us.

13 MS. GRUDER: My name is Deborah Gruder.
14 In the fall of 2004, I spoke before a similar
15 committee urging them to utilize their power to
16 bring awareness and protection to the public
17 regarding SSRIs and suicidality not only as it
18 related to children and adolescents, but also to
19 bring awareness regarding the lethal side-effects
20 connected with adult suicidality.

21 Not two years ago, not fifteen years ago,
22 not today has suicidal thoughts or behavior been

0134

1 isolated to just children and adolescents. Because
2 on March 30, 2004, my husband, Scott Gruder age 52,
3 just only 13 days after beginning Paxil at the
4 recommendation of his physician, just eight days

5 after this Committee was warned by Dr. Andrew
6 Mosholder to notify and alert not only the
7 physicians who were allowed to prescribe these
8 antidepressants but demanded that the
9 pharmaceutical industry warn the public.

10 In spite of this warning, on that Tuesday
11 morning in 2004, Scott Gruder -- my husband, a good
12 man, a father, a son, a friend to many, and a man
13 who loved life -- somewhere between 7:00 and 7:30
14 a.m. walked into a Walmart and purchased a shotgun
15 and went back to his office and turned this weapon
16 on himself and took his life.

17 He definitely held the gun, but it is
18 GlaxoSmithKline and this Committee as the
19 accomplice by way of negligent misrepresentation
20 and wilful omission of the truth who killed my
21 husband and many other. It has been nothing short
22 of a blood bath and mass murder.

0135

1 (Applause.)

2 DR. PINE: Thank you.

3
4
5 DR. PINE: The next speaker is
6 Gwen Olsen.

7 MS. OLSEN: My name is Gwen Olsen. My
8 20-year-old niece, Megan Leslie Blanchard,
9 committed suicide on December 2, 2004, while
10 attempting to withdraw from Effexor®.

11 She ended her life by self-emulation
12 after first trying to hang herself with her
13 shoelaces. She was unsuccessful because the
14 ceiling fan she had attached them to gave way to
15 her body's weight, so she entered her younger
16 sister's room, took an oil lantern, immersed
17 herself, and ignited a flame.

18 This was a young woman of extraordinary
19 intelligence, beauty and talent who burned herself
20 alive only three weeks before Christmas. The
21 coroner said she sustained second- and third-degree
22 burns over 95 percent of her body. Only her feet

0136

1 were spared.

2 It is not only as Meg's survivor that I
3 felt compelled to be here, but also because of my
4 own adverse response to SSRIs at the age of 33. In
5 1992, I developed a severe case of akathisia and
6 became suicidal for the first and only time in my
7 life.

8 My niece's experience only further
9 convinced me that this phenomenon is not limited to
10 children and adolescents but occurs in all ages and
11 across all patient types.

12 Most importantly, I am here to contribute
13 my perspective as a 15-year veteran in
14 pharmaceutical sales who sold and educated doctors
15 on psychiatric drugs.

16 While working for five major
17 manufacturers, I learned several reasons why much
18 of the data presented here has little to no
19 clinical relevance.

20 For example, the participants in drug
21 trials are cherry picked by the researchers to
22 ensure maximum positive outcomes for reporting
0137 purposes.

1 Less than 50 percent of a drug's adverse
2 events are known prior to the drug's approval, and
3 only 1 to 10 percent of side-effects are reported
4 after market through the current MedWatch system.

5 Moreover, pharmaceutical reps are
6 artfully trained to minimize side-effects and to
7 dodge doctor's objections while detailing drugs.
8 This practice severely impairs the fair, balanced
9 education necessary for doctors to develop good
10 clinical judgment.

11 Over the years, my job moved away from
12 educating physicians about my product's
13 indications, contraindications, and side-effect
14 profiles to courting and obligating doctors and
15 their staff with food, gimmicks, and other monetary
16 inducements in order to gain access to busy
17 practices.

18 These activities coupled with my
19 observation of the marketing department's skillful
20 disguise of potential problems in flow charts, bar
21 graphs, and through the manipulation of statistics
22
0138

1 make it imperative that we have an aggressive and
2 accurate postmarketing drug risk assessment
3 performed by the FDA.

4 It is also necessary that warnings be
5 issued promptly without political stonewalling when
6 deadly risks surface. I know from my research that
7 there is blatant corruption in the integrity of the
8 science surrounding the SSRI drugs.

9 We, the people, have become a disposable
10 human commodity, and our welfare has taken a
11 backseat to profit where drug safety is concerned.

12 Someone must be held accountable, and
13 someone must take the authoritative action to
14 rectify the problem before it further escalates.
15 You are the responsible party.

16 (Applause.)

17 DR. PINE: Thank you.

18 The next speaker is Beverly Hatcher.

19 MS. HATCHER: My name is Beverly Hatcher,
20 and I am also a nurse. On August 18, 2003, my
21 mother, the late Ms. Barbara Jean Darden, was
22 prescribed Paxil. On September 2, 2003, one day
0139

1 before her youngest daughter's birthday, she took
2 her life.

3 She was only on Paxil for 16 days. My

4 mother had no history of depression. For far too
5 long, drug companies have been allowed to be under
6 no legal obligation to report or expose the risk of
7 all cognitive effects of the medications they
8 market.

9 On the other hand, drug companies are
10 allowed to provide an abundance of information to
11 the public and the medical community via
12 television, newspapers, and magazines about the
13 alleged positive aspects about their products, but
14 at the same time they still deliberately withhold
15 the negative trial studies to the same population.

16 In doing some research on GSK, the maker
17 of Paxil the drug that was the ultimate cause of my
18 mother's death, I came across these alarming
19 findings. These alarming findings come straight
20 out of the headlines from their articles on their
21 website.

22 GSK professes their mission is to improve
0140

1 the quality of life by enabling people to do more,
2 feel better, and live longer. They boast about how
3 they have over 100,000 employees worldwide, and
4 they go on to say how some 40,000 of them alone
5 just work in marketing and sales. They have 24
6 research and develop centers in 11 countries.

7 For some quotes from the drug company's,
8 GSK's, employees they have been quoted saying on
9 12/8/2003, Dr. Allen Roses, GSK's senior vice
10 president of genetics, said that the vast majority
11 of drugs only work in about 90 percent of the
12 people.

13 I'm sorry, "The vast majority of drugs,
14 more than 90 percent, only work in about 30 to
15 50 percent of the people. I would not say that the
16 drugs don't work in 30 to 50 percent of the people.
17 Drugs out there work, but they don't work in
18 everybody."

19 6/6/2004, Jean-Pierre, executive officer
20 said: "We are a high-integrity company. We know
21 the rules, and we follow them." She also said,
22 "All drugs have side-effects. We are spending too

0141
1 many hundreds of millions of dollars on lawyers."

2 Alan Metz, GSK vice president for
3 clinical development said: "We do not know with
4 absolute certainty how any of the antidepressants
5 work."

6 Her spokesperson Mary Ann Ryan quoted in
7 2006: "GSK said the sales for Paxil alone was \$33
8 million. For Paxil CR, sales were \$209 million."
9 Ms. Ryan also went on to say they conducted a new
10 analysis and revised the label at the request of
11 the FDA.

12 In May 2006, GSK sent out letters to the
13 doctors informing them of the risk of suicide in
14 adults 18 to 30. Ms. Ryan also went on to say on

15 behalf of GSK, "We believe, however, that overall
16 risk/benefit remains positive."

17 In 2004, the FDA was forced to take a
18 harder look at the antidepressant sector, requiring
19 all drug companies to change their labels and
20 reflect the risk of suicide.

21 In March 2004, according to the
22 information pulled from the pages of the FDA

0142

1 website, the FDA issued a public advisory about
2 worsening of the side-effects of depression and
3 suicidality in patients being treated with
4 antidepressants.

5 DR. PINE: Thank you.

6 The next speaker is Ellen Liversidge.

7 MS. LIVERSIDGE: Good morning. My name
8 is Ellen Liversidge from Silver Spring, Maryland,
9 and I am glad I got a chance to speak after all. I
10 have no financial ties to any group, particularly
11 pharma. I would never have financial ties to
12 pharma.

13 I am a member of the Alliance for Human
14 Research Protection, and I speak on behalf of my
15 children and my friends Diane, Kathy, Theresa, and
16 Leslie who also lost family members to psychotropic
17 drugs.

18 My family's psychiatric history is grim
19 with a grandmother who died in the early twenties
20 due to manic depression we think and a father who
21 died from electroconvulsive therapy when I was
22 one year old.

0143

1 Each of my two children acquired manic
2 depression at age 20, my son in 1984 and my
3 daughter in 1987. My son did very well, for the
4 most part, on lithium obtaining his bachelor's and
5 master's from Cornell and having a real life.

6 But in 2004 he made a fatal mistake and
7 went on Maryland Medicaid and was put on Lilly's
8 Zyprexa®. He was told repeatedly that it was
9 safe.

10 I am very suspicious of Maryland
11 Medicaid's formulary choices. He gained almost a
12 hundred pounds. In October 2002, he fell into a
13 coma and died.

14 The FDA failed, having done a study of
15 MedWatch data in 2001 with a professor from Duke,
16 in finding hundreds of cases of diabetes and
17 23 deaths. Prior to my son's death, both Japan and
18 the U.K. required a warning on this drug of
19 Lilly's. The FDA did nothing.

20 In 2004, my daughter, who had done well
21 on lithium for 17 years, began to feel suicidal.
22 Among the many potions given to her was the drug

0144

1 Lexapro.

2 I will never forget the day she came to

3 my office looking all around and looking very
4 agitated. I realized she was looking for her
5 kitchen knives, which I had taken from her
6 apartment for safekeeping. She was acutely either
7 suicidal or homicidal.

8 I didn't know which because fortunately
9 we survived. She had to go into the hospital for
10 safekeeping. She had never been in a state like
11 that.

12 FDA, you almost took my daughter as well
13 as my son.

14 The FDA needs to meet its original
15 mandate, which is to protect the public health of
16 American citizens instead of the bottom line of the
17 pharmaceutical industry.

18 (Applause.)

19 DR. PINE: Thank you.

20 The next speaker is Lisa van Syckel.

21 MS. VAN SYCKEL: Good morning. Good
22 morning, ladies and gentlemen. My name is Lisa van

0145

1 Syckel. I am the mother of a fifteen-year-old
2 Paxil survivor who attempted suicide and became
3 violent.

4 On August 31, 2006, of this year, Dr. von
5 Eschenbach received a letter from my Congressman,
6 Mike Ferguson, a member of the Oversight and
7 Investigations Committee.

8 Congressman Ferguson stated to
9 Dr. von Eschenbach, "As you know, the use of
10 antidepressant medication is controversial,
11 particularly by children and adolescents."

12 In September 2004, I participated in
13 hearings conducted by the House Energy and Commerce
14 Committee's oversight investigations concerning the
15 pediatric use of antidepressants.

16 At that hearing I strongly advocated that
17 the FDA issue black box warnings, the highest FDA
18 warning on prescription drug labels, regarding the
19 potential serious side-effects in the pediatric
20 population.

21 It was my belief in 2004 during the
22 congressional hearings and it remains so now that

0146

1 these drugs must be administered to children and
2 adolescents under the strictest scrutiny.

3 I believe that the medication guides are
4 a vital component to the overall strategy ensuring
5 that fully informed decisions are made by parents
6 before their child begins a regimen of
7 antidepressant medications.

8 Indeed, it is for this reason that I find
9 deeply troubling the apparent lack of regulatory
10 oversight to ensure the medication guides are being
11 distributed. We know the medication guides are not
12 being distributed.

13 Dr. Goodman, in February 2004, you gave

14 an interview to your local reporter and I quote
15 you, "I hope there will be some mechanism in the
16 meantime to warn both parents and physicians to be
17 alert for what I call `behavioral toxicity.'"

18 On October 10, I had the wonderful
19 opportunity to speak with Attorney General Alberto
20 Gonzales about this behavioral toxicity and the
21 violence in our schools.

22 It is very important that we keep the

0147

1 black box warnings and we add the black box warning
2 to the adult population. If it were up to me, you
3 would have the suicide warning right there on the
4 bottle.

5 We are the parents, we are the consumer.
6 It is our right to make an informed decision. If
7 FDA cannot do the proper thing, we will go to
8 Congress, and we will make Congress demand that you
9 do your job. If you can't do it, then they will
10 have to do it for you.

11 A PARTICIPANT: Here, here.

12 (Applause.)

13 MS. VAN SYCKEL: We now know that it is
14 the holiday season and many people would have liked
15 to have been here and they cannot be, so the
16 remainder of my 15 minutes (sic) will be in a
17 moment of silence for those who have lost their
18 lives.

19 Thank you.

20 DR. PINE: Thank you.

21 (Applause.)

22 DR. PINE: The next speaker is

0148

1 Charles Carpenter.

2 MR. CARPENTER: Thank you for allowing me
3 this opportunity. In the spring of 2002, my wife
4 started seeing a psychologist because she would
5 sometimes jump when she was riding in a car, not
6 all the time just once in a while.

7 In the fall of 2002, the psychologist
8 recommended Paxil. Since she couldn't write the
9 prescription, a general practitioner in the clinic
10 wrote it for her. She was assured that Paxil was
11 safe but was told she could experience dry mouth,
12 nausea, and drowsiness.

13 By the end of May 2003, she was a
14 completely different person. Her likes, dislikes,
15 and interests had all changed. Gaping holes had
16 been eroded into the boundaries she had established
17 for the way she lived her life.

18 A person's whose goal it had been for us
19 to work together in our photography studio, who
20 looked forward to the time, extra time, we could
21 spend together on vacation and the person that told
22 my mom when she was dying not to worry that she

0149

1 would always be there to take care of me, just

2 walked away -- not just from me but from everything
3 and everyone that had been important in her life.

4 (Crying) I knew something was wrong
5 other than the obvious, but at the time I had no
6 idea it was the Paxil. I frantically searched for
7 answers, but answers were scarce.

8 The person who had always been so close
9 for so long suddenly saw me as the source of
10 everything that had ever happened bad in her life.

11 Don't misunderstand me. I am not being
12 critical of my wife. She had no idea when she took
13 that first pill what laid in store for her because
14 she wasn't adequately warned. We didn't know.

15 A few weeks later, I went to the doctor
16 and he prescribed Zoloft®. I took the sample pack,
17 and I got the prescription filled twice. Most of
18 the second prescription I still have. The reason
19 for that is because I became suicidal.

20 I wrote and I changed the lyrics to songs
21 to reflect what I wanted to do. Then, one day the
22 police showed up at work to check on me. I

0150

1 convinced them I was fine and went back to work.

2 I knew then that I couldn't be alone for
3 extended periods of time, so I stayed with family
4 members. I continued to do research. I found on
5 the Internet mentions of SSRIs and suicide. I
6 decided to get off the Zoloft.

7 DR. PINE: Thank you.

8 The next speaker is Paula Clayton.

9 DR. CLAYTON: Hello. My name is
10 Paula Clayton. I am a psychiatrist and the medical
11 director for the American Foundation for Suicide
12 Prevention.

13 Prior to joining the Foundation, I was
14 chairman of the department of psychiatry at the
15 University of Minnesota for 20 years. I have
16 prescribed antidepressants since 1958. I was a
17 member of the FDA Psychopharm Panel in the 1980s.
18 I was also one of the 10 suicide experts who
19 blindly rated the adverse events for the FDA.

20 The studies presented here show no
21 significant differences in death by suicide in
22 depressed patients treated with antidepressants and

0151

1 those who received placebo.

2 For instance, many have found no
3 increased risk for completed suicide among the
4 adults. Furthermore, other studies cited in your
5 document show that suicide rates have decreased
6 probably due to increased use of antidepressants,
7 suggesting that these medications work in adults to
8 reduce suicide.

9 More recently, Simon showed that in
10 adults death by suicide and suicidal actions were
11 not significantly higher after the first month of
12 treatment nor in the following months. In fact,

13 his data showed that the highest risk for suicide
14 attempts was in the month prior to beginning the
15 treatment.

16 As a physician, I was taught that all
17 medications have risks and side-effects so that I
18 must consider the risk-to-benefit ratio of any
19 medication I prescribe. Here the benefits outweigh
20 the risks.

21 Depression is an illness with high
22 morbidity and mortality. I believe that the best

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1 way to prevent suicide is through early detection,
2 diagnosis, treatment, and careful followup of
3 patients with depression.

4 The first dictum of a physician is do no
5 harm. My concern is that any additional black box
6 warning runs the risk of making the effective
7 treatments less available for many depressed
8 patients. It is imperative that the FDA focus on
9 this.

10 Preliminary numbers from 2004 show that
11 prescription rates for antidepressants for children
12 and adolescents dropped significantly while suicide
13 rates have increased for the first time in 10
14 years. As predicted, this is a horrible natural
15 experiment.

16 In the Simon study, he pointed out that
17 any data on suicide attempts should not be equated
18 with death by suicide. Along these lines, I urge
19 the FDA and the people listening to understand the
20 differences.

21 DR. PINE: Thank you.

22 The next speaker is Diane Dorlester.

0153

1 MS. DORLESTER: Thank you. Chairman Pine
2 and members of the Committee, my name is Diane
3 Dorlester. I greatly appreciate the opportunity to
4 speak before you today. I, too, am here to ask for
5 your help. I ask that you not take any action that
6 would discourage people who have depression from
7 getting the help they so badly need.

8 About 10 years ago, I began to experience
9 symptoms of depression with no logical cause. They
10 were not debilitating but definitely affected my
11 life, and so I began to seek counseling.

12 For about two years, I felt okay off and
13 on. I certainly had ups and downs, good times and
14 bad, but I was able to go about my life. After
15 about two years, my depression began to get worse.

16 At that time a doctor, my psychiatrist,
17 suggested that I try antidepressant medications. I
18 was very reluctant to do so. I just had a fear of
19 what it would feel like to be on these medications.

20 I also, like so many of the 19 million of
21 us that have depression, fell victim to the stigma
22 that if I couldn't fix this myself it was a flaw in

0154

1 me and so I really resisted that.
2 My depression continued to get worse.
3 After about six months, I did take my doctor's
4 advice and began taking antidepressant medications.
5 Treatment was, for the most part,
6 effective for about a year, then it suddenly got
7 much, much worse and I spiraled into a condition
8 where I could not sleep at times and other times I
9 was sleeping for days on end and not getting out of
10 bed.

11 I lost about 25 pounds. I could not eat.
12 Every day, when it was at its worst, I would wake
13 up with a gut-wrenching pain, emotional pain, that
14 is similar to what any of us would feel if we just
15 got devastating news of maybe a loved one who has
16 passed on. On those days that I woke up feeling
17 that, that pain never went away.

18 My doctor wanted me to switch to a
19 different antidepressant, because he said some
20 things work better with certain people. I was
21 reluctant again to do so.

22 Because despite how horrible I felt and
0155

1 how much I was at that time thinking of suicide and
2 at times sitting in my car in my garage turning the
3 engine off and on, I was afraid to switch.
4 Eventually, I did so. About three weeks later, I
5 got my life back.

6 Had there been a black box warning on the
7 medication, the second medication that saved my
8 life, that may have been the one additional piece
9 that I needed to not switch.

10 DR. PINE: Thank you.

11 The next speaker is Lewis Kopolow.

12 DR. KOPOLOW: I am Dr. Kopolow, currently
13 president of Suburban Maryland Psychiatric Society.
14 I am speaking today from the perspective of an
15 adult psychiatrist who has treated thousands of
16 depressed patients with psychotherapy and
17 medication over the course of my thirty-year
18 career. I will be making three points for the
19 Committee's consideration.

20 One, depression can be a lethal disease;
21 two, there is a significant link between untreated
22 depression and physical illness; and, three,

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1 depression is an illness that is already
2 underdiagnosed and undertreated in this country.

3 Elaborating on point one, depression is a
4 disease with a high likelihood of severe,
5 unalterable consequences. Suicidal thoughts,
6 gestures, and actions are an inherent part of major
7 depressive illness itself. People with untreated
8 mental illness such as depression face up to a 15
9 percent lifetime risk of dying of suicide.

10 Point two, depression is not only an
11 illness affecting an individual's emotional state

12 but their physical health as well. Patients
13 suffering from major depressive illness have one
14 and a half to two times greater risk than the
15 general public of developing hypertension,
16 cardiovascular disease, and diabetes. The World
17 Health Organization has identified depression as
18 the leading cause of disability in the world.
19 Point three, the Surgeon General's report
20 in 1999 noted that more than half of all people
21 with a mental disorder such as depression do not
22 get the help they need.

0157

1 I am concerned that a black box will lead
2 to an actual increase in untreated depression and
3 suicide by discouraging physicians from
4 recommending antidepressant medication and causing
5 patients to discontinue the treatments that are
6 helping them.

7 Data shows the number of antidepressant
8 prescriptions dispensed to patients age 18 and
9 under dropped nearly 22 percent in the wake of
10 FDA's pediatric black box hearing. This situation
11 may be a harbinger of what will happen if a black
12 box label is added to antidepressant prescriptions
13 for adults.

14 Another consequence of greater hesitancy
15 or avoidance of prescribing antidepressant
16 medications may be a decrease in the chances of a
17 person ever achieving recovery from the depression.
18 This is based on an NIMH collaborative study by
19 Dr. Marty Keller.

20 In conclusion, the Committee must weigh
21 the lethal consequences of untreated major
22 depressive illness versus the questionable clinical

0158

1 significance of an increase risk of suicidal
2 thoughts and gestures.

3 An unfortunate consequence of a black box
4 label is that physicians will be reluctant to
5 prescribe antidepressants and their patients will
6 face needless suffering.

7 Thank you.

8 DR. PINE: Thank you.

9 The next speaker is Joseph Glenmullen.

10 DR. GLENMULLEN: My name is Joe

11 Glenmullen. I am a clinical instructor in
12 psychiatry at Harvard Medical School and the author
13 of two books, "Prozac Backlash" and "The
14 Antidepressant Solution," both of which describe my
15 experience with patients having this side-effect.

16 The data the Advisory Committee is
17 looking at today is flawed as the FDA well knows.
18 Although the FDA has known about this side-effect
19 since 1990, it has never insisted that a
20 pharmaceutical company study the phenomenon with
21 sensitive measures of treatment-emergent
22 suicidality.

0159

1 On September 20, 1991, the FDA held a
2 hearing just like today's and swept this issue
3 under the carpet. At the time the FDA and
4 Eli Lilly, Prozac's manufacturer, agreed that Lilly
5 would do the gold standard research.

6 Lilly developed the protocol for the
7 research including sensitive scales of treatment-
8 emergent suicidality, yet Lilly never did the
9 research, and the FDA still hasn't gotten the gold
10 standard research done.

11 Given the limitations of the data the
12 Advisory Committee is looking at today, the
13 powerful evidence of antidepressant-induced
14 suicidality occurring in patients under 25 years
15 old and 45 to 64 years old mandates a warning for
16 all age groups.

17 The increased risk for under 25 year olds
18 is statistically significant as acknowledged by the
19 FDA. Although not statistically significant, the
20 powerful evidence of risk for 45 to 64 year olds
21 meets the statutory requirements for FDA to issue a
22 warning.

0160

1 You cannot leave out 25 to 45 year olds
2 because the limitations of the data are the most
3 likely reason why the risk for this age group does
4 not appear into today's data set.

5 Statisticians know that when low-quality
6 data such as today's shows a risk, higher-quality
7 data would show a stronger data. Especially since
8 the FDA has not done the gold standard research,
9 you must extend the warning to all age groups.

10 Warning patients does not scare them away
11 from treatment. It allows them to make informed
12 choices and save lives. Think how many lives could
13 have been saved if the FDA warned about this side-
14 effect back in 1991 when it first evaluated the
15 issue and swept it under the carpet. Think how
16 many families and communities have been devastated
17 by this side-effect in those 15 years.

18 Do the right thing today and extend the
19 black box warning to all age groups. If you do
20 anything short of that, once again the FDA has
21 failed to protect the American public and American
22 patients.

0161

1 Thank you.

2 (Applause.)

3 DR. PINE: The next speaker is
4 Dan Reidenberg.

5 DR. REIDENBERG: Good morning. My name
6 is Dr. Daniel Reidenberg, and I am here on behalf
7 of the National Council for Suicide Prevention,
8 eleven national nonprofit organizations sharing a
9 mission to prevention suicide.

10 Collectively, we represent clinicians and

11 researchers and advocates, but we also speak for
12 millions of constituents, many of whom are
13 survivors, parents, siblings, coworkers, and
14 neighbors who have lost ones to suicide. We speak
15 to you from a unique perspective, intimately
16 knowing what it is like to live as a survivor.

17 With suicide being the 11th leading cause
18 of death, with more than 30,000 suicides and an
19 estimated 750,000 to 1.8 million attempts each
20 year, we must do everything we can to raise
21 awareness, educate, and help those in need to
22 prevent unnecessary loss of life.

0162

1 Suicide is a complex and multifaceted
2 problem as there is no one cause of suicide.
3 Neither is there just one treatment approach to
4 prevent suicide.

5 Overwhelmingly, research suggests that
6 antidepressant medications are safe and effective.
7 Every medication has benefits, side-effects and
8 potential risks, yet few medications are black box
9 labeled.

10 Despite inconsistent research results on
11 increased suicidality for antidepressants in youth,
12 studies have shown that antidepressants are not
13 associated with increased risk of suicide in
14 adults.

15 For 20 million to 30 million Americans
16 living with depression, antidepressants are life
17 saving. Millions more living with other mental
18 illnesses are also being treated with these same
19 life-saving medications with remarkable success.

20 Responsible health care requires that we
21 seriously consider the evidence of efficacy versus
22 risk before instituting a black box label. Without

0163

1 a replacement therapy, patients currently well-
2 maintained but removed from their current
3 medication regime will be left with inadequate care
4 and be at risk for suicide.

5 Suicidal ideation is a symptom of
6 depression. Research has shown that suicidal
7 ideation is often denied by patients when asked by
8 their healthcare professionals but admitted to when
9 these caregivers showed greater interest in the
10 patients.

11 Thus, the expression of suicidal thoughts
12 after initiating antidepressant treatment does not
13 give evidence that these medications cause suicidal
14 thinking.

15 As we survivors and experts on suicide,
16 we implore you to be careful making your decision.
17 We know that a black box label will decrease the
18 use of these life-altering medications and increase
19 the fear in Americans in need of them.

20 This is why we support better education
21 for physicians regarding risk assessment and

22 monitoring of these patients on medications, all of
0164

1 which can be readily accomplished without a warning
2 label.

3 With the largest number of people in one
4 generation, the baby boomers, moving into the
5 highest rate category of suicides, senior citizens,
6 a group already stigmatized about mental illnesses,
7 the time is now to be proactive and not reactive.
8 You have the power to save lives for this and
9 future generations.

10 If you knew your son, daughter, husband,
11 or wife were suffering from a treatable disease of
12 depression but they were scared away from taking
13 medication because of a warning label placed on a
14 package with yet insufficient evidence but died as
15 a result of suicide, how would you feel?

16 Please do not make it any more difficult
17 to get these live-saving treatments into the hands
18 of people across the country.

19 Thank you.

20 DR. PINE: Thank you.

21 The next speakers are Karen Menzies and
22 Debra Tucker.

0165

1 MS. MENZIES: Thank you. Debra is not up
2 here with me. She is staying a little bit less --
3 more anonymous. Thank you.

4 My name is Karen Menzies, and I am an
5 attorney from Los Angeles. My firm has represented
6 since 1990 over a hundred families of the victims
7 of suicide attempts and suicides from Prozac,
8 Paxil, and Zoloft.

9 I submitted a written statement to you
10 with some formerly confidential documents that have
11 now come out into the public that illustrate,
12 first, that the drug companies have known about
13 this risk for over 20 years. It also illustrates
14 though, however, FDA's failure to protect all
15 patients, not just those that feel the drugs help
16 them.

17 FDA now concedes that the data shows an
18 increased risk but only up to 25. Do the drugs
19 know the age of the person? Do they know when a
20 person turns 25 or 44?

21 When a company seeks approval for a drug,
22 does the FDA parse out the data for efficacy to

0166

1 determine which age groups it is effective for? I
2 would like to see that data.

3 We know that breast cancer most often
4 occurs in women over fifty. Does that mean women
5 who are in their thirties can't have breast cancer?
6 Of course not.

7 As Ian Oswald said in the BMJ back in
8 1990 back in 1991 about the analysis Lilly
9 presented to FDA of the Prozac data:

10 "The term `meta-analysis' sounds rather
11 grand, but it is worth no more than the quality of
12 the original data collection. A negative result of
13 research, a failure to find something can arise
14 from the lack of sensitive research techniques."

15 I ask you, Why does the algorithm contain
16 not one search term for akathisia, hypomania,
17 mania, or psychosis? We know like the neuroleptics
18 drug-induced akathisia can lead to suicidality.
19 This algorithm only looks at the methods by which
20 somebody may attempt or commit suicide. It has not
21 one word even related to agitation.

22 Your current black box warning includes
0167

1 anxiety, agitation, panic attacks, insomnia,
2 irritability, hostility, aggression, impulsivity,
3 akathisia, hypomania, and mania as symptoms in both
4 kids and adults. Why aren't these part of the
5 search terms?

6 These are the search terms we use in the
7 litigation to get the evidence out from the drug
8 companies that shows this clear risk. It
9 distinguishes it from depression-related suicide.

10 I know that the FDA can't have all the
11 documents that we get in litigation. They don't
12 see how you are manipulated by the drug companies,
13 but you can get this evidence. You are just not
14 asking for it.

15 I have just a hint. I strongly recommend
16 you ask for the companies' case report forms for
17 patients who reported as placebo suicides. You
18 will be surprised what you find.

19 Dr. Laughren, you state in your memo of
20 November 16 that "The increased risk has been part
21 of medical lore for years." This is so
22 misleading.

0168

1 We are not talking about a recall. We
2 never have been. We are talking about doctors and
3 patients being given the whole story, both the good
4 and the bad, an informed choice.

5 When did it become FDA's job to promote
6 the drugs or promote the diseases? The
7 pharmaceutical companies are great at that. They
8 don't need help in that. What we need you to do
9 and the Advisory Committee, please help us inform
10 the patients so that all patients, even those who
11 have the side-effect will be well aware and doctors
12 can see it and they can prevent the deaths.

13 (Applause.)

14 DR. PINE: Thank you.

15 The next speaker is Michelle Moore.

16 MS. MOORE: May 23, 2001, my husband
17 Darren Ali was murdered. He was murdered and torn
18 away from his wife, his kids, his family, and
19 friends due to a force far more powerful than
20 himself: the dangerous antidepressant drugs of

21 Prozac and Paxil.

22 To think that this amazingly strong

0169

1 husband, father of two, son, best friend to so
2 many, police sergeant, and SWAT team commander
3 could be taken over by these horrific drugs is
4 beyond comprehension.

5 Let me tell you about this special man
6 that the world will forever miss. This is the man
7 that I loved the moment I saw him. He was a
8 policeman and I a nurse. He lit up the room when
9 he was in it, vibrant and full of life. He was an
10 incredibly loving husband to me for nine and a half
11 years.

12 Three years after we were married, we
13 were blessed to start a family. Our son Jack was
14 born. Two years later, we were blessed with our
15 daughter Rachel. He was a playful and devoted
16 father to both J.D. and Rachel. He was J.D.'s
17 hockey coach. He went to Rachel's dance recitals.
18 The kids adored their father. They were seven and
19 five at the time of his murder.

20 I will never forget the moment I had to
21 tell them their father died. It was the worst and
22 difficult moment of my life. They screamed in

0170

1 horror.

2 Besides the deep love for his family,
3 Darren also had another love in his life, this was
4 for his work and his fellow officers. He loved
5 being a police officer. "He was one of the best,"
6 the sheriff said. He rose to the position of
7 sergeant and was a commander of the SWAT team.

8 I will never forget some of his fellow
9 officers telling me that if they ever went to war
10 they wanted Darren beside them. As part of the
11 motorcycle unit, he provided security for President
12 George W. Bush. The sheriff's department didn't
13 know what they were going to do without him. He
14 was irreplaceable.

15 He graduated from Northern Michigan
16 University with a degree in criminal justice. He
17 wanted to be a police officer all of his life.
18 Darren was diagnosed with depression three weeks
19 before his death. It was described as a minor
20 depression.

21 He was put on Prozac, and he took that
22 for three days. He was then taken off Prozac and

0171

1 put on Paxil. He took one Paxil, and immediately
2 he started feeling very anxious. I being a
3 registered nurse realized quickly this was not a
4 normal reaction. He never had any suicidal
5 thoughts or behaviors.

6 I returned home from work, after him
7 being on the Paxil for one day and Prozac for the
8 previous three days, and found him dead. My

9 husband adversely reacted to these drugs. He was
10 never warned properly and I also. I know that
11 Darren would never make this decision.

12 In closing, I hope that everyone walks
13 away today with an increased knowledge of the
14 possibility of what these very dangerous drugs can
15 do to someone. These are mind-altering drugs.

16 (Applause.)

17 DR. PINE: Thank you.

18 The next speaker is Tony Noll.

19 MR. NOLL: I come to speak to you today
20 on behalf of the statistically insignificant. My
21 father was a police officer for 32 years in the
22 city of West Dallas, which is a Milwaukee suburb.

0172

1 In July, July 1st of 2003, he was having
2 a little anxiety over some things at his house and
3 not getting some sleep, so he called his family
4 doctor and they prescribed Effexor, the SNRI. They
5 prescribed it to him over the phone and even told
6 him how safe it was. My mom told me this over the
7 phone.

8 The night before, I talked to my dad on
9 the phone. His voice tone was real odd. It was
10 unfamiliar to me. My dad was the type of person
11 who would talk my ear off, and I had do things to
12 try to get him off the phone. His conversation was
13 short and he said he wasn't feeling himself.

14 My mom told me, "Something is really
15 wrong with your dad. He's not doing okay."

16 I asked her if she needed me to come down
17 to help and she asked me, "Why don't we see how
18 tonight goes?" That was the last time I would
19 speak to either of them.

20 At 7:45 the next morning my father called
21 911, which I have listened to the tape, in what I
22 would describe as a zombie-like voice said that he

0173

1 had just killed his wife and before anyone got
2 there he would be dead.

3 When the police arrived, they found my
4 father and my mother dead, my dad having put my
5 mom's arm around him before he took his own life.
6 My dad was only 58 years old, just three years out
7 of retirement and my mom 56.

8 I am convinced this drug caused the death
9 of both of my parents. They were smiling and happy
10 people enjoying their retirement just in the weeks
11 and days before July 3, 2003. That picture there
12 (indicating) is only two weeks prior to it
13 happening.

14 They had everything to live for. They
15 had four grandchildren that they adored and even
16 had plans for a Fourth of July party the day after,
17 family reunions and anniversaries in the coming
18 weeks and months.

19 That my father could be described as

20 someone who would commit suicide is unfathomable to
21 me, but someone that was a murderer is completely
22 unfathomable to me.

0174

1 My father referred to my mom in his
2 retirement speech as the wind beneath his wings. I
3 never saw my mom and dad fight. I never saw them
4 argue.

5 People describe my dad as the best friend
6 anybody ever had. He was buried with full police
7 honors. The police department felt that this
8 wasn't him who committed this.

9 The Catholic Church didn't bury him as a
10 murderer and someone who committed suicide because
11 they did not believe this was something he was
12 capable of.

13 This doesn't just affect the people that
14 it kills. It affects everybody's lives. My life
15 is forever changed because of this incident.

16 (Applause.)

17 DR. PINE: Thank you.

18 The next speaker is Mary Margaret Dick.

19 MS. DICK: I don't like drug companies,
20 and I don't own stock, but I am a consumer of
21 medications. I have had five major debilitating
22 depressive episodes, and I am on social security

0175

1 disability because of it. I hope to make four
2 points.

3 One, that depressive disorders are real
4 medical illnesses, that it can take several months
5 to find the right mix and the right dosage of meds
6 before they even start to work, and that medication
7 alone is only one part of a treatment plan.
8 Therapy, talking to family and friends, getting
9 into a counselor, and lifestyle changes are key to
10 recovery. Monitoring is vital.

11 I learned how to do it with the Families
12 for Depression Awareness' "Depression Wellness
13 Guide." Families need this type of help because
14 the clinicians aren't available to do the
15 monitoring.

16 My first point is that depressive
17 disorders are real and for me require medication.
18 I used the FDA's family tree tool and realized that
19 mental illness ran in four generations of my
20 family, with one suicide. It helped me see that
21 there was a genetic link to my illness and that it
22 was a biologically based medical problem.

0176

1 My second point is that expectations need
2 to be set up with patients. The information that
3 came with my meds led me to believe that the meds
4 alone would fix me, that I would stabilize after
5 taking them for a couple of weeks.

6 When a couple of weeks passed and I still
7 wasn't any better, I became even more depressed. I

8 didn't understand that I may have to try several
9 different meds before I found one that worked whose
10 side-effects I could tolerate.

11 I gained energy but was still having
12 suicidal thoughts that I could now act on. I am
13 now in a meds combination that minimizes both the
14 frequency and the intensity of my episodes.

15 My third point is that medications are
16 only one part of a treatment plan. I was given a
17 treatment plan that included a meds adjustment,
18 ongoing talk therapy, communication with family,
19 and making some lifestyle changes.

20 I now work out three times a week. I eat
21 a healthier diet, and I don't drink. I am learning
22 coping mechanisms in my depression support group,

0177

1 and I make sure I get adequate sleep and downtime.

2 My fourth point is that we patients need
3 specific instruction to be included in the
4 medication information on how to monitor ourselves.

5 All my life I have struggled with
6 depression, yet it was only last year when I used
7 the Families for Depression Awareness' "Wellness
8 Guide" that I understood what I was supposed to be
9 tracking.

10 The FDA Advisory may be our only source
11 of this information because access to qualified
12 clinicians is severely limited. Please include in
13 your advisory specific information on what mental
14 illness is and what we can realistically expect
15 from the medications and that it takes more than
16 medications to recover.

17 DR. PINE: Thank you.

18 The next speaker is Donna Barnes.

19 MS. BARNES: My name is Donna Holland
20 Barnes, president of the National Organization for
21 People of Color Against Suicide. Let me just first
22 say I am extremely sorry and feel empathy for those

0178

1 people who have lost someone to suicide. I also am
2 a suicide survivor. I lost my son in 1990.

3 This is an organization that has for many
4 years spent critical and relentless time educating
5 our minority communities on depression and suicide
6 so that individuals suffering from any mental
7 disorders would understand what it is and that
8 treatment is available.

9 African Americans and/or blacks are the
10 least likely to go to treatment, the least likely
11 to stay in treatment, and the least likely to
12 comply if in treatment.

13 Any mental health challenges that rest in
14 the white communities are amplified in the African
15 American communities. The stigma for taking
16 medication, for instance, is overwhelming.

17 So much so that in a case in 2003 in
18 Prince George's County a young 17-year-old was seen

19 by a psychiatrist who prescribed medication for his
20 diagnosed psychosis. He brought the medication
21 home, showed it to his father who then flushed the
22 medication down the toilet, telling his son that he

0179

1 was not going to take this crap. His son suicided
2 within a month of the incident.

3 In 2004, I conducted a study at the
4 Howard University Mental Health Clinic and
5 evaluated 74 cases of individuals screened positive
6 for bipolar. Sixty-one percent of them were not on
7 any antidepressants or mood stabilizers and over 50
8 percent of them made multiple suicide attempts.

9 In our communities, we are not only
10 concerned about untreated depression that can cause
11 suicide attempts and completed suicides, but we
12 also have to be concerned about mental health
13 disparities and, more specifically, the degree of
14 uncertainty that primary care physicians hold in
15 prescribing antidepressants, since primary care
16 physicians are really the main people that we go
17 through, too, for treatment.

18 If there are bold and aggressive warning
19 signs on antidepressants, antidepressants are not
20 going to get prescribed by the primary care
21 physicians.

22 All the work that we have done educating

0180

1 communities that medication is okay if prescribed
2 correctly and is monitored in a responsible manner
3 will be wasted and set us back 30 years.

4 Finally, I reject with enthusiasm a
5 warning label that is bold and aggressive because
6 blacks already have a high degree of mistrust in
7 the mental health medication medical arena.

8 Primary care physicians are already
9 reluctant to prescribe antidepressants, and a black
10 box will further increase our reluctance to take
11 medication for mental health treatment. The
12 warning sign that it increases the risk for suicide
13 will move my people away from that.

14 DR. PINE: Thank you.

15 The next speaker is Sarah Bostock.

16 MS. BOSTOCK: Five years ago, my life
17 changed forever when my 25-year-old daughter,
18 Cecily, stabbed herself today after three weeks on
19 Paxil. I am sure she would be alive today if she
20 had never taken Paxil.

21 Since that fateful day, I have been
22 warning others and searching for proven ways that

0181

1 SSRIs can do harm. There is good neuroscientific
2 evidence of iatrogenesis, or treatment-induced
3 illness, and adverse effects.

4 However, the most compelling evidence for
5 treatment-induced harm comes from the hundreds of
6 narratives that I have read in the media or heard

7 firsthand from antidepressant users and their loved
8 ones. Patterns of inappropriate dosing, drug
9 induced mania and psychosis, and misunderstood
10 withdrawal and rebound are unmistakable.

11 Few professionals, patients or
12 caregivers, understand the intense activation that
13 can occur when treatment begins or the very slow
14 rate of taper required to get off SSRIs safely.

15 Directors of Drugawareness.org and I put
16 these narratives into a format where their
17 cumulative power could be recognized by creating an
18 online, sortable database, SSRIstories.com. We
19 have loaded over 1,200 media stories dating back to
20 1988 in which antidepressants are associated with
21 an act of violence or bizarre behavior.

22 There are over 200 suicides, 300 murders,
0182
1 100 completed murder/suicides, incidents of road
2 rage, arson, and fraud, 18 school and 14 workplace
3 shootings.

4 Beloved family members including children
5 murdering each other and themselves. Priests, new
6 mothers, scholars, Iraq veterans, and senior
7 citizens -- all dying violently, all were on
8 antidepressants.

9 In many cases, journalists describe
10 behavior consistent with adverse reactions that
11 precede the criminal act, just as Cecily's behavior
12 changed uncharacteristically before her suicide.

13 The narrative details that point to drug
14 effects have been highlighted on the website at the
15 top of each complete story available through a link
16 to the date.

17 Besides some notorious stories and some
18 with celebrities, there are 13 stories in which a
19 jury or judge with medical experts acknowledge
20 causation and legal rulings. Mostly, these are
21 stories of ordinary people: friends, families,
22 neighbors, colleagues. It could happen to any

0183
1 innocent person just as it did to Cecily.

2 SSRIstories.com is our best effort to
3 demonstrate a signal that something is dangerously
4 amiss, not in industry-run trials but in real
5 clinical practice. Read it yourself.

6 No one should underestimate the power of
7 antidepressants to play a causative role in these
8 tragedies. Black box warnings would be one step in
9 the right direction.

10 (Applause.)

11 DR. PINE: Thank you.

12 The next speaker is Kim Witczak.

13 MS. WITCZAK: Hi. My name is
14 Kim Witczak, and I am from Minneapolis, Minnesota.
15 I came here on my own.

16 This (indicating) is Woody, my husband of
17 almost 10 years. Woody was outgoing, gregarious,

18 smart, and full of energy. Everyone loved him. To
19 me he was simply Woody, my best friend and the one
20 that greeted me every day, "Hello, Sunshine."

21 He was guy that I was supposed to have a
22 family and grow old with. However, on August 6,
0184

1 2003, that day it changed. I became a widow.

2 Woody was found dead hanging from the
3 rafters of our garage of Zoloft-induced suicide at
4 age 37. Woody wasn't depressed. He had no history
5 of depression or suicidality.

6 He was just starting his job as vice
7 president of sales with a startup company two
8 months prior and was having trouble sleeping, which
9 is not uncommon for entrepreneurs.

10 He went into his GP who gave him a
11 diagnosis of insomnia and sent him home with a
12 three-week Pfizer sample pack. This sample pack
13 automatically doubled the dose from 25 to
14 50 milligrams after week one.

15 No cautionary warning was given to him or
16 me about the need to be closely monitored about
17 going on the drug or dosage changes. In fact, I
18 was out of the country for the first three weeks he
19 was on this drug.

20 Within days, Woody had the side-effects
21 like profuse night sweats, diarrhea, and worsened
22 insomnia. He also experienced others that were
0185

1 known only to Pfizer, but not to Woody his doctor
2 or his family.

3 Shortly before he died, I found Woody
4 curled up in a fetal position on our kitchen floor
5 with his hands around his head like a vice crying,
6 "Help me, help me. My head is outside my body
7 looking in."

8 Pfizer acknowledges this in an internal
9 document which you guys all have copies of, "It
10 occurs on all SSRIs. We don't know why," the first
11 sentence on the top of that document.

12 Something did not add up with Woody's
13 death. We started searching the only thing that
14 changed during this time, and that was Zoloft.
15 Woody and I never questioned the drug. Why would
16 we? Zoloft is FDA approved and sold as safe and
17 effective.

18 Our journey for the truth has led us to
19 the courts, Congress, and HHS. We were able to get
20 internal confidential documents, ones that are here
21 in my packet to you and other ones that you have
22 not seen.

0186

1 Here is one that came from Pfizer Zoloft
2 U.K. that the Irish Medical Board asked them to
3 give. Look at their clinical studies. The highest
4 percent in Pfizer's study of 31 to 40,
5 50 milligrams, 15 to 30 days -- all three Woody.

6 This next one, in conclusion, this is
7 Pfizer's causality analysis, 54 of the 252 of their
8 case studies were directly related to the event, to
9 Zoloft.

10 We deserve to be told all side-effects,
11 not the ones that you find are acceptable and which
12 ones you want to keep from us because you are
13 afraid to scare us away. Woody deserved it. We all
14 deserve it.

15 (Applause.)

16 DR. PINE: Thank you.

17 The next speaker is Joseph Weiner.

18 DR. WEINER: My name is Joseph Weiner,
19 and I am a psychiatrist on the faculty of
20 Long Island Jewish Medical Center. The American
21 Psychiatric Association is reimbursing me for my
22 travel expenses to this meeting. I have no

0187

1 financial relationships with any pharmaceutical
2 company.

3 I greatly appreciate both this
4 opportunity to share my thoughts with the FDA
5 Advisory Committee and the crucial work you all do
6 in protecting the public's health.

7 The heartfelt stories that are being
8 shared with everyone today further underscores the
9 great importance of the decisions that are going to
10 be made.

11 I have come from New York today because I
12 believe so strongly in the issues at stake. I will
13 share my perspective as a nationally regarded
14 expert in the interface between psychiatric and
15 medical illness. I will also share my personal
16 victory over major depression due in large part to
17 antidepressant treatment.

18 To state my conclusion at the outset, I
19 believe that a black box label will harm a large
20 group of patients both medically and
21 psychiatrically much more than a label would
22 protect people from the possible risk of suicidal

0188

1 thinking.

2 Harm from a black box label will occur
3 because of the following factors. A significant
4 number of primary care physicians will misperceive
5 that antidepressants are too dangerous for them to
6 prescribe.

7 Because most people receive treatment for
8 depression in the primary care setting not from
9 mental health specialists, diminished prescribing
10 of antidepressants would place a large group of
11 people at risk for sustained depression.

12 In addition, strong evidence demonstrates
13 that preexisting depression greatly increases the
14 likelihood for developing atherosclerotic heart
15 disease, cardiovascular disease, diabetes,
16 dementia, and osteoporosis.

17 Once a depressed patient develops a
18 coexisting medical problem, the risk of medical
19 complications, even death, increases dramatically.

20 Therefore, depression worsens medical
21 health. Although we need much more research in
22 this area, there is evidence that the that of

0189

1 depression can improve some medical outcomes.

2 From a personal perspective, I suffered
3 with serious depression from childhood through my
4 early thirties. Although I benefitted greatly from
5 years of psychotherapy, I still had to push through
6 each day because of suicidal thoughts.

7 Sometimes I could not imagine how I would
8 get through the rest of my life. It was only after
9 I was prescribed an antidepressant that I felt the
10 enormous weight of depression lift from my
11 shoulders. I have a second wife.

12 When I told my wife, Lisa, also a
13 healthcare professional that I would be speaking
14 here today, she asked me to tell you that she also
15 conquered serious depression through the use of
16 antidepressant medication.

17 If only our physicians had prescribed
18 antidepressants for us earlier in our lives, we
19 would have avoided many years of excruciating
20 suffering.

21 I hope the Advisory Committee strongly
22 considers the great medical and psychiatric harm

0190

1 from the likely reduction of antidepressant
2 prescribing in reaction to a black box label.

3 DR. PINE: Thank you.

4 The next speaker is Angela Heck.

5 DR. HECK: Hello. My name is
6 Angela Heck. My husband William and I are both
7 here of our own accord from Toledo, Ohio. My
8 husband and I had been together for 12 years at the
9 time he attacked me tried to kill me with a knife
10 (weeping).

11 Approximately, three years ago, my
12 husband was prescribed Paxil for anxiety. My
13 husband is not an alcoholic. He has never tried
14 illegal drugs in his lifetime. In addition, he has
15 no prior history of assault, violence, or
16 aggressiveness issues. He does not have any
17 history of mental illness. He is a normal, healthy
18 male.

19 Do you know what it is like to be trapped
20 in your own bedroom thinking you're going to be
21 wrapped in a blanket and your parents are not going
22 to know what happened to you? Or, do you know what

0191

1 it's like to wonder how you could do something so
2 terrible, so contradictory to your values and
3 beliefs?

4 My husband and I do because of what a

5 well-respected psychiatrist stated in the attached
6 letter regarding the whole incident, and I quote:
7 "I find it to be consistent with
8 dissociative episode and in all likelihood caused
9 by serotonin reuptake inhibitor, Paxil. You are
10 familiar with the details of the unfortunate
11 assault on his wife during that dissociative
12 episode."

13 To this day, he still does not remember
14 what happened on that horrible day. He only knows
15 what has happened from me telling him. This tragic
16 event turned out lives upside down.

17 Resentment and anger do not even begin to
18 describe how we feel towards the makers of these
19 dangerous antidepressants. I always knew that
20 money made the world go around, but I did not think
21 a company was so greedy that they would not care
22 how many people's lives are ruined or lost.

0192

1 I know some people have trouble believing
2 that a drug like Paxil could cause something like
3 this. If it wasn't me and how well I know my
4 husband, I would probably be one of those people.

5 There is no doubt in my mind that these
6 drugs have several terrible side-effects. If I had
7 any doubt, I would not be back with my husband.

8 I also strongly believe that the drug
9 companies are aware of these side-effects as well
10 or they would not have hidden the clinical trials
11 for so long.

12 I strongly urge the FDA to do something
13 about SSRIs and how they are prescribed. These
14 drugs are being given to people as though they are
15 as safe as Tylenol®. We all know this is not the
16 case.

17 Antidepressants are something that either
18 should not be used at all or as a last resort.
19 They have become the first choice for all sorts of
20 problems due to a lot of expensive marketing by the
21 drug companies.

22 We trusted the medical profession, drug

0193

1 companies, and the FDA to give us safe medication,
2 and that obviously has not happened. The drug
3 companies have gained control of the entire process
4 with their deep pockets.

5 We hope and pray that the FDA finally
6 makes a drastic change regarding antidepressants as
7 these drugs are extremely dangerous and family
8 physicians should not be prescribing.

9 Thank you for your time and
10 consideration.

11 (Applause.)

12 DR. PINE: Thank you.

13 The next speaker is Sheila Matthews.

14 MS. MATTHEWS: My name is Sheila
15 Matthews. I am the co-founder of Ablechild.org, a

16 national, nonprofit organization representing more
17 than 10,000 families.

18 Our organization is dedicated to informed
19 consent regarding the subjectivity of psychiatric
20 diagnoses and the dangers of the drugs used to
21 treat them.

22 I also have personal experience with the
0194

1 subject of today's hearing. Two years ago, my
2 brother-in-law, Michael, committed suicide while
3 under the influence of an antidepressant.

4 I'm sure the FDA considers my brother-in-
5 law's suicide, in fact the thousands of
6 antidepressant-induced suicides, anecdotal.

7 However, we the people, the consumers, do not.

8 By the FDA's own admission, only 1 to
9 10 percent of adverse drug reactions are reported.
10 While DTC marketing has skyrocketed the use of
11 psychiatric drugs, international warnings continue
12 to surface.

13 The FDA has done nothing to increase the
14 public's ability to report their adverse drug
15 reactions. You have set up a great deal for the
16 pharmaceutical industry, but a lousy one for the
17 consumer.

18 In accordance with the National Academy
19 of Science, which reported on the importance of
20 postmarketing surveillance, Ablechild conducted a
21 survey of 150 people at the Washington, D.C., Mall
22 this March. Ninety-eight percent had never heard
0195

1 of MedWatch, the FDA adverse reporting system.

2 In June, we helped commission a large
3 study on a thousand people covering all
4 fifty states. Ninety-six percent had never heard
5 of MedWatch, but, most importantly, ninety-seven
6 percent of the public said the government should
7 provide a public service campaign to inform them
8 where they could report drug side-effects.

9 On October 4, 2006, Congressman Dan
10 Burton issued a formal request to the FDA cosigned
11 by several members of Congress. This letter stated
12 that, "Given the results of DTC marketing and the
13 documented risks of the drugs, the FDA should
14 require all drug advertising to include information
15 regarding MedWatch."

16 It said that, "Granting consumers this
17 right would help spot serious side-effects of these
18 powerful drugs much sooner."

19 We agree. You cannot continue to dismiss
20 our reports as anecdotal, for we are in the tens of
21 thousands. It is actually your job to find out how
22 high these numbers go. As Congressman Burton
0196

1 wrote, "We firmly believe that this lack of
2 awareness of the MedWatch represents a threat to
3 the public's overall safety."

4 (Applause.)

5 DR. PINE: Thank you.

6 The next speaker is Mr. Robert Carolla.

7 MR. CAROLLA: Thank you.

8 My name is Bob Carolla, testifying for
9 the National Alliance on Mental Illness. I am a
10 consumer. My life was saved by antidepressants. I
11 have lost friends and colleagues to suicide.

12 I can offer you a before and after
13 perspective. My first major depression occurred in
14 the early 1980s in the era before Prozac. All I
15 got was talk therapy, twice a week with no
16 medication.

17 Every week, I slid farther down. I
18 thought about suicide silently. It was a constant
19 risk. I lost my job and my apartment. I was
20 hospitalized twice for a total of six weeks and
21 unemployed for a year.

22 Following my recovery, largely through
0197

1 the grace of God, I lived without any further
2 treatment until one day 10 years later, while
3 working as a senior aide to the U.S. Senate
4 Majority Leader a slide into depression turned into
5 a psychotic episode.

6 I wandered the streets of Washington,
7 D.C., until I sought refuge in a homeless shelter.
8 That time I was hospitalized for two or three days
9 and started on medication including
10 antidepressants. I was diagnosed with bipolar
11 illness and hospitalized again for a week. In less
12 than a month, I was back at work.

13 My second recovery process still took two
14 years. Thoughts of suicide were part of the
15 territory and it was still a risk. I want to be
16 frank. "Suicidality" and "ideation" are clinical
17 terms, but consumers know what they mean.

18 We talk about them in hospital day rooms,
19 in group therapy sessions, and in support groups
20 nationwide. They mean staring at the approach of a
21 subway train, jogging on a bridge, stopping and
22 looking down.

0198

1 Farther down the spectrum is planning
2 silently, buying an over-the-counter drug, going to
3 sleep with a belt wrapped around the neck, silent
4 contemplation, decision, hesitation, and maybe an
5 attempt.

6 There are risks in any treatment
7 including antidepressants, particularly during the
8 initial period of recovery when medication is still
9 taking effect or being changed and energy and force
10 of will are returning.

11 I believe that causation is a function of
12 the illness, not the medication. Whatever
13 medication risk exists it is exceeded by the risk
14 of untreated depression.

15 During recovery, there is still the risk
16 of relapse and tragically the illness can overwhelm
17 our best efforts, including the medication. Please
18 whatever you do or say don't discourage people from
19 getting treatment and don't stigmatize them.

20 DR. PINE: Thank you.

21 The next speaker is Toby Tyler Watson.

22 (No response.)

0199

1 DR. PINE: Okay. I'll go to the next
2 one. The next speaker is Erin Crowley.

3 MS. CROWLEY: I flew here from Chicago
4 with my brother and aunt to share my mother's,
5 Kathleen Crowley's, story. In late October 2003,
6 my mother was a mentally healthy, vibrant woman.
7 Ten short weeks later, my mother committed suicide.
8 Those 10 weeks tell the story of a woman whose
9 mental and physical health deteriorated at a
10 shocking rate on antidepressants.

11 In late October, my mother approached her
12 general practitioner because she had been
13 experiencing anxiety about selling and moving from
14 her home of 32 years.

15 Her doctor prescribed Lexapro. After
16 four weeks on the medication, my mother
17 discontinued use of her own accord because she was
18 experiencing insomnia; had lost 15 pounds; and, in
19 her own words, preferred anxiety to the agitated
20 mania she experienced on the medication.

21 Over Thanksgiving, just one week after
22 she stopped Lexapro, I noticed she seemed overly

0200

1 anxious and thin, and I suggested she see a
2 psychiatrist.

3 My mother resisted, explaining she felt
4 better before the Lexapro and was concerned a
5 psychiatrist would suggest medication. She feared
6 she could not tolerate the side-effects. On
7 December 10, still struggling with insomnia, she
8 did consult a psychiatrist who prescribed RemeronR,
9 explaining it should help her sleep.

10 The psychiatrist asked her if she was
11 suicidal. Her response was, according to the
12 psychiatrist after her death, "No, it's not in that
13 category."

14 After beginning Remeron, my mother's
15 anxiety worsened drastically. She complained the
16 medication made her feel wired, would go days at a
17 time without any sleep whatsoever, and lost an
18 additional 15 pounds. She diligently stayed on the
19 Remeron, however, because her psychiatrist had
20 assured her that it should kick in, in three
21 weeks.

22 Upon coming home for Christmas, I could

0201

1 not believe the sudden change in my mother. She
2 was no longer just anxious. She had completely

3 transformed into an emaciated woman who paced the
4 floors, picked her skin, barely slept, and
5 struggled to perform the simplest tasks like
6 cooking a meal.

7 The mother I had known for 29 years who
8 went on daily walks, had a full social calendar,
9 and always worked now avoided leaving the house,
10 stopped returning phone calls, and had decided to
11 quit her job because of her extreme agitation. This
12 drastic change literally happened between
13 Thanksgiving and Christmas.

14 On January 2, only her second appointment
15 with the psychiatrist, her psychiatrist instructed
16 my mother to stop taking Remeron immediately and
17 prescribed Effexor. Six days later, she hung
18 herself. She left no note and never expressed any
19 suicidal thoughts to anyone.

20 One week before her death, convinced the
21 medication was causing my mother's extreme
22 agitation, I went online to research Remeron. The

0202

1 only information I found assured me Remeron was
2 safe and would kick in after an adjustment period.

3 If my family had any idea that some
4 patients simply cannot tolerate the side-effects
5 and can become suicidal on antidepressants, we
6 never would have encouraged my mother to stick it
7 out. Suicide was not on her radar screen until
8 medication was introduced to her.

9 (Applause.)

10 DR. PINE: Thank you.

11 The next speaker is Andy Vickery.

12 MR. VICKERY: My name is Andy Vickery. I
13 am a trial lawyer from Houston, Texas. Many of the
14 people that you have heard from or will hear from,
15 the victims of SSRI-induced violence and suicide,
16 are my friends and clients.

17 I wish they didn't have to meet me in
18 that way. I wish that I didn't have to answer the
19 question for them of where is the justice in the
20 "justice for all" when they have lost someone close
21 to them.

22 I am supposed to compress about twelve

0203

1 year's worth of my professional life into three
2 minutes today, and I don't know how to do that
3 really, so let me make as many points as I can.

4 First, Dr. Clayton is right, do no harm
5 -- no harm. Don't balance that you might maybe do
6 some benefit to someone else -- do no harm.

7 Secondly, I have provided you with a
8 written statement that's called "Needle in the
9 Haystack." They are not my words. They are the
10 words of Charles Beasley at Eli Lilly in 1990 when
11 they looked at this, and he said:

12 "If you want to see if this is a real
13 phenomenon, don't look at the clinical trial data.

14 It's not there. You won't find it there. It's
15 like looking for a needle in a haystack because
16 these trials were not designed to measure it."
17 What have you done for the last two
18 years? You have done precisely that, you have
19 looked for the needle in a haystack, in a place
20 where it is not likely to be in the first place.
21 You have looked at a hundred thousand patients, and
22 you have ignored the millions of patients.

0204

1 Why do you have a MedWatch system? Why
2 did you abandon some years ago the FDA causality
3 algorithm that was used to assess causality? Assess
4 causality on these "anecdotes." These are not
5 anecdotes, and these deaths are neither significant
6 statistically, Dr. Stone, or otherwise.

7 Why did you abandon the FDA causality
8 algorithm that you used to assess these events when
9 Dr. Temple and Dr. Laughren started with the FDA?
10 Because if you take the published literature, if
11 you take Anthony Rothschild's article in '91 that
12 shows akathisia and suicide, and if you subject it
13 to the causality algorithm that the FDA itself
14 used, it will show that it is highly probable that
15 the akathisia and the suicidality experienced by
16 the three patients that these Harvard
17 psychopharmacologist rechallenged was probably
18 caused by the Prozac.

19 That was 15 years ago. Fifteen years ago
20 when this Committee was summoned, the issue was
21 swept under the rug, and a lot of people have died
22 since then.

0205

1 I wonder, as I read the report, why you
2 have been summoned 12 days before Christmas on
3 short notice this year? The FDA says the Advisory
4 Committee isn't even going to be asked for advice.
5 You might ask yourself, Why are we being
6 summoned? Are we being used in some way before the
7 change in the Congress in January? What's going on
8 here?

9 (Applause.)

10 MR. VICKERY: In 1991, this gentleman
11 right here (pointing) before he became a paid
12 expert for Pfizer and GSK wrote, "From making the
13 cure more grievous than the disease, good Lord,
14 deliver us." You deliver us.

15 (Applause.)

16 DR. PINE: Thank you.

17 The next speaker is Mr. John R. Hays.

18 DR. HAYS: Good morning. I am
19 Dr. John Hays. I am a physician trained in
20 internal medicine and psychiatry. I have been in
21 clinical practice, a medical academic, the
22 president of a Catholic hospital system, and for

0206

1 just the past eight years I've worked for Eli Lilly

2 & Company where I am vice president for Lilly
3 Research Laboratories.

4 I joined Lilly because they gave me the
5 opportunity to do work that might influence the
6 mental health of millions of people. Still, I
7 speak to you today in my identity as a clinician
8 who has spent many hours with depressed people just
9 one at a time. It is they who have most shaped my
10 career.

11 I have not come to discuss Lilly's
12 extensive research in the area under discussion,
13 rather I will urge a very deliberate course to
14 avoid bringing unintended harm to the patient's we
15 all wish to protect.

16 Depression is recognized as one of the
17 most serious and economically burdensome illnesses
18 in the world. Effective treatment exists and yet
19 irrational fears and stigmas still discourage
20 recognition and treatment of depression.

21 Seeking help for depression requires
22 courage. A depressed person must overcome fear and

0207

1 embrace hope to seek help. Even accepting help is
2 difficult for depressed people who may feel that
3 they are unworthy or hopeless.

4 Treating depression also requires
5 courage. Caregivers must also overcome fear of
6 criticism or litigation, embrace hope themselves,
7 and prescribe treatment whenever needed.

8 We, all of us in healthcare, must not
9 dash that often fragile courage. We must do
10 whatever we can to help depressed patients and
11 those who care for them to address the illness in
12 an atmosphere of rationality.

13 We now believe that doctors and patients
14 confronted by warnings about a real but infrequent
15 risk have lost some of the courage as a result of
16 those warnings and the media attention that has
17 surrounded them.

18 Scientists such as Drs. Valuck, Gibbons,
19 Mann, and others who have done elegant work to
20 assess this are speaking. Please heed them. Their
21 findings of the unintended, negative impact of the
22 previous warnings are alarming.

0208

1 Eli Lilly & Company applauds the FDA's
2 efforts to draw credible inferences about a
3 critical public health issue from such a large data
4 set.

5 Please use this opportunity to
6 communicate about depression with the same kind of
7 rationality that exists in other areas of medicine
8 and to foster more understanding rather than more
9 fear and stigma.

10 We urge you to be clear about the
11 infrequent occurrence of the risks under
12 discussion. We urge you to align any warnings to

13 the magnitude of risk and the benefits.

14 Also, we urge you, if you make treatment
15 recommendations, to make recommendations that
16 doctors, patients, and families can actually
17 implement in today's healthcare environment.

18 Thank you for your time, and thank you
19 all for your courage in considering this
20 complicated issue in such a public forum.

21 DR. PINE: Thank you.

22 Heidi Bryan is the next speaker.

0209

1 MS. BRYAN: My name is Heidi Bryan. I am
2 48 years old, and I have battled with depression
3 most of my entire life. Antidepressants saved my
4 life.

5 I first began a course of tricyclic
6 antidepressants approximately 25 years ago after
7 almost killing myself during a major depressive
8 episode. The antidepressant changed my life and my
9 mood and I was able to go on living.

10 After a few years, I stopped taking them
11 and battled on and off with depression.
12 Eventually, I suffered another major depressive
13 episode and was given Zoloft then Paxil. I was on
14 Paxil for about a year but felt no real sustainable
15 benefit and stopped taking it.

16 Finally, I entered a drug study for an
17 MAOI patch and my mood and my life improved
18 dramatically. The study ended and I was placed on
19 an oral MAOI which worked but would lose its
20 efficacy, so periodically the dosage was increased
21 and a catalyst added until I reached maximum
22 dosage.

0210

1 When it bottomed out again, I changed
2 doctors and was placed on Wellbutrin. That was
3 over four years ago, and I have been on WellbutrinR
4 the entire time.

5 I was never more suicidal while either
6 beginning to take or taking the antidepressant.
7 As I said, I know the medication saved my life. I
8 do not believe there is an increased risk of
9 suicidality with antidepressants if they are
10 administered properly.

11 In my opinion, the problem stems from
12 lack of mental health insurance parity. The
13 average person can't afford to go to a psychiatrist
14 or there isn't one available in their plan in a
15 timely manner, so they go to their primary care
16 physician.

17 Oftentimes, the primary care physician
18 hasn't had the education in dispensing psychiatric
19 medication, and therefore doesn't titrate the
20 dosage to monitor the patient and manage the side-
21 effects. The full dosage is given immediately, and
22 that can have a significant effect on one's mind

0211

1 and body.

2 I also don't believe there has been
3 enough data on this topic, but I'm not a
4 researcher. I just know what I know, and I cannot
5 emphasize enough the fact that antidepressants
6 saved my life and gave me a new life.

7 I began thinking about suicide when I was
8 around 11 years old and, as I aged, that happiness
9 was just for other people. I accepted that as part
10 of my fate.

11 Because of the medication, I now know
12 what happiness is and have experienced it on a
13 daily basis. I now look forward to each day
14 instead of waking up and wondering if today is the
15 day I'm going to die.

16 I am afraid a black box warning will turn
17 people away rather than encourage them. This is
18 already a population plagued by lethargy,
19 indecision, fear, and shame.

20 I know antidepressants work and save
21 lives, and I want as many people as possible to
22 know that, too. We have enough obstacles in

0212

1 obtaining help for our condition. We don't need
2 another one added to the list.

3 Thank you.
4 (Applause.)

5 DR. PINE: Thank you.
6 The next speaker is Donald Farber.

7 MR. FARBER: I am Don Farber from
8 San Rafael, California. I have handled
9 antidepressant cases for about seven years. I
10 appreciate every speaker this morning. Certainly,
11 in my own mind, they are very sincere,
12 distinguished ladies and gentlemen, but this is
13 America.

14 I don't know how many people of good will
15 here want to manipulate the system. There are
16 psychiatrists who say "We know everything, and 60
17 percent of the GPs that prescribe these
18 antidepressants they don't know anything even
19 though they went to medical school."

20 This is America. Every individual has
21 the right to make decisions for themselves. Every
22 physician has the right. I am very surprised that

0213

1 all, mostly psychiatrists get up here and want to
2 filter information away from the GPs. They should
3 have all of the information.

4 I do appreciate the panelists, very
5 distinguished panelists. My question to the FDA
6 is, Where are the other panelists? Where are the
7 other panelists on the black vote?

8 In the black box vote on September 14,
9 2004, it was fifteen to eight. The ten
10 psychiatrists split, five/five on the vote. It
11 gives you an indication there your dealing with the

12 issue.

13 Of all the eight pediatricians, all eight
14 voted for the black box. I say I appreciate your
15 input, but we're not getting the right input for,
16 as Bill Clinton said, "It's the labeling, stupid."

17 This data is inside baseball, very
18 valuable, it's got a place, but we are all talking
19 here about labeling for the GPs. I think the GPs
20 and the labeling is only the real issue today.

21 You have to be honest. You have to get a
22 bucket full of or a barrel of information into a

0214

1 little label and it has got to be accurate. It has
2 to be accurate.

3 In the past, the FDA has withheld
4 unfavorable information on the antidepressants, and
5 they are still doing it. You never put in the
6 label that these trials were never designed to pick
7 up suicidality. You never put that there are
8 sedatives used to get the drugs through the trials.
9 You have never put the failed trials.

10 On October 10, 2002, the FDA suppressed
11 all the MDD failed studies on Paxil. They weren't
12 going to tell the providers of the failures. The
13 only reason the label came in later was because the
14 British blew the whistle.

15 I am sure they had a reason for it.
16 There are reasons I suppose that good drugs do fail
17 trials. However, this is the type of information
18 GPs need. Be honest in the label. I'm not going
19 to sit here and say I want a black box, but be
20 honest in the label.

21 (Applause.)

22 DR. PINE: Thank you.

0215

1 The next speaker is David Healy.

2 MR. HEALY: Hello, Colleagues. Could you
3 have a quick look at the first slide there?

4 (Slide presentation in progress.)

5 MR. HEALY: "Truth is stranger than
6 fiction."

7 "Well, of course it is," said Mark Twain.
8 "Fiction has to make sense."

9 The question is, What would Mark Twain
10 have classified this posting from the FDA as?
11 Truth or fiction?

12 That is the distribution of the suicidal
13 acts that happened in the registration trials of
14 these three drugs here. Slide 2, and I do not know
15 how to move the slides forward.

16 (FDA staff complies.)

17 DR. HEALY: Yes. This is how the company
18 reports, FDA reviews the drug, and journal articles
19 report those acts. You referred earlier to the
20 Fergusson, et al., article, of which I am a
21 coauthor.

22 We had to cope with this. We didn't undo

0216

1 this particular bit of bias to come to the results
2 we had. The results we had would have been worse
3 if we had undone this.

4 You referred to the MHRA article. Well,
5 MHRA included three placebo suicides that weren't
6 placebo in clinical trials. People who a week
7 after going on Prozac went on to commit suicide.

8 Dr. Laughren has an article from 2001 in
9 which he is the author that repeats this mistake.
10 Dr. Laughren in this particular document here gives
11 you no hint that all of the articles that he refers
12 to showing that there is no increase in risk also
13 repeats the mistake that you see here.

14 Now, this is the most interesting slide.
15 This you won't have seen perhaps. This is data
16 from three and a half years ago. This is data from
17 FDA that FDA put in the public domain. This shows
18 you a clearly, statistically significant increase
19 risk of suicide.

20 FDA said three and a half years ago, "But
21 we can get this risk to go away if we control for
22 age and sex."

0217

1 Now, controlling for age and sex in
2 controlled RCTs to begin with suggests you're doing
3 something awfully odd, that the clinical trials
4 were invalid to begin with.

5 The FDA also said that when we control
6 for location, if that actually makes a difference,
7 and this year FDA reported that when you look at
8 the clinical trials that happened in the U.S. here,
9 the placebo-controlled trials, that there were
10 fewer people who went on to actually commit
11 suicide.

12 I am sure you know that there are
13 clinical trialists here in the U.S. who have ended
14 up in jail for entering fake patients into this
15 clinical trial program.

16 Fake or bogus patients do all sorts of
17 interesting things. They get well on treatment.
18 They don't commit suicide. It is just inconvenient
19 for the audit trail, if they do. Does this explain
20 FDA's findings?

21 I think you have asked the right
22 questions. You have asked, Why has FDA left out

0218

1 the people who seem to be doing poorly, the people
2 who drop out from the trials?

3 (Applause.)

4 DR. PINE: Thank you.

5 The next speaker is Lee Spiller.

6 MR. SPILLER: My name is Lee Spiller. I
7 am with Citizens Commission on Human Rights.

8 (Slide presentation in progress.)

9 MR. SPILLER: Somebody came up with the
10 idea that somehow antidepressants were keeping kids

11 from committing suicide as much or that the black
12 box warning would make them not try to commit
13 suicide.

14 This data out of Oregon shows otherwise.
15 That is from 1994 to 2004. I honestly think that
16 we wouldn't see much change in that trend. Had the
17 black box warning not gone on, I think they still
18 would have been committing suicide.

19 I am waiting for the remote here. Yes,
20 thank you.

21 (FDA staff complies.)

22 MR. SPILLER: The other thing is this.

0219

1 Suicides have remained relatively steady, but
2 suicide attempts are increasing incredibly. In
3 2000, there were 97 suicide attempts for 100,000.
4 By 2005, it was 135.12. That is a major jump. If
5 there is any chance that antidepressants are
6 causing that, we need to know.

7 In 2004, 26,787 antidepressant-related
8 suicide attempts entered an emergency department.
9 That is one every 20 minutes, 75 a day, 515 a week.

10 There were more antidepressant-related
11 suicide attempts entering emergency rooms than
12 there were attempts related to heroine, marijuana,
13 amphetamine, methamphetamine, LSD, PCP, club drugs,
14 and inhalants combined.

15 However, actual mortality is scary, too.
16 New York, New York, 59 drug-related suicides,
17 29 involved antidepressants; Houston, Texas,
18 89 drug-related suicides, 28 involved
19 antidepressants; Washington, D.C., 36 drug-related
20 suicides, 18 involved antidepressants; Portland,
21 Oregon, 27 drug-related suicides, 14 involved
22 antidepressants. That was in 2003. That comes

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1 from good data. It isn't something we just made
2 up. That data comes from SAMHSA.

3 The National Violent Death Reporting
4 System has started to come on line. They are not
5 in all states yet, but one of their preliminary
6 report said something interesting. Fifty-eight
7 percent of suicides that they examined involved
8 people who were already on a prescription for a
9 mental health drug.

10 You guys have known about the
11 antidepressants for years. I remember the original
12 hearings. It is time to go ahead and warn people.
13 We can take it. It is time to go ahead and put a
14 black box on these drugs.

15 Thank you.

16 (Applause.)

17 DR. PINE: The next speaker is
18 Carolyn Robinowitz.

19 DR. ROBINOWITZ: I am a general child and
20 adolescent psychiatrist practicing in Washington,
21 D.C., since 1968, speaking as a clinician. I don't

22 receive any funding from industry.

0221

1 As we know, depression is a chronic,
2 recurring, and progressive illness that has a major
3 negative impact on the quality of life of those who
4 suffer from it and their families in society as a
5 whole.

6 Depression is the leading cause of
7 disability according to the World Health
8 Organization. Depression can be lethal. Persons
9 with untreated depression face a 15 percent greater
10 likelihood of dying by suicide.

11 Science and clinical practice have
12 repeatedly shown that depression can be reliably
13 diagnosed and effective treatments are available
14 and that medication is often a vital tool in its
15 treatment. These medications have revolutionized
16 treatment and outcome for millions.

17 The suicide rate in the U.S. has been on
18 the decline since the SSRI antidepressants were
19 introduced in the late eighties. In areas of the
20 country where rates of SSRI prescriptions are
21 highest, rates of completed suicide are among the
22 lowest.

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1 Now, we need to be clear on the use of
2 the term "suicidality," clarifying a major
3 difference between suicidal thinking, suicidal
4 actions or attempts, and completed suicide.

5 Of course, my heart goes out to those who
6 have lost a loved one. That is truly a tragedy.
7 It has to be prevented wherever possible. However,
8 suicidal thoughts are a red flag to clinicians and
9 family members alike.

10 Now, all medications, not just
11 antidepressants but anticancer medications and even
12 over-the-counter drugs such as aspirin, have side-
13 effects. Their use must be considered clinically
14 in terms of potential benefit and risks, risks of
15 not treating as well as risks of treatment.

16 Patients must be counseled on medication
17 side-effects and possible adverse reactions of all
18 sorts, and clinical care requires appropriate
19 monitoring.

20 Unfortunately, the FDA's imposition of
21 the black box label has resulted in unintended
22 negative consequences restricting access to care

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1 and adding to risk without providing measurable
2 benefit.

3 Since the black box, there has been at
4 least 20 percent reduction in prescribing. CDC has
5 reported an increase in completed suicides,
6 reversing the downward trend of the past decade.

7 The black box has contributed to further
8 stigmatization of depression, those who suffer from
9 it, and its treatment with unwarranted fear, black

10 box panic for families who now view these
11 potentially life-saving treatments as highly
12 dangerous.

13 On a personal note, I have seen the
14 benefits of treatment for my family members,
15 colleagues, and friends, as well as my patients.
16 Regulatory decisions need to be based on science,
17 not emotion and not politics. I urge you to be
18 careful to avoid unintended consequences in the
19 labeling.

20 Thank you.

21 DR. PINE: Thank you.

22 The next speaker is Sheri Walton.

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1 MS. WALTON: My name is Sheri Walton. I
2 have major depression, and I am one of millions of
3 people who take antidepressant medication to
4 control depression.

5 I am here today to share my story and to
6 urge you to consider the harm that any changes in
7 labeling or access to antidepressant medication may
8 cause. Suicide claims the lives of 30 million
9 Americans each year.

10 Major depression, the most treatable of
11 all mental disorders, is the leading cause. The
12 one and only time I attempted suicide I was not
13 taking antidepressant medication. I was in my
14 early twenties and was severely depressed.
15 Luckily, I survived.

16 Though I did not yet realize it, I was
17 and had been suffering with undiagnosed and
18 untreated depression for most of my young life.
19 Because no one took my suicide attempts seriously
20 and because no one in the medical profession
21 followed up with me, my depression remained
22 undiagnosed for another 20 years.

0225

1 To the outside world, I had a successful
2 career, an active social life and lots of friends,
3 but I was moody, sad, and quick-tempered, and true
4 happiness always seemed to elude me.

5 Like all chronic diseases left untreated,
6 depression is progressive. As my life progressed,
7 my depression progressed until it took over my life
8 and, unfortunately, my husband's life and my
9 children's lives.

10 When I was finally diagnosed with major
11 depression, I was 42 years old and my life was out
12 of control. I was always angry. I cried for no
13 reason. I forgot things, misplaced and lost
14 things. I could hardly get out of bed each day. I
15 felt like a total failure.

16 Antidepressant medications saved me.
17 Along with therapy, medication gave me back my
18 life. It gave my children back their mother. It
19 gave my husband back his wife. For the first time
20 in my life I have self-esteem, and I know what it

21 is to feel true happiness.

22 I was lucky. I had the resources to go

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1 around my insurance company and seek out a mental
2 health professional who helped me find the right
3 medication that worked best for me and who educated
4 me on the risks and possible side-effects, not
5 everyone is as fortunate.

6 As the "gatekeepers of treatment,"
7 insurance companies often direct diagnosis and
8 treatment to primary care providers who are not
9 trained mental health professionals and are not
10 always knowledgeable and up to date on medications
11 and their side-effects.

12 Without antidepressant medication, I
13 would not be standing here today. Antidepressant
14 medication is a critical and effective tool for
15 fighting depression, yet fewer than half of
16 Americans with depression seek treatment. For
17 those that do, adding unnecessary warnings may
18 scare them, their family members, and the doctors
19 treating them away from their proven, prescribed
20 treatment.

21 Access to mental health professionals and
22 better monitoring and education of patients taking

0227

1 these medications about the risks and benefits of
2 treatment would be preferable to any action that
3 could negatively affect the millions of people who
4 need treatment, putting them at risk of the very
5 problem this Agency is trying to avoid, suicide.

6 Thank you.

7 DR. PINE: Thank you.

8 The next speaker is Jayne Richner.

9 MS. RICHNER: On August 16, 120 days ago
10 today, our lives were shattered beyond any words I
11 can express to you today. Our beloved 22-year-old
12 son, Sean, was horrifically killed and we were
13 brutally robbed. Sean had no history of
14 depression. He had visited his primary care doctor
15 just for general situational anxiety in which he
16 was given a 90-day prescription of Celexa in a
17 10-minute office visit.

18 After being on these for approximately
19 two and a half months, he could no longer sleep.
20 His mind kept racing and thinking all the time,
21 among other effects.

22 He went to his doctor, as a result of

0228

1 these feelings, four weeks prior to this death.
2 His doctor recommended no further medication and
3 said these are side-effects and they should resolve
4 themselves in three to four weeks.

5 We and Sean trusted that the FDA and the
6 doctors are educated and well-informed about these
7 drugs and the risks and dangers in order to be able
8 to prescribe these. We now know how wrong we were.

9 Without a doubt, we stand before you
10 today knowing Sean was a victim of the withdrawal
11 effects of discontinuing the antidepressant,
12 Celexa, suicide by hanging in the middle of the
13 night in our home.

14 At only 22 Sean had the world in his
15 palms of his hands. He worked for almost two years
16 in a high-tech company, my company. He has his car
17 and his dream bike paid for.

18 He was pursuing a career as a
19 firefighter. He was enrolled in an EMT paramedic
20 program and was in the top of his class with one
21 month left to go. The state trooper teaching his
22 class is devastated by this and has awarded Sean

0229

1 all of his certificates.

2 Sean was also in training with the local
3 auxiliary fire department and had just received his
4 protective gear, which he proudly wore. He had
5 taken the Firefighter Civil Service Exam in June.
6 We just received his score result of 91 last month.
7 Sean would have been excited and proud, although he
8 knew he aced it when he took it.

9 Sean had it all going for him and he knew
10 it. He was excited that he had a direction, and
11 that it was all falling into place. He was
12 articulate. He was outgoing and social with a
13 sense of humor and a smile that drew everybody to
14 him. He was athletic, played the guitar, and
15 sang.

16 He openly loved his family, his future,
17 and his friends -- who are all as devastated as we
18 are knowing this is incomprehensible. Sean loved
19 life.

20 Sean did not choose to end his life.
21 That was done for him by the drug-induced fatal
22 withdrawal effects of the antidepressant that he

0230

1 was prescribed.

2 A few nights prior to his death he
3 appeared to be disconnected and then could be in
4 and out of altered states. He jumped out of a
5 second-story bedroom window and then requested that
6 a friend stay over with him.

7 He was extremely restless and agitated as
8 he slept and then awoke during the night and had to
9 keep moving around. No one knew what was wrong.
10 We now know this is referred to as akathisia. He
11 was found kneeling at his bed with his hands
12 clenched over his head.

13 When we found him, his feet were touching
14 the floor. We can't imagine the psychotic state he
15 must have been in. Without a doubt, Sean had no
16 control over this and was overtaken by these drugs.

17 (Applause.)

18 DR. PINE: Thank you.

19 The next speaker is Nancy Sharby.

20 MS. SHARBY: Good morning. Thank you for
21 allowing me to come. I am truly moved and very
22 saddened by the story of the woman and the family

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1 who spoke before me, but I have a very different
2 story.

3 I come here today from Boston,
4 Massachusetts, but I really come from a farther
5 place than that. I come from a place that has a
6 long legacy of mental illness and suicidality.

7 In 1915, my great-grandfather walked into
8 his kitchen, and while his family was eating
9 dinner, he drank a bottle of lye. My grandmother's
10 brother committed suicide; my grandmother attempted
11 suicide; and my mother was suicidal. For all of
12 them, there was no effective intervention nor
13 effective treatment, but we are different.

14 I have two children with bipolar
15 disorder, and I have depression myself. My
16 daughter was diagnosed at 17, although she was sick
17 for many years before that. My son was diagnosed
18 at 19.

19 Both of them have told me that if it were
20 not for my efforts of extensive advocacy and
21 intervention for them, they would not be alive
22 today.

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1 My daughter has told me she is eternally
2 grateful for interventions on her behalf, even
3 though there were times when she looked at me and
4 told me how much she hated me for dragging her to
5 all of her clinicians.

6 Both of them have been hospitalized on
7 numerous occasions as we attempted to stop their
8 downward spiral into self-destruction. We are
9 extremely fortunate that we have fabulous
10 clinicians who are able to work with them and to
11 prescribe effective psychotropic medications.

12 The only reason they are alive and
13 thriving today is because of the integrated effects
14 of family collaboration, my children's
15 collaboration, and effective care by their care
16 providers.

17 I can speak personally of the effects of
18 depression on myself. It is not a matter of being
19 sad or unhappy or sometimes feeling unmotivated.
20 Depression takes you to another altered state where
21 you aren't able to think, to remember, to make good
22 decisions, or to express any joy in life. There is

0233

1 no hope that tomorrow will be any better than
2 today. It disorganizes your brain.

3 Clearly, depression has a high personal
4 cost, but it also has a high cost to society as
5 well. As I mentioned before, there was high loss
6 of work or productivity, there was decreased
7 ability on disability claims, high health insurance

8 costs, and traumatically shattered families.
9 The good news is that depression is a
10 treatable disorder, and there are many effective
11 treatments available. However, no medication is
12 effective for every person, and each medication is
13 to be carefully calibrated to meet the exact needs
14 of the individual who gets them.
15 I have to say in my family we have
16 definitely needed to adjust medications. It can
17 only happen when treatment is effectively monitored
18 by the family, the care provider, and the patient
19 alike.
20 Please do not set any barriers in place
21 for effective treatment of patients who can benefit
22 from drug rehabilitation.

0234

1 Thank you.
2 DR. PINE: Thank you.
3 The next speaker is Vera Sharav.
4 MS. SHARAV: Our organization
5 disseminates credible information to challenge such
6 reassuring documents as this report. I am
7 overwhelmed to hear people worry about informing
8 about risks. What is important is that the
9 information in the black box is accurate.
10 In 1991, the FDA withheld evidence of
11 suicides from the Advisory Committee. German
12 documents revealed increased suicides in Prozac, so
13 did FDA's own safety review. Confirmatory evidence
14 from Pfizer and Glaxo were withheld from the
15 Committee. FDA argued against warnings.
16 In 2003, it was the U.K. who issued the
17 contraindicated warning against using any
18 antidepressants in kids except Prozac. FDA did not
19 issue a black box warning until Eliot Spitzer
20 brought legal action against Glaxo.
21 Agency officials continued to obscure the
22 scientific evidence with reassurances. They failed

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1 to acknowledge suicides such as Tracy Johnson, a
2 healthy volunteer.
3 In May, Glaxo finally acknowledged that
4 the suicide risk extends to adults. FDA's review
5 is about damage control. It is designed to
6 minimize and distort.
7 How did FDA reduce 16 suicides in 40,000
8 patients to 8 suicides in a 100,000 patients?
9 Where did 4 Zoloft suicides and 13 attempts
10 disappear? Shouldn't FDA analyze the very studies
11 that have the most occurrences of these risks?
12 To exclude events which occurred during
13 discontinuation periods and during dose tapering is
14 dubious. That is when patients are at greater
15 risk, and the label says so. The possibility that
16 a five-fold, even a seven-fold increase risk of
17 suicide can be described as "no effect" is
18 unbelievable.

19 What the FDA presented to you is a
20 reassuring interpretation of selected data by the
21 very officials who have dodged the issue for 15
22 years claiming it is the condition, not the drugs.

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1 What the FDA did not show you is evidence
2 to support that SSRI safety for any age group or
3 any indication. They are all at risk. They failed
4 to provide you a complete SSRI data analysis.

5 They failed to provide you peer-reviewed
6 critical analyses by independent scientists who
7 have been proven right. FDA was wrong then; it is
8 wrong now. Don't collaborate in this.

9 (Applause.)

10 DR. PINE: Thank you.

11 The next speaker is Kendrick Moxon.

12 MR. MOXON: My name is Kendrick Moxon. I
13 am counsel to the Citizens Commission on Human
14 Rights established in 1969 as a mental health
15 watchdog.

16 After the first SSRI drug, Prozac, was
17 approved by the FDA, CCHR began receiving
18 complaints from consumers. In 1990, we submitted a
19 petition on behalf of many of its victims to
20 withdraw Prozac from the market.

21 In '91, the head of the statistical
22 section of the FDA informed us that Prozac had the

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1 highest number of adverse event reports ever
2 submitted to the FDA.

3 As of 1991, the FDA had received over
4 17,000 adverse reaction reports for Prozac
5 including 60 deaths, nearly 500 cases of psychosis,
6 and 991 suicide attempts.

7 In August '91, the FDA responded saying
8 this was not unexpected for a drug that had been
9 the subject of intense public interest. In other
10 words, the FDA believed it was acceptable for a
11 substantial percentage of consumers to attempt
12 suicide.

13 The FDA stated it would convene a hearing
14 to review all pertinent data on the relationship
15 between the drugs and suicidality, but an honest
16 and genuine review of relevant data did not happen.

17 CCHR lodged a complaint with the FDA
18 because two of the 1991 committee members had
19 conflicts of interest by receiving funds from
20 Eli Lilly.

21 The FDA ignored that conflict of these
22 two members and admitted that five other members

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1 had conflicts of interest and simply provided them
2 waivers of criminal prosecution. Thus, at least 7
3 of the 10 members on that Committee had conflicts
4 of interest that should have barred them from
5 participating.

6 The panel acted in the interest of their

7 paychecks, not in the public interest. Seventeen
8 thousand adverse reactions were brushed off as
9 anecdotal, justification for misfeasance, which is
10 still being used, Dr. Laughren.

11 Worse, every single one of these
12 conflicted committee members in the `91 hearings
13 voted not to change the labeling for the SSRI
14 drugs. The three members who were not conflicted
15 voted to strengthen the warning labels.

16 Let me repeat that. One hundred percent
17 of the members who voted against a stronger label
18 had conflicts of interest. One hundred percent of
19 those not conflicted wanted to give consumers more
20 knowledge.

21 I brought DVDs of CCHR's video footage of
22 those 1991 hearings and I have provided copies for

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1 everyone on the Committee and for the media, if I
2 wish them, to illustrate that nothing has changed.

3 You have again chosen three persons to
4 whom you had to give conflict waivers of criminal
5 prosecution for their admitted conflicts of
6 interest.

7 Dr. Laughren's comment from the 1991
8 Committee, they felt no change was needed for SSRI
9 labeling is most disingenuous. That Committee had
10 a terminal case of conflict of interest and bias,
11 and so does this one. It is clear that many more
12 must die before impartial officials take the reins
13 in this Agency.

14 (Applause.)

15 DR. PINE: Thank you.

16 The next speaker is David Shern.

17 DR. SHERN: Hi. I am David Shern. I am
18 the president and CEO of Mental Health America,
19 which was formerly known as the National Mental
20 Health Association.

21 I joined Middle Health America or the
22 NMHA on September 5, the first workday after Labor

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1 Day, giving up a tenured, full-professor position
2 as a dean at the University of South Florida, the
3 Florida Mental Health Institute.

4 I did that because of family experiences,
5 my nephew having trouble ascertaining adequate care
6 for some very serious behavioral problems he was
7 having even though we knew all of the best people
8 in the United States who were delivering care to
9 children.

10 Out of a commitment to do more than I
11 thought I could do as a professor and as a dean to
12 sort of move science in to action, having my own
13 family experiences as well as knowing many, many
14 other people who have, I am deeply moved by all the
15 stories that we are hearing today.

16 I am deeply moved by the people whose
17 lives have been saved by pharmacological treatment

18 and by those families who have experience profound
19 tragedies associated with that treatment.

20 For me the moral of the story, and many
21 people have made this point as they have spoken
22 today, is the importance of informed choices and

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1 good information for people.

2 It is also quite important for us I think
3 to understand and act on the public health
4 consequences of our decisions. This is a difficult
5 calculus; it is not a simple calculus.

6 I am quite impressed by Dr. Mann's and
7 Dr. Gibbons' work showing that a decrease in the
8 use of SSRI following the black box warning, that
9 the 22 percent decrease might be attributable to
10 200 excess deaths from suicide. It is very
11 important that we balance this equation, and it is
12 a very difficult decision.

13 I think that the data are reasonably
14 clear that the availability of SSRIs has been
15 clearly associated with a decrease in suicide. We
16 look at ZIP code data with regard to the
17 penetration of SSRI prescriptions.

18 We see that there is also an association
19 between the availability or use of those drugs and
20 decreasing suicide. The CDC's report of an
21 increase after several years of decrease of suicide
22 in adolescents has got to cause great pause.

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1 I don't envy you your decision. It is a
2 very difficult one. On balance for me, the issues
3 are raising the bar in terms of the quality of care
4 that people receive. That is a resident theme
5 which occurs in almost every testimony that we have
6 heard today.

7 Informing the public about the possible
8 risks and benefits for treatment, informing
9 clinicians about that treatment and doing in a way
10 that promotes the public health, I think on balance
11 a black box warning for adults would not promote a
12 public health objective.

13 Thank you.

14 (Applause.)

15 DR. PINE: Thank you.

16 The next speaker is Alison Malmon.

17 MS. MALMON: Good afternoon. My name is
18 Alison Malmon, and I am the founder and president
19 of Active Minds, Inc. Active Minds is the only
20 national nonprofit organization dedicated to
21 raising mental health awareness and supporting
22 young adults at the peer level.

0243

1 We work with college students ages 18 to
2 25 on college campuses nationwide to improve
3 awareness about issues in mental health, to educate
4 students about available resources, and to increase
5 the dialogue around the issues so everyone feels

6 comfortable getting the professional help they need
7 and deserve.

8 In working with these students, the
9 youngest group of the population you are looking at
10 today and being a part of it, I wanted to be here
11 today to represent the voice of young adults who
12 find themselves in situations, transitions, and
13 under stressors they have never felt before, to let
14 you know to what extent they are suffering and
15 emphasize the need for accessibility to all
16 potential treatments to help them regain their
17 lives.

18 To do this, I want to tell you the story
19 of my brother, Brian. Brian was a brilliant,
20 funny, and talented student in an Ivy League
21 university, president of his a cappella group,
22 sports editor of the school newspaper with a

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1 3.8 GPA.

2 In his senior year of school, when he was
3 21, he sought counseling from the school psych
4 services. At that point we learned that Brian had
5 been living in shame with serious depression since
6 his freshman year.

7 The stigma, both internal and social, had
8 overwhelmed him to the point that he kept his pain
9 from everyone. He was terrified to admit anything
10 was wrong, and he really didn't know what it was.

11 Eventually, Brian did seek help, but it
12 was too late. He had lived for three years in
13 college in total isolation and in the throes of
14 depression.

15 When he finally sought the help, part of
16 his treatment regimen did include psychiatric
17 medications. The problem was that he had lived
18 with his depression for so long and he had spiraled
19 down so far that he died eventually of suicide from
20 his illness, not from what was helping get him
21 through it.

22 Many young adults first experience any

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1 symptoms of a mental health issue in this critical
2 age of 18 to 24, the age when in fact most serious
3 mental illnesses first present.

4 In a study done last year by the American
5 College Health Association, nearly half of all
6 students reported feeling so depressed they could
7 not function, nearly half. One in ten reported
8 having serious considered suicide.

9 Taking from the statistic offered by the
10 U.S. Census that states that 17.6 million students
11 are attending colleges or universities nationwide,
12 this means that almost 9 million young adults are
13 going through this world, through the best time of
14 their lives, feeling so debilitated that they
15 cannot function. Nearly 2 million have thought
16 about taking their own lives.

17 This issue is much broader than the
18 effects of antidepressants. These are students who
19 are not even yet in the mental health system. In
20 fact, anecdotally, most campus counseling centers
21 will tell you that suicides that do occur on campus
22 are primarily of students who are not in any sort

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1 of psychiatric treatment at all. While you
2 are weighing the benefits and risks of the
3 psychiatric medications being presented today, keep
4 this in mind.

5 DR. PINE: Thank you.

6 The next speaker is Ann Blake Tracy.

7 DR. TRACY: Ann Blake Tracy, Ph.D., head
8 of International Coalition for Drug Awareness,
9 author of "Prozac: Panacea or Pandora?" The last
10 17 years of my life have been devoted to
11 researching, writing, and lecturing about these
12 drugs.

13 In spite of that, two of my nieces in
14 their early twenties, a decade apart, attempted
15 suicide on antidepressants, the first on Prozac and
16 the second just a month ago on Wellbutrin.

17 Due to time constraints, I refer you to
18 my September 2004 testimony in my packet on the
19 damaging effects of inhibiting serotonin
20 metabolism, the very mode of action of
21 antidepressants.

22 Impairing serotonin metabolism results in
0247

1 a multitude of symptoms including suicide, violent
2 crime, mania, and psychosis. Suicidal ideation is
3 without question associated with these drugs
4 according to medical research.

5 Rosie Meysenburg, Sara Bostock, and I
6 have collected and posted 1,200 news articles
7 documenting many exaggerated acts of violence
8 against self or others at Drugawareness.org with a
9 direct link to SSRistorise.com.

10 Beyond suicidal ideation, we have mania
11 or bipolar increasing dramatically.
12 Antidepressants have always been known to trigger
13 both as has the withdrawal of antidepressants.

14 According to "Pharmaceutical Business
15 Review," in the last 11 years alone the number of
16 people in the U.S. with bipolar disorders has
17 increased by 4.8 million.

18 Dr. Malcolm Bowers of Yale found in the
19 late nineties over 200,000 people yearly are
20 hospitalized with antidepressant-induced manic
21 psychosis. They also pointed out that most go
22 unrecognized as medication-induced, remain

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1 unhospitalized, and a threat to themselves and
2 others. What types of threats from these manias?

3 Pyromania, the compulsion to start fires.

4 Kleptomania, a compulsion to embezzle, shoplift,