FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION RESEARCH (CDER)

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PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

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

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

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(Voting Member)

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C O N T E N T S

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C O N T E N T S (C O N T)

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

(8:00 A.M.)

CALL TO ORDER AND OPENING REMARKS

DR. PINE: My name is Daniel Pine, and I am the acting chair of the Psychopharmacologic Drugs Advisory Committee. I would like to begin by calling today's meeting to order.

As many of you know, we are gathered here today as a Committee to discuss the results of an ongoing meta-analysis of data on suicidality emerging from antidepressant trials.

Historically, this has been an issue that has been examined by many organizations including the FDA in great detail over the last five or so years.

Today, the specific purpose is to look at newly available data that focuses on results compiled by the FDA in trials among adults where

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

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

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

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

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

INTRODUCTION OF COMMITTEE

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

Tom.

DR. LAUGHREN: Tom Laughren. I'm the

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director of the Division of Psychiatry Products at FDA.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In terms of the next item of business, Cicely.

CONFLICT OF INTEREST STATEMENT

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

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

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the authority of the Federal Advisory Committee Act of 1972.

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

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

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

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

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

Dr. Bruce Pollock has been granted a

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

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

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

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

In the event that the discussions involve

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

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

DR. PINE: Thanks, Cicely.

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

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

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

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

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

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

FDA INTRODUCTORY REMARKS & OVERVIEW OF ISSUES

(PowerPoint™ presentation in progress.)

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

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

We are going to be using the term

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

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

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

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

Now, this standard statement did not, of

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

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

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

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

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suicide once more becomes serious as retardation fades."

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

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

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

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

Now, despite this fairly widely held

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

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

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

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

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

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

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

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

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

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

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

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

We reached a similar conclusion to

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others, that there did not appear to be an increased risk of completed suicides associated with assignment to either active drug or placebo in adults with major depression or various anxiety disorders. These results were published in Hammad, et al., in 2006.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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changes to labeling and give us your feedback.

Thank you.

DR. PINE: Thank you, Dr. Laughren.

Any questions or clarifications?

(No response.)

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

Lisa.

FDA PRESENTATION

ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:

DATA OVERVIEW

DR. JONES: Thank you.

(PowerPoint presentation in progress.)
DR. JONES: I would like to present to the Committee this morning an overview of the data that was the basis for the FDA's adult suicidality analysis. An overview of both the data collection process and what the final data set was composed of.
Unless otherwise specified, persons in
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the presentations this morning will be referring to these eleven drugs, composed of the six selective serotonin reuptake inhibitors, "SSRIs," and five non-SSRIs.
I'm showing here that drugs which were a combination of an antidepressant and another drug such as Symbyax®, a fluoxetine/olanzepine combination, were not included in the final analysis.
The data used in this analysis was taken from randomized, controlled trials that had been performed by the sponsors of the eleven antidepressant drugs from the previous slide.
For some times perspective on the data collection, the FDA sent four data request letters to the sponsor from December 2004 to August 2005. The resulting data sets were received back by the FDA from September 2005 to September 2006.
The total of four letters or four requests letters were sent to the sponsors in order to address the various issues which arose during the earlier review of the data sets.
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The FDA data request letter contained fairly detailed guidance to the sponsors on what trials should be included in the data set for each drug.
Specifically, the letter stated that the trial should be randomized, placebo-controlled trials only, that the trial could be for any indication or of any length, but you have at least 20 subjects per treatment arm.
Prior to the submission of the final data set, the sponsors submitted a list of the trials they intended to include and exclude, and the FDA provided feedback on the composition of the final data sets.
The previous slide noted that trials for any indication could be submitted and we did indeed receive trials from a wide variety of indications. These indications were first divided into two broad groups: those for major depressive disorder or "MDD," and those which were not for major depressive disorder.
The non-MDD trials were further divided
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into four subgroups: other depressive disorders, other psychiatric disorders, behavioral disorders,

and other disorders.

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

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

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

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

Finally, under the "other disorders" were

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fibromyalgia, incontinence, sexual dysfunction, and various pain-related indications.

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

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

The previous slides have described the collection of the denominator data for the analysis, and the next few slides will describe the collection of the numerator or event data. TO identify potentially suicide-related adverse

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

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

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

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

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

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

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

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

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

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

Events were classified into one of the

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

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

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

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

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one was present.

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

Thank you.

DR. PINE: Thank you, Dr. Jones.

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

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

ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:

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STATISTICAL SAFETY REVIEWER EVALUATION

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

(PowerPoint presentation in progress.)

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

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

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

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

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

The primary analysis population, which we

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

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

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preparatory acts, and suicide ideation.

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

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

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

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

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

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

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

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

The first set of methods we looked at are traditional model-based methods often used in meta-analysis including Mantel-Haenszel odds ratio methods with and without continuity corrections. It has been pointed out that continuity corrections may bias the results in the present setting.

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

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

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

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

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

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trials.

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

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

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

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

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

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

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

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

When we looked at subject characteristics, comparing differences between the

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test drug subjects and the placebo subjects, there were no noticeable differences for age, gender, race, baseline history of suicide attempts, baseline history of suicide ideation, and treatment exposure. Because there were no significant differences in treatment exposure, we chose subject, not subject years, as a unit of analysis.

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

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

Looking at unadjusted events, a number of events per subjects over the five indication classes and looking at the placebo arm, you see that the three indication classes that make up the primary analysis population have, roughly, similar

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unadjusted rates.

Unadjusted rates for the other indiction classes are notably lower. For the three indication classes, the unadjusted rates for the placebo are higher than those for the test drugs.

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

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

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

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ideation and psychiatric indications.

The key value here to look at is the value of one. A value less than one would imply that the test drugs are associated with lower rates of suicidality than the placebo.

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

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

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

The chief advantage of this approach in

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the sensitivity analysis is it makes use of all the trials including the 40 percent of the trials that did not have events. It also may have more readily interpretable estimates.

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

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

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

The first thing to note is that generally

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all the sensitivity methods that produce odds ratios give very similar results. Mantel-Haenszel, Mantel-Haenszel with continuity correction, you can see that the estimate is slightly lower, which is to be expected by our understanding of the continuity correction.

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

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

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

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

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

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

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

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

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similar to what they were when they were previously presented.

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

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

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

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

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

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

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

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

The youngest adult age group, the estimate is four additional subjects, but that confidence interval goes negative. This negative would imply we might see one less patient in the test drug versus the placebo until we get up to the
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oldest age group where the estimate is six less patients and the whole interval falls below zero.

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

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

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

Finally, that brings me to the summary. For the primary analysis population endpoint, the overall odds ratio was .84. Again, that estimate would imply that the test drugs associated with
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lower rates of events than the placebos, but that confidence interval overlaps one, so it is not a statistically significant result.

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

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

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

Thank you. That concludes the presentation.

DR. PINE: Thanks, Dr. Levenson.

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

Yes, Dr. Pollock.

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QUESTIONS

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

DR. LEVENSON: Okay. What was the range?

DR. POLLOCK: The age range.

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

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

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

DR. PINE: Roughly, 200 subjects.

Yes, Dr. Goodman.

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

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

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

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

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

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

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

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

Marc, do you have any information on that?

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

DR. PINE: Any other final questions?

Yes, Dr. Robinson.

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

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

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

DR. POSNER: Six or seven of the nine,

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

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

ANTIDEPRESSANTS AND SUICIDALITY IN ADULTS:
MEDICAL REVIEWER EVALUATION

(PowerPoint presentation in progress.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If you look at the incidents, which is

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

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

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

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

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

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

We think it would be kind of a mistake to

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

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

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

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

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

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

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

We made the classification to see if

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

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

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

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

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

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

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

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

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

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

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

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

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

Again, this is a translation of the risk

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

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

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

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

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gradient.

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

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

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

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

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

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

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

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

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highly significant.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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results.

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

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

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

In this case, if you look at SSRIs and

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

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

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

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

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

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

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

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

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

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

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

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

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

I think it is also important to note that

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

I think what this implies is that there is something different about the psychopharmacology

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of suicide, that it's different than the psychopharmacology of depression, that they are two separate phenomenon.

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

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

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

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

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

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

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

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

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

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

but that middle-aged people have more trouble reporting than older people. I think that would take a lot of very ingenious explanation.

Finally, I think for further investigation that there may be some differences between drugs and drug classes, and that is discussed in the review document. It could well be a chance finding. I don't think it's anything to get excited out.

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

DR. PINE: Okay. Thank you, Dr. Stone.

I would actually like to thank all of the

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

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

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

Thank you.

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

Yes, Dr. Leon.

QUESTIONS

DR. LEON: When we evaluate the safety

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

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

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

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

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

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

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

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there are a fairly large number of negative trials.

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

DR. STONE: No.

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

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

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

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

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

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

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

DR. PINE: Dr. Goodman?

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

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

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

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

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

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ratio is similar whether it is placebo or drug.

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

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

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

DR. PINE: I am going to summarize this

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

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

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

Dr. Temple.

DR. TEMPLE: The results you have just

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

It is also worth remembering that over the years, and very consistently, half of all reasonably sized adult depression studies failed to

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show a statistically significant difference.

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

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

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

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

DR. TEMPLE: Oh.

DR. PINE: No, it's good because I don't

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think the point has been realized by the fact that you keep making it but other people don't make it.

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

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

DR. PINE: Dr. Goodman.

DR. GOODMAN: I had a question about the other behavioral category. I understand the limitations of that data set and that you are starting with a small denominator and you don't have that many events. That said, did you examine

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the relationship by age in the same fashion, and was there any pattern in terms of the so-called

"suicidality signal" and the behavioral conditions by age?

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

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

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

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

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

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

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

DR. PINE: Dr. Laughren.

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

DR. PINE: Ms. Bronstein.

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

As I looked at what was included and what

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

get at when you don't have a controlled setting.
DR. PINE: Dr. Armenteros.
DR. ARMENTEROS: Yes, I understand this is a large data set. Do we have an idea as to how frequently were older medications being used concomitantly, for example, benzodiazepines or things of that sort that may perhaps modulate a little bit what is going on?
DR. STONE: No, we didn't ask for that to be reported. It would just make the database too large and to unwieldy.
DR. PINE: Dr. Slattery?
DR. SLATTERY: I am wondering if there were differences in severity of illness, you implied that you had looked at both inpatient and outpatient treatment studies, and whether the numbers of inpatient versus outpatient studies differed significantly between the different age groups and whether that had any impact on outcome?
DR. LEVENSON: The only thing I have to say to address that is we didn't see a difference

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in the inpatient versus the outpatient setting and only a small minority of the trials were inpatient, so there is not a lot of information there.
DR. PINE: We are going to take three more questions before the break. Again, there will be a lot of other time for discussion. We are going to take in this order a question from Dr. Mehta, a question from Dr. Leon, then a question from Dr. Goodman, and then we will take a break.
Dr. Mehta.
DR. MEHTA: I have a question one of the Marks. Were you able to look at the data in terms of suicidality during the first three weeks of study compared to the remaining seven or eight weeks of average treatment? Because most of the time efficacy of an antidepressant doesn't kick until about three weeks.
DR. LEVENSON: We had some information there, but, no, at this point we haven't looked at it.
DR. PINE: Dr. Leon.

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DR. LEON: The briefing document mentions the problem of ascertainment bias in this, I mean, in these post hoc analyses of the large data set. There was a varying degree of scrutiny of a collection of the data across the trials.
I wonder, though, if you did analyses of the Ham-D suicide item that was used in the pediatric analysis and that might be more systematically collected across the trials?
DR. STONE: We asked for it. It was reported in various differing ways, some different subscales, different groups. I tried to look at

it. It didn't seem to show us anything.
DR. PINE: That was the conclusion from the pediatric studies as well, that it really didn't reveal anything in the face of positive events.
Okay. With that, I would actually like to once again thank the speakers and thank the Committee. I think, knock on wood, hoping not to jinx us, we are off to a very good start.
We are going to take a fifteen-minute

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break, and we are going to start promptly at 10 o'clock. Thank you again. We will see you in fifteen minutes.
(Recess taken.)
OPEN PUBLIC HEARING
DR. PINE: We are going to begin the public hearing. If I could ask everybody to either move outside, if you would like to continue your conversations or take your seat if you would like to be here for the public hearing.
I just also want to warn everybody that we are going to be going without a break from now until 1:30, and we are only going to have a half an hour break for lunch. For the next three and a half hours, there will not be any breaks.
For this section, again, if I could ask people standing to please either find a seat or move into the hall for their conversations. For this section of the meeting what we are going to do is we are going to devote considerable time for public testimony. I have to say that from the past meetings, this has been one of the most powerful

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parts of the meeting.
We always face a great conflict in terms of trying to balance issues of being fair to everybody who has very important things to say on the one hand, but on the other hand limiting this section of the program to the point where it is weighed appropriately, given our desire to balance issues of science and issues of public health concern.
Due to those issues, the way that we are going to proceed is that each speaker will have three minutes when they come to the podium. You can see that there is a podium in the middle of our table. We have a timer who is the official keeper of the three minutes.
Igor, if you can, raise your hand.
(Igor complies.)
DR. PINE: As you can see, when you are a speaker, Igor is the official keeper of your time. When you get to the podium, your time will begin. You will have a 30-second warning that will appear on the podium when the light turns yellow, and then

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

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

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

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

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

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

Those who knew Ray remember his loving,

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

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

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

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

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

Within a couple of days of starting

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

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

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

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

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

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

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

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

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

The American people have a right to know that SSRIs can cause suicide, and that holds true regardless of whether you are age 5 or 75. We have a right to make informed decisions.

DR. PINE: Thank you.

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

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

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

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

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

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

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

For the next speaker, Mr. Chris Coffin.

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

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

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

A couple of issues that I would like to

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

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

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

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

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

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

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

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

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

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

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

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

Thank you.

DR. PINE: Thank you.

Our next speaker is Ms. Ellen Hanson.

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

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

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

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

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

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

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

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

death was Mother's Day. There was no hint that he would become suicidal.

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

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

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

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

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

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

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

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

DR. PINE: Thank you.

The next speaker is Ms. Julie Totten.

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

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

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

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

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

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

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

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

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

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

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

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

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

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when I could barely see a ray of hope."

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

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

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

Thank you.

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

MS. GONZALEZ: Good morning. I would rather be anywhere than here. There is supposed to be a picture of my husband up there with my son.
My husband was 40 years old. We tried for 10 years for another child. This (indicating) is my daughter Elaina. Four pills into Paxil, he woke up, within an hour he shot himself in the head. He did this less than 10 feet from where my son was sleeping.
If I would have done our usual routine, this little boy would have found his father facing ours with a bullet wound to his head.
You people have known about this for 15 years or more. I hold you all responsible for his death, and I always will. I wasn't prepared for this speech. I wasn't prepared for his suicide.
I just keep asking myself, or I did in the beginning, what was my husband thinking? I hear these stories of people just taking the pills and going crazy.
How crazy did you make him that morning that he would get up, not think, and do this to himself? You have ruined my life, my daughter's life, my son's life. How in the hell do I tell a kid that his father committed suicide?
How dare him. The bullet was a .357. It could have ricocheted and done something to this boy. Worst yet, my husband could have killed us. She (pointing) wasn't home. What if she would have come home and found all of us dead?
There are so many stories out there. I read about this stuff every damn day and cannot believe that you people sit on this and do nothing.
You have made everybody a wreck. These people have to come here before Christmas. They've got kids. They've got families. Ho, ho, ho, to you.
(Applause.)
MS. GONZALEZ: I don't know. I wake up every morning and I say to myself, "Oh, my God, he's dead. He is fricking dead."
Do you wake up and think, "How many people are going to die today because I'm not doing nothing?"
You're not doing nothing. I was worried about coming here. Who in the hell are you? Who are the pharmacy people? It may appear like I'm upset and I'm not conducting myself in a proper way. I don't give a damn.
I used to be a hell of a nice person. I

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

DR. PINE: Thank you.

MS. GONZALEZ: Yeah. Thank you for nothing.

(Applause.)

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

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

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Prevention as its immediate past president.

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

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

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

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

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

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

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

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

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

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

DR. PINE: Thank you.

The next speaker is Allen Jones.

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

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

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

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

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

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

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

(Applause.)

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

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

our health and economy.

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

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

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

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

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

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that sort of thing.

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

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

(Applause.)

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

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Nick Korzie.

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

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

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

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

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

I met all these wonderful people and

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

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

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

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Christopher Kratochvil.

MR. KRATOCHVIL: Good morning. My name is Chris Kratochvil, and I am a child and adolescent psychiatrist at the University of Nebraska Medical Center in Omaha, Nebraska. I have conducted research in mood disorders funded by the National Institute of Mental Health as well as pharmaceutical companies.

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

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

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

First, as one of the principal investigators in the NIMH-funded Treatment for Adolescents with Depression Study, we demonstrated that fluoxetine, both alone and in combination with cognitive behavioral therapy, was safe and effective for the treatment of adolescent depression.

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

placebo.

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

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

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

For example, recent data presented by

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

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

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

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

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

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DR. PINE: Thank you.

The next speaker is Darrel Reiger.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

untreated depression.
Thank you.
DR. PINE: Thank you.
The next speaker is Moira Dolan.
DR. DOLAN: Hello. My name is Dr. Moira Dolan, executive director of Medical Accountability Network. We are a nonprofit accepting donations from individuals only and have no support from commercial interests or from other groups. Our purpose is to make medicine accountable based on full informed consent.
Here are some of our grave concerns with the adult suicidality studies that were discussed this morning. Inexplicably, the drug makers only had to report one event per subject.
Incredibly, events occurring within the tapering period were not included. Events more

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than one day after the last double-blind treatment period were not included, and this is in spite of drug half lives from five hours to over a week.
The attempted compensation for informative censoring was wholly inadequate. Again, inexplicably the FDA made no attempt to adjudicate the drug makers' reports of what consisted of "suicidality."
Even with these handicaps, however, the data did show an increased incidence of suicidality in 18- to 24-year-olds. Remarkable increased suicidality was found in the evidence supplied by the makers of Celexa®; Cymbalta®; BuSpar®; and, to a lesser extent, Luvox®.
There is no biological explanation for such a drug effect on adolescence and young adults and yet not on people over age 25. In fact, there is no precedent for any adverse drug event warning to be given for children but not for adults when it doesn't specifically relate to growth or maturation.
Obviously, more studies need to be done.

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This time with data collection that is designed to give some answers. However, to have this data in hand and yet to continue to refrain from undertaking an urgent, broadly disseminated information campaign with immediate and plainly worded warnings -- warnings against the possibility of tragic, unnecessary deaths by drug-induced suicide -- well, this is nothing less than a gross abdication of the patient protection responsibilities of the FDA.
The concerns of the Medical Accountability Network are that physicians and pharmacists have legal and ethical obligations. We have to provide patients with adequate information so that they can give informed consent for any given treatment.

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

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

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Deborah Gruder.

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

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

Multinational drug companies let their seemingly endless R&D expenditures justify valuing profits over the sanctity of human life. This shortsightedness has led to the emergence of a vast new array of dangers to the health of the American people.

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

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

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

Not two years ago, not fifteen years ago, not today has suicidal thoughts or behavior been isolated to just children and adolescents. Because on March 30, 2004, my husband, Scott Gruder age 52, just only 13 days after beginning Paxil at the recommendation of his physician, just eight days

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

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

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

(Applause.)

DR. PINE: Thank you.

DR. PINE: The next speaker is Gwen Olsen.

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

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

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

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

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

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

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

For example, the participants in drug trials are cherry picked by the researchers to ensure maximum positive outcomes for reporting

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purposes.

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

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

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

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

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

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

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

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

(Applause.)

DR. PINE: Thank you.

The next speaker is Beverly Hatcher.

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

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

She was only on Paxil for 16 days. My

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

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

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

GSK professes their mission is to improve

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

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

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

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

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many hundreds of millions of dollars on lawyers."

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

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

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

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

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

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

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

DR. PINE: Thank you.

The next speaker is Ellen Liversidge.

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

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

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

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

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

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

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

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

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Lexapro.

I will never forget the day she came to

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

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

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

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

(Applause.)

DR. PINE: Thank you.

The next speaker is Lisa van Syckel.

MS. VAN SYCKEL: Good morning. Good morning, ladies and gentlemen. My name is Lisa van Syckel. I am the mother of a fifteen-year-old Paxil survivor who attempted suicide and became violent.

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

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

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

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

It was my belief in 2004 during the congressional hearings and it remains so now that these drugs must be administered to children and adolescents under the strictest scrutiny.

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

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

Dr. Goodman, in February 2004, you gave

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

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

It is very important that we keep the

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

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

A PARTICIPANT: Here, here.

(Applause.)

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

Thank you.

DR. PINE: Thank you.

(Applause.)

DR. PINE: The next speaker is

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Charles Carpenter.

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

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

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

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

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would always be there to take care of me, just

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

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

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

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

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

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

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convinced them I was fine and went back to work.

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

DR. PINE: Thank you.

The next speaker is Paula Clayton.

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

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

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

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those who received placebo.

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

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

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

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

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

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

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

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

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

DR. PINE: Thank you.

The next speaker is Diane Dorlester.

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

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

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

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

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

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me and so I really resisted that.
My depression continued to get worse. After about six months, I did take my doctor's advice and began taking antidepressant medications.
Treatment was, for the most part, effective for about a year, then it suddenly got much, much worse and I spiraled into a condition where I could not sleep at times and other times I was sleeping for days on end and not getting out of bed.
I lost about 25 pounds. I could not eat. Every day, when it was at its worst, I would wake up with a gut-wrenching pain, emotional pain, that is similar to what any of us would feel if we just got devastating news of maybe a loved one who has passed on. On those days that I woke up feeling that, that pain never went away.
My doctor wanted me to switch to a different antidepressant, because he said some things work better with certain people. I was reluctant again to do so.
Because despite how horrible I felt and

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how much I was at that time thinking of suicide and at times sitting in my car in my garage turning the engine off and on, I was afraid to switch. Eventually, I did so. About three weeks later, I got my life back.
Had there been a black box warning on the medication, the second medication that saved my life, that may have been the one additional piece that I needed to not switch.
DR. PINE: Thank you.
The next speaker is Lewis Kopolow.
DR. KOPOLOW: I am Dr. Kopolow, currently president of Suburban Maryland Psychiatric Society. I am speaking today from the perspective of an adult psychiatrist who has treated thousands of depressed patients with psychotherapy and medication over the course of my thirty-year career. I will be making three points for the Committee's consideration.
One, depression can be a lethal disease; two, there is a significant link between untreated depression and physical illness; and, three,

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depression is an illness that is already underdiagnosed and undertreated in this country.
Elaborating on point one, depression is a disease with a high likelihood of severe, unalterable consequences. Suicidal thoughts, gestures, and actions are an inherent part of major depressive illness itself. People with untreated mental illness such as depression face up to a 15 percent lifetime risk of dying of suicide.
Point two, depression is not only an illness affecting an individual's emotional state

but their physical health as well. Patients suffering from major depressive illness have one and a half to two times greater risk than the general public of developing hypertension, cardiovascular disease, and diabetes. The World Health Organization has identified depression as the leading cause of disability in the world.

Point three, the Surgeon General's report in 1999 noted that more than half of all people with a mental disorder such as depression do not get the help they need.

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

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

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

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

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significance of an increase risk of suicidal thoughts and gestures.

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

Thank you.

DR. PINE: Thank you.

The next speaker is Joseph Glenmullen.

DR. GLENMULLEN: My name is Joe Glenmullen. I am a clinical instructor in psychiatry at Harvard Medical School and the author of two books, "Prozac Backlash" and "The Antidepressant Solution," both of which describe my experience with patients having this side-effect.

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

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

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

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

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

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

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

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

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

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Thank you.

(Applause.)

DR. PINE: The next speaker is Dan Reidenberg.

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

Collectively, we represent clinicians and

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

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

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

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

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

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

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

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

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

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

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

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

monitoring of these patients on medications, all of which can be readily accomplished without a warning label.

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

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

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

Thank you.

DR. PINE: Thank you.

The next speakers are Karen Menzies and Debra Tucker.

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

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

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

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

When a company seeks approval for a drug, does the FDA parse out the data for efficacy to determine which age groups it is effective for? I would like to see that data.

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

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

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

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

Your current black box warning includes

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

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

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

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

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

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

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

(Applause.)

DR. PINE: Thank you.

The next speaker is Michelle Moore.

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

Prozac and Paxil.

To think that this amazingly strong husband, father of two, son, best friend to so many, police sergeant, and SWAT team commander could be taken over by these horrific drugs is beyond comprehension.

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

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

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

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

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

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

He was put on Prozac, and he took that for three days. He was then taken off Prozac and put on Paxil. He took one Paxil, and immediately he started feeling very anxious. I being a registered nurse realized quickly this was not a normal reaction. He never had any suicidal thoughts or behaviors.

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

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

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

(Applause.)

DR. PINE: Thank you.

The next speaker is Tony Noll.

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

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

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

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

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

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

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

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

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

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

That my father could be described as

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

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

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

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

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

(Applause.)

DR. PINE: Thank you.

The next speaker is Mary Margaret Dick.

MS. DICK: I don't like drug companies, and I don't own stock, but I am a consumer of medications. I have had five major debilitating depressive episodes, and I am on social security disability because of it. I hope to make four points.

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

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

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

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

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

didn't understand that I may have to try several different meds before I found one that worked whose side-effects I could tolerate.

I gained energy but was still having suicidal thoughts that I could now act on. I am now in a meds combination that minimizes both the frequency and the intensity of my episodes.

My third point is that medications are only one part of a treatment plan. I was given a treatment plan that included a meds adjustment, ongoing talk therapy, communication with family, and making some lifestyle changes.

I now work out three times a week. I eat a healthier diet, and I don't drink. I am learning coping mechanisms in my depression support group,

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and I make sure I get adequate sleep and downtime.

My fourth point is that we patients need specific instruction to be included in the medication information on how to monitor ourselves.

All my life I have struggled with depression, yet it was only last year when I used the Families for Depression Awareness' "Wellness Guide" that I understood what I was supposed to be tracking.

The FDA Advisory may be our only source of this information because access to qualified clinicians is severely limited. Please include in your advisory specific information on what mental illness is and what we can realistically expect from the medications and that it takes more than medications to recover.

DR. PINE: Thank you.

The next speaker is Donna Barnes.

MS. BARNES: My name is Donna Holland Barnes, president of the National Organization for People of Color Against Suicide. Let me just first say I am extremely sorry and feel empathy for those

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people who have lost someone to suicide. I also am a suicide survivor. I lost my son in 1990.

This is an organization that has for many years spent critical and relentless time educating our minority communities on depression and suicide so that individuals suffering from any mental disorders would understand what it is and that treatment is available.

African Americans and/or blacks are the least likely to go to treatment, the least likely to stay in treatment, and the least likely to comply if in treatment.

Any mental health challenges that rest in the white communities are amplified in the African American communities. The stigma for taking medication, for instance, is overwhelming.

So much so that in a case in 2003 in Prince George's County a young 17-year-old was seen

by a psychiatrist who prescribed medication for his diagnosed psychosis. He brought the medication home, showed it to his father who then flushed the medication down the toilet, telling his son that he

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was not going to take this crap. His son suicided within a month of the incident.

In 2004, I conducted a study at the Howard University Mental Health Clinic and evaluated 74 cases of individuals screened positive for bipolar. Sixty-one percent of them were not on any antidepressants or mood stabilizers and over 50 percent of them made multiple suicide attempts.

In our communities, we are not only concerned about untreated depression that can cause suicide attempts and completed suicides, but we also have to be concerned about mental health disparities and, more specifically, the degree of uncertainty that primary care physicians hold in prescribing antidepressants, since primary care physicians are really the main people that we go through, too, for treatment.

If there are bold and aggressive warning signs on antidepressants, antidepressants are not going to get prescribed by the primary care physicians.

All the work that we have done educating

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communities that medication is okay if prescribed correctly and is monitored in a responsible manner will be wasted and set us back 30 years.

Finally, I reject with enthusiasm a warning label that is bold and aggressive because blacks already have a high degree of mistrust in the mental health medication medical arena.

Primary care physicians are already reluctant to prescribe antidepressants, and a black box will further increase our reluctance to take medication for mental health treatment. The warning sign that it increases the risk for suicide will move my people away from that.

DR. PINE: Thank you.

The next speaker is Sarah Bostock.

MS. BOSTOCK: Five years ago, my life changed forever when my 25-year-old daughter, Cecily, stabbed herself today after three weeks on Paxil. I am sure she would be alive today if she had never taken Paxil.

Since that fateful day, I have been warning others and searching for proven ways that

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SSRIs can do harm. There is good neuroscientific evidence of iatrogenesis, or treatment-induced illness, and adverse effects.

However, the most compelling evidence for treatment-induced harm comes from the hundreds of narratives that I have read in the media or heard

firsthand from antidepressant users and their loved ones. Patterns of inappropriate dosing, drug induced mania and psychosis, and misunderstood withdrawal and rebound are unmistakable.

Few professionals, patients or caregivers, understand the intense activation that can occur when treatment begins or the very slow rate of taper required to get off SSRIs safely.

Directors of Drugawareness.org and I put these narratives into a format where their cumulative power could be recognized by creating an online, sortable database, SSRIstories.com. We have loaded over 1,200 media stories dating back to 1988 in which antidepressants are associated with an act of violence or bizarre behavior.

There are over 200 suicides, 300 murders,

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100 completed murder/suicides, incidents of road rage, arson, and fraud, 18 school and 14 workplace shootings.

Beloved family members including children murdering each other and themselves. Priests, new mothers, scholars, Iraq veterans, and senior citizens -- all dying violently, all were on antidepressants.

In many cases, journalists describe behavior consistent with adverse reactions that precede the criminal act, just as Cecily's behavior changed uncharacteristically before her suicide.

The narrative details that point to drug effects have been highlighted on the website at the top of each complete story available through a link to the date.

Besides some notorious stories and some with celebrities, there are 13 stories in which a jury or judge with medical experts acknowledge causation and legal rulings. Mostly, these are stories of ordinary people: friends, families, neighbors, colleagues. It could happen to any

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innocent person just as it did to Cecily.

SSRIstories.com is our best effort to demonstrate a signal that something is dangerously amiss, not in industry-run trials but in real clinical practice. Read it yourself.

No one should underestimate the power of antidepressants to play a causative role in these tragedies. Black box warnings would be one step in the right direction.

(Applause.)

DR. PINE: Thank you.

The next speaker is Kim Witczak.

MS. WITCZAK: Hi. My name is Kim Witczak, and I am from Minneapolis, Minnesota. I came here on my own.

This (indicating) is Woody, my husband of almost 10 years. Woody was outgoing, gregarious,

smart, and full of energy. Everyone loved him. To me he was simply Woody, my best friend and the one that greeted me every day, "Hello, Sunshine."

He was guy that I was supposed to have a family and grow old with. However, on August 6, 2003, that day it changed. I became a widow.

Woody was found dead hanging from the rafters of our garage of Zoloft-induced suicide at age 37. Woody wasn't depressed. He had no history of depression or suicidality.

He was just starting his job as vice president of sales with a startup company two months prior and was having trouble sleeping, which is not uncommon for entrepreneurs.

He went into his GP who gave him a diagnosis of insomnia and sent him home with a three-week Pfizer sample pack. This sample pack automatically doubled the dose from 25 to 50 milligrams after week one.

No cautionary warning was given to him or me about the need to be closely monitored about going on the drug or dosage changes. In fact, I was out of the country for the first three weeks he was on this drug.

Within days, Woody had the side-effects like profuse night sweats, diarrhea, and worsened insomnia. He also experienced others that were known only to Pfizer, but not to Woody his doctor or his family.

Shortly before he died, I found Woody curled up in a fetal position on our kitchen floor with his hands around his head like a vice crying, "Help me, help me. My head is outside my body looking in."

Pfizer acknowledges this in an internal document which you guys all have copies of, "It occurs on all SSRIs. We don't know why," the first sentence on the top of that document.

Something did not add up with Woody's death. We started searching the only thing that changed during this time, and that was Zoloft. Woody and I never questioned the drug. Why would we? Zoloft is FDA approved and sold as safe and effective.

Our journey for the truth has led us to the courts, Congress, and HHS. We were able to get internal confidential documents, ones that are here in my packet to you and other ones that you have not seen.

Here is one that came from Pfizer Zoloft U.K. that the Irish Medical Board asked them to give. Look at their clinical studies. The highest percent in Pfizer's study of 31 to 40, 50 milligrams, 15 to 30 days -- all three Woody.

This next one, in conclusion, this is Pfizer's causality analysis, 54 of the 252 of their case studies were directly related to the event, to Zoloft.

We deserve to be told all side-effects, not the ones that you find are acceptable and which ones you want to keep from us because you are afraid to scare us away. Woody deserved it. We all deserve it.

(Applause.)

DR. PINE: Thank you.

The next speaker is Joseph Weiner.

DR. WEINER: My name is Joseph Weiner, and I am a psychiatrist on the faculty of Long Island Jewish Medical Center. The American Psychiatric Association is reimbursing me for my travel expenses to this meeting. I have no

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financial relationships with any pharmaceutical company.

I greatly appreciate both this opportunity to share my thoughts with the FDA Advisory Committee and the crucial work you all do in protecting the public's health.

The heartfelt stories that are being shared with everyone today further underscores the great importance of the decisions that are going to be made.

I have come from New York today because I believe so strongly in the issues at stake. I will share my perspective as a nationally regarded expert in the interface between psychiatric and medical illness. I will also share my personal victory over major depression due in large part to antidepressant treatment.

To state my conclusion at the outset, I believe that a black box label will harm a large group of patients both medically and psychiatrically much more than a label would protect people from the possible risk of suicidal

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thinking.

Harm from a black box label will occur because of the following factors. A significant number of primary care physicians will misperceive that antidepressants are too dangerous for them to prescribe.

Because most people receive treatment for depression in the primary care setting not from mental health specialists, diminished prescribing of antidepressants would place a large group of people at risk for sustained depression.

In addition, strong evidence demonstrates that preexisting depression greatly increases the likelihood for developing atherosclerotic heart disease, cardiovascular disease, diabetes, dementia, and osteoporosis.

Once a depressed patient develops a coexisting medical problem, the risk of medical complications, even death, increases dramatically.

Therefore, depression worsens medical health. Although we need much more research in this area, there is evidence that the that of

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depression can improve some medical outcomes.

From a personal perspective, I suffered with serious depression from childhood through my early thirties. Although I benefitted greatly from years of psychotherapy, I still had to push through each day because of suicidal thoughts.

Sometimes I could not imagine how I would get through the rest of my life. It was only after I was prescribed an antidepressant that I felt the enormous weight of depression lift from my shoulders. I have a second wife.

When I told my wife, Lisa, also a healthcare professional that I would be speaking here today, she asked me to tell you that she also conquered serious depression through the use of antidepressant medication.

If only our physicians had prescribed antidepressants for us earlier in our lives, we would have avoided many years of excruciating suffering.

I hope the Advisory Committee strongly considers the great medical and psychiatric harm

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from the likely reduction of antidepressant prescribing in reaction to a black box label.

DR. PINE: Thank you.

The next speaker is Angela Heck.

DR. HECK: Hello. My name is Angela Heck. My husband William and I are both here of our own accord from Toledo, Ohio. My husband and I had been together for 12 years at the time he attacked me tried to kill me with a knife (weeping).

Approximately, three years ago, my husband was prescribed Paxil for anxiety. My husband is not an alcoholic. He has never tried illegal drugs in his lifetime. In addition, he has no prior history of assault, violence, or aggressiveness issues. He does not have any history of mental illness. He is a normal, healthy male.

Do you know what it is like to be trapped in your own bedroom thinking you're going to be wrapped in a blanket and your parents are not going to know what happened to you? Or, do you know what

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it's like to wonder how you could do something so terrible, so contradictory to your values and beliefs?

My husband and I do because of what a

well-respected psychiatrist stated in the attached letter regarding the whole incident, and I quote:

"I find it to be consistent with dissociative episode and in all likelihood caused by serotonin reuptake inhibitor, Paxil. You are familiar with the details of the unfortunate assault on his wife during that dissociative episode."

To this day, he still does not remember what happened on that horrible day. He only knows what has happened from me telling him. This tragic event turned out lives upside down.

Resentment and anger do not even begin to describe how we feel towards the makers of these dangerous antidepressants. I always knew that money made the world go around, but I did not think a company was so greedy that they would not care how many people's lives are ruined or lost.

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I know some people have trouble believing that a drug like Paxil could cause something like this. If it wasn't me and how well I know my husband, I would probably be one of those people.

There is no doubt in my mind that these drugs have several terrible side-effects. If I had any doubt, I would not be back with my husband.

I also strongly believe that the drug companies are aware of these side-effects as well or they would not have hidden the clinical trials for so long.

I strongly urge the FDA to do something about SSRIs and how they are prescribed. These drugs are being given to people as though they are as safe as Tylenol®. We all know this is not the case.

Antidepressants are something that either should not be used at all or as a last resort. They have become the first choice for all sorts of problems due to a lot of expensive marketing by the drug companies.

We trusted the medical profession, drug

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companies, and the FDA to give us safe medication, and that obviously has not happened. The drug companies have gained control of the entire process with their deep pockets.

We hope and pray that the FDA finally makes a drastic change regarding antidepressants as these drugs are extremely dangerous and family physicians should not be prescribing.

Thank you for your time and consideration.

(Applause.)

DR. PINE: Thank you.

The next speaker is Sheila Matthews.

MS. MATTHEWS: My name is Sheila Matthews. I am the co-founder of Ablechild.org, a

national, nonprofit organization representing more than 10,000 families.

Our organization is dedicated to informed consent regarding the subjectivity of psychiatric diagnoses and the dangers of the drugs used to treat them.

I also have personal experience with the

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subject of today's hearing. Two years ago, my brother-in-law, Michael, committed suicide while under the influence of an antidepressant.

I'm sure the FDA considers my brother-in-law's suicide, in fact the thousands of antidepressant-induced suicides, anecdotal. However, we the people, the consumers, do not.

By the FDA's own admission, only 1 to 10 percent of adverse drug reactions are reported. While DTC marketing has skyrocketed the use of psychiatric drugs, international warnings continue to surface.

The FDA has done nothing to increase the public's ability to report their adverse drug reactions. You have set up a great deal for the pharmaceutical industry, but a lousy one for the consumer.

In accordance with the National Academy of Science, which reported on the importance of postmarketing surveillance, Ablechild conducted a survey of 150 people at the Washington, D.C., Mall this March. Ninety-eight percent had never heard

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of MedWatch, the FDA adverse reporting system.

In June, we helped commission a large study on a thousand people covering all fifty states. Ninety-six percent had never heard of MedWatch, but, most importantly, ninety-seven percent of the public said the government should provide a public service campaign to inform them where they could report drug side-effects.

On October 4, 2006, Congressman Dan Burton issued a formal request to the FDA cosigned by several members of Congress. This letter stated that, "Given the results of DTC marketing and the documented risks of the drugs, the FDA should require all drug advertising to include information regarding MedWatch."

It said that, "Granting consumers this right would help spot serious side-effects of these powerful drugs much sooner."

We agree. You cannot continue to dismiss our reports as anecdotal, for we are in the tens of thousands. It is actually your job to find out how high these numbers go. As Congressman Burton

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wrote, "We firmly believe that this lack of awareness of the MedWatch represents a threat to the public's overall safety.

(Applause.)
DR. PINE: Thank you.
The next speaker is Mr. Robert Carolla.
MR. CAROLLA: Thank you.
My name is Bob Carolla, testifying for the National Alliance on Mental Illness. I am a consumer. My life was saved by antidepressants. I have lost friends and colleagues to suicide.
I can offer you a before and after perspective. My first major depression occurred in the early 1980s in the era before Prozac. All I got was talk therapy, twice a week with no medication.
Every week, I slid farther down. I thought about suicide silently. It was a constant risk. I lost my job and my apartment. I was hospitalized twice for a total of six weeks and unemployed for a year.
Following my recovery, largely through
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the grace of God, I lived without any further treatment until one day 10 years later, while working as a senior aide to the U.S. Senate Majority Leader a slide into depression turned into a psychotic episode.
I wondered the streets of Washington, D.C., until I sought refuge in a homeless shelter. That time I was hospitalized for two or three days and started on medication including antidepressants. I was diagnosed with bipolar illness and hospitalized again for a week. In less than a month, I was back at work.
My second recovery process still took two years. Thoughts of suicide were part of the territory and it was still a risk. I want to be frank. "Suicidality" and "ideation" are clinical terms, but consumers know what they mean.
We talk about them in hospital day rooms, in group therapy sessions, and in support groups nationwide. They mean staring at the approach of a subway train, jogging on a bridge, stopping and looking down.
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Farther down the spectrum is planning silently, buying an over-the-counter drug, going to sleep with a belt wrapped around the neck, silent contemplation, decision, hesitation, and maybe an attempt.
There are risks in any treatment including antidepressants, particularly during the initial period of recovery when medication is still taking effect or being changed and energy and force of will are returning.
I believe that causation is a function of the illness, not the medication. Whatever medication risk exists it is exceeded by the risk of untreated depression.

During recovery, there is still the risk of relapse and tragically the illness can overwhelm our best efforts, including the medication. Please whatever you do or say don't discourage people from getting treatment and don't stigmatize them.

DR. PINE: Thank you.

The next speaker is Toby Tyler Watson.

(No response.)

DR. PINE: Okay. I'll go to the next one. The next speaker is Erin Crowley.

MS. CROWLEY: I flew here from Chicago with my brother and aunt to share my mother's, Kathleen Crowley's, story. In late October 2003, my mother was a mentally healthy, vibrant woman. Ten short weeks later, my mother committed suicide. Those 10 weeks tell the story of a woman whose mental and physical health deteriorated at a shocking rate on antidepressants.

In late October, my mother approached her general practitioner because she had been experiencing anxiety about selling and moving from her home of 32 years.

Her doctor prescribed Lexapro. After four weeks on the medication, my mother discontinued use of her own accord because she was experiencing insomnia; had lost 15 pounds; and, in her own words, preferred anxiety to the agitated mania she experienced on the medication.

Over Thanksgiving, just one week after she stopped Lexapro, I noticed she seemed overly anxious and thin, and I suggested she see a psychiatrist.

My mother resisted, explaining she felt better before the Lexapro and was concerned a psychiatrist would suggest medication. She feared she could not tolerate the side-effects. On December 10, still struggling with insomnia, she did consult a psychiatrist who prescribed RemeronR, explaining it should help her sleep.

The psychiatrist asked her if she was suicidal. Her response was, according to the psychiatrist after her death, "No, it's not in that category."

After beginning Remeron, my mother's anxiety worsened drastically. She complained the medication made her feel wired, would go days at a time without any sleep whatsoever, and lost an additional 15 pounds. She diligently stayed on the Remeron, however, because her psychiatrist had assured her that it should kick in, in three weeks.

Upon coming home for Christmas, I could not believe the sudden change in my mother. She was no longer just anxious. She had completely

transformed into an emaciated woman who paced the floors, picked her skin, barely slept, and struggled to perform the simplest tasks like cooking a meal.

The mother I had known for 29 years who went on daily walks, had a full social calendar, and always worked now avoided leaving the house, stopped returning phone calls, and had decided to quit her job because of her extreme agitation. This drastic change literally happened between Thanksgiving and Christmas.

On January 2, only her second appointment with the psychiatrist, her psychiatrist instructed my mother to stop taking Remeron immediately and prescribed Effexor. Six days later, she hung herself. She left no note and never expressed any suicidal thoughts to anyone.

One week before her death, convinced the medication was causing my mother's extreme agitation, I went online to research Remeron. The

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only information I found assured me Remeron was safe and would kick in after an adjustment period.

If my family had any idea that some patients simply cannot tolerate the side-effects and can become suicidal on antidepressants, we never would have encouraged my mother to stick it out. Suicide was not on her radar screen until medication was introduced to her.

(Applause.)

DR. PINE: Thank you.

The next speaker is Andy Vickery.

MR. VICKERY: My name is Andy Vickery. I am a trial lawyer from Houston, Texas. Many of the people that you have heard from or will hear from, the victims of SSRI-induced violence and suicide, are my friends and clients.

I wish they didn't have to meet me in that way. I wish that I didn't have to answer the question for them of where is the justice in the "justice for all" when they have lost someone close to them.

I am supposed to compress about twelve

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year's worth of my professional life into three minutes today, and I don't know how to do that really, so let me make as many points as I can.

First, Dr. Clayton is right, do no harm -- no harm. Don't balance that you might maybe do some benefit to someone else -- do no harm.

Secondly, I have provided you with a written statement that's called "Needle in the Haystack." They are not my words. They are the words of Charles Beasley at Eli Lilly in 1990 when they looked at this, and he said:

"If you want to see if this is a real phenomenon, don't look at the clinical trial data.

It's not there. You won't find it there. It's like looking for a needle in a haystack because these trials were not designed to measure it."

What have you done for the last two years? You have done precisely that, you have looked for the needle in a haystack, in a place where it is not likely to be in the first place. You have looked at a hundred thousand patients, and you have ignored the millions of patients.

Why do you have a MedWatch system? Why did you abandon some years ago the FDA causality algorithm that was used to assess causality? Assess causality on these "anecdotes." These are not anecdotes, and these deaths are neither significant statistically, Dr. Stone, or otherwise.

Why did you abandon the FDA causality algorithm that you used to assess these events when Dr. Temple and Dr. Laughren started with the FDA? Because if you take the published literature, if you take Anthony Rothschild's article in `91 that shows akathisia and suicide, and if you subject it to the causality algorithm that the FDA itself used, it will show that it is highly probable that the akathisia and the suicidality experienced by the three patients that these Harvard psychopharmacologist rechallenged was probably caused by the Prozac.

That was 15 years ago. Fifteen years ago when this Committee was summoned, the issue was swept under the rug, and a lot of people have died since then.

I wonder, as I read the report, why you have been summoned 12 days before Christmas on short notice this year? The FDA says the Advisory Committee isn't even going to be asked for advice.

You might ask yourself, Why are we being summoned? Are we being used in some way before the change in the Congress in January? What's going on here?

(Applause.)

MR. VICKERY: In 1991, this gentleman right here (pointing) before he became a paid expert for Pfizer and GSK wrote, "From making the cure more grievous than the disease, good Lord, deliver us." You deliver us.

(Applause.)

DR. PINE: Thank you.

The next speaker is Mr. John R. Hays.

DR. HAYS: Good morning. I am Dr. John Hays. I am a physician trained in internal medicine and psychiatry. I have been in clinical practice, a medical academic, the president of a Catholic hospital system, and for just the past eight years I've worked for Eli Lilly

& Company where I am vice president for Lilly Research Laboratories.

I joined Lilly because they gave me the opportunity to do work that might influence the mental health of millions of people. Still, I speak to you today in my identity as a clinician who has spent many hours with depressed people just one at a time. It is they who have most shaped my career.

I have not come to discuss Lilly's extensive research in the area under discussion, rather I will urge a very deliberate course to avoid bringing unintended harm to the patient's we all wish to protect.

Depression is recognized as one of the most serious and economically burdensome illnesses in the world. Effective treatment exists and yet irrational fears and stigmas still discourage recognition and treatment of depression.

Seeking help for depression requires courage. A depressed person must overcome fear and

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embrace hope to seek help. Even accepting help is difficult for depressed people who may feel that they are unworthy or hopeless.

Treating depression also requires courage. Caregivers must also overcome fear of criticism or litigation, embrace hope themselves, and prescribe treatment whenever needed.

We, all of us in healthcare, must not dash that often fragile courage. We must do whatever we can to help depressed patients and those who care for them to address the illness in an atmosphere of rationality.

We now believe that doctors and patients confronted by warnings about a real but infrequent risk have lost some of the courage as a result of those warnings and the media attention that has surrounded them.

Scientists such as Drs. Valuck, Gibbons, Mann, and others who have done elegant work to assess this are speaking. Please heed them. Their findings of the unintended, negative impact of the previous warnings are alarming.

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Eli Lilly & Company applauds the FDA's efforts to draw credible inferences about a critical public health issue from such a large data set.

Please use this opportunity to communicate about depression with the same kind of rationality that exists in other areas of medicine and to foster more understanding rather than more fear and stigma.

We urge you to be clear about the infrequent occurrence of the risks under discussion. We urge you to align any warnings to

the magnitude of risk and the benefits.

Also, we urge you, if you make treatment recommendations, to make recommendations that doctors, patients, and families can actually implement in today's healthcare environment.

Thank you for your time, and thank you all for your courage in considering this complicated issue in such a public forum.

DR. PINE: Thank you.

Heidi Bryan is the next speaker.

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MS. BRYAN: My name is Heidi Bryan. I am 48 years old, and I have battled with depression most of my entire life. Antidepressants saved my life.

I first began a course of tricyclic antidepressants approximately 25 years ago after almost killing myself during a major depressive episode. The antidepressant changed my life and my mood and I was able to go on living.

After a few years, I stopped taking them and battled on and off with depression. Eventually, I suffered another major depressive episode and was given Zoloft then Paxil. I was on Paxil for about a year but felt no real sustainable benefit and stopped taking it.

Finally, I entered a drug study for an MAOI patch and my mood and my life improved dramatically. The study ended and I was placed on an oral MAOI which worked but would lose its efficacy, so periodically the dosage was increased and a catalyst added until I reached maximum dosage.

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When it bottomed out again, I changed doctors and was placed on Wellbutrin. That was over four years ago, and I have been on WellbutrinR the entire time.

I was never more suicidal while either beginning to take or taking the antidepressant. As I said, I know the medication saved my life. I do not believe there is an increased risk of suicidality with antidepressants if they are administered properly.

In my opinion, the problem stems from lack of mental health insurance parity. The average person can't afford to go to a psychiatrist or there isn't one available in their plan in a timely manner, so they go to their primary care physician.

Oftentimes, the primary care physician hasn't had the education in dispensing psychiatric medication, and therefore doesn't titrate the dosage to monitor the patient and manage the side-effects. The full dosage is given immediately, and that can have a significant effect on one's mind

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and body.
I also don't believe there has been enough data on this topic, but I'm not a researcher. I just know what I know, and I cannot emphasize enough the fact that antidepressants saved my life and gave me a new life.
I began thinking about suicide when I was around 11 years old and, as I aged, that happiness was just for other people. I accepted that as part of my fate.
Because of the medication, I now know what happiness is and have experienced it on a daily basis. I now look forward to each day instead of waking up and wondering if today is the day I'm going to die.
I am afraid a black box warning will turn people away rather than encourage them. This is already a population plagued by lethargy, indecision, fear, and shame.
I know antidepressants work and save lives, and I want as many people as possible to know that, too. We have enough obstacles in

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obtaining help for our condition. We don't need another one added to the list.
Thank you.
(Applause.)
DR. PINE: Thank you.
The next speaker is Donald Farber.
MR. FARBER: I am Don Farber from San Rafael, California. I have handled antidepressant cases for about seven years. I appreciate every speaker this morning. Certainly, in my own mind, they are very sincere, distinguished ladies and gentlemen, but this is America.
I don't know how many people of good will here want to manipulate the system. There are psychiatrists who say "We know everything, and 60 percent of the GPs that prescribe these antidepressants they don't know anything even though they went to medical school."
This is America. Every individual has the right to make decisions for themselves. Every physician has the right. I am very surprised that

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all, mostly psychiatrists get up here and want to filter information away from the GPs. They should have all of the information.
I do appreciate the panelists, very distinguished panelists. My question to the FDA is, Where are the other panelists? Where are the other panelists on the black vote?
In the black box vote on September 14, 2004, it was fifteen to eight. The ten psychiatrists split, five/five on the vote. It gives you an indication there your dealing with the

issue.
Of all the eight pediatricians, all eight voted for the black box. I say I appreciate your input, but we're not getting the right input for, as Bill Clinton said, "It's the labeling, stupid."
This data is inside baseball, very valuable, it's got a place, but we are all talking here about labeling for the GPs. I think the GPs and the labeling is only the real issue today.
You have to be honest. You have to get a bucket full of or a barrel of information into a

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little label and it has got to be accurate. It has to be accurate.
In the past, the FDA has withheld unfavorable information on the antidepressants, and they are still doing it. You never put in the label that these trials were never designed to pick up suicidality. You never put that there are sedatives used to get the drugs through the trials. You have never put the failed trials.
On October 10, 2002, the FDA supressed all the MDD failed studies on Paxil. They weren't going to tell the providers of the failures. The only reason the label came in later was because the British blew the whistle.
I am sure they had a reason for it. There are reasons I suppose that good drugs do fail trials. However, this is the type of information GPs need. Be honest in the label. I'm not going to sit here and say I want a black box, but be honest in the label.
(Applause.)
DR. PINE: Thank you.

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The next speaker is David Healy.
MR. HEALY: Hello, Colleagues. Could you have a quick look at the first slide there?
(Slide presentation in progress.)
MR. HEALY: "Truth is stranger than fiction."
"Well, of course it is," said Mark Twain. "Fiction has to make sense."
The question is, What would Mark Twain have classified this posting from the FDA as? Truth or fiction?
That is the distribution of the suicidal acts that happened in the registration trials of these three drugs here. Slide 2, and I do not know how to move the slides forward.
(FDA staff complies.)
DR. HEALY: Yes. This is how the company reports, FDA reviews the drug, and journal articles report those acts. You referred earlier to the Fergusson, et al., article, of which I am a coauthor.
We had to cope with this. We didn't undo

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this particular bit of bias to come to the results we had. The results we had would have been worse if we had undone this.

You referred to the MHRA article. Well, MHRA included three placebo suicides that weren't placebo in clinical trials. People who a week after going on Prozac went on to commit suicide.

Dr. Laughren has an article from 2001 in which he is the author that repeats this mistake. Dr. Laughren in this particular document here gives you no hint that all of the articles that he refers to showing that there is no increase in risk also repeats the mistake that you see here.

Now, this is the most interesting slide. This you won't have seen perhaps. This is data from three and a half years ago. This is data from FDA that FDA put in the public domain. This shows you a clearly, statistically significant increase risk of suicide.

FDA said three and a half years ago, "But we can get this risk to go away if we control for age and sex."

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Now, controlling for age and sex in controlled RCTs to begin with suggests you're doing something awfully odd, that the clinical trials were invalid to begin with.

The FDA also said that when we control for location, if that actually makes a difference, and this year FDA reported that when you look at the clinical trials that happened in the U.S. here, the placebo-controlled trials, that there were fewer people who went on to actually commit suicide.

I am sure you know that there are clinical trialists here in the U.S. who have ended up in jail for entering fake patients into this clinical trial program.

Fake or bogus patients do all sorts of interesting things. They get well on treatment. They don't commit suicide. It is just inconvenient for the audit trail, if they do. Does this explain FDA's findings?

I think you have asked the right questions. You have asked, Why has FDA left out

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the people who seem to be doing poorly, the people who drop out from the trials?

(Applause.)

DR. PINE: Thank you.

The next speaker is Lee Spiller.

MR. SPILLER: My name is Lee Spiller. I am with Citizens Commission on Human Rights.

(Slide presentation in progress.)

MR. SPILLER: Somebody came up with the idea that somehow antidepressants were keeping kids

from committing suicide as much or that the black box warning would make them not try to commit suicide.

This data out of Oregon shows otherwise. That is from 1994 to 2004. I honestly think that we wouldn't see much change in that trend. Had the black box warning not gone on, I think they still would have been committing suicide.

I am waiting for the remote here. Yes, thank you.

(FDA staff complies.)

MR. SPILLER: The other thing is this.

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Suicides have remained relatively steady, but suicide attempts are increasing incredibly. In 2000, there were 97 suicide attempts for 100,000. By 2005, it was 135.12. That is a major jump. If there is any chance that antidepressants are causing that, we need to know.

In 2004, 26,787 antidepressant-related suicide attempts entered an emergency department. That is one every 20 minutes, 75 a day, 515 a week.

There were more antidepressant-related suicide attempts entering emergency rooms than there were attempts related to heroine, marijuana, amphetamine, methamphetamine, LSD, PCP, club drugs, and inhalants combined.

However, actual mortality is scary, too. New York, New York, 59 drug-related suicides, 29 involved antidepressants; Houston, Texas, 89 drug-related suicides, 28 involved antidepressants; Washington, D.C., 36 drug-related suicides, 18 involved antidepressants; Portland, Oregon, 27 drug-related suicides, 14 involved antidepressants. That was in 2003. That comes

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from good data. It isn't something we just made up. That data comes from SAMHSA.

The National Violent Death Reporting System has started to come on line. They are not in all states yet, but one of their preliminary report said something interesting. Fifty-eight percent of suicides that they examined involved people who were already on a prescription for a mental health drug.

You guys have known about the antidepressants for years. I remember the original hearings. It is time to go ahead and warn people. We can take it. It is time to go ahead and put a black box on these drugs.

Thank you.

(Applause.)

DR. PINE: The next speaker is Carolyn Robinowitz.

DR. ROBINOWITZ: I am a general child and adolescent psychiatrist practicing in Washington, D.C., since 1968, speaking as a clinician. I don't

receive any funding from industry.

As we know, depression is a chronic, recurring, and progressive illness that has a major negative impact on the quality of life of those who suffer from it and their families in society as a whole.

Depression is the leading cause of disability according to the World Health Organization. Depression can be lethal. Persons with untreated depression face a 15 percent greater likelihood of dying by suicide.

Science and clinical practice have repeatedly shown that depression can be reliably diagnosed and effective treatments are available and that medication is often a vital tool in its treatment. These medications have revolutionized treatment and outcome for millions.

The suicide rate in the U.S. has been on the decline since the SSRI antidepressants were introduced in the late eighties. In areas of the country where rates of SSRI prescriptions are highest, rates of completed suicide are among the lowest.

Now, we need to be clear on the use of the term "suicidality," clarifying a major difference between suicidal thinking, suicidal actions or attempts, and completed suicide.

Of course, my heart goes out to those who have lost a loved one. That is truly a tragedy. It has to be prevented wherever possible. However, suicidal thoughts are a red flag to clinicians and family members alike.

Now, all medications, not just antidepressants but anticancer medications and even over-the-counter drugs such as aspirin, have side-effects. Their use must be considered clinically in terms of potential benefit and risks, risks of not treating as well as risks of treatment.

Patients must be counseled on medication side-effects and possible adverse reactions of all sorts, and clinical care requires appropriate monitoring.

Unfortunately, the FDA's imposition of the black box label has resulted in unintended negative consequences restricting access to care and adding to risk without providing measurable benefit.

Since the black box, there has been at least 20 percent reduction in prescribing. CDC has reported an increase in completed suicides, reversing the downward trend of the past decade.

The black box has contributed to further stigmatization of depression, those who suffer from it, and its treatment with unwarranted fear, black

box panic for families who now view these potentially life-saving treatments as highly dangerous.

On a personal note, I have seen the benefits of treatment for my family members, colleagues, and friends, as well as my patients. Regulatory decisions need to be based on science, not emotion and not politics. I urge you to be careful to avoid unintended consequences in the labeling.

Thank you.

DR. PINE: Thank you.

The next speaker is Sheri Walton.

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MS. WALTON: My name is Sheri Walton. I have major depression, and I am one of millions of people who take antidepressant medication to control depression.

I am here today to share my story and to urge you to consider the harm that any changes in labeling or access to antidepressant medication may cause. Suicide claims the lives of 30 million Americans each year.

Major depression, the most treatable of all mental disorders, is the leading cause. The one and only time I attempted suicide I was not taking antidepressant medication. I was in my early twenties and was severely depressed. Luckily, I survived.

Though I did not yet realize it, I was and had been suffering with undiagnosed and untreated depression for most of my young life. Because no one took my suicide attempts seriously and because no one in the medical profession followed up with me, my depression remained undiagnosed for another 20 years.

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To the outside world, I had a successful career, an active social life and lots of friends, but I was moody, sad, and quick-tempered, and true happiness always seemed to elude me.

Like all chronic diseases left untreated, depression is progressive. As my life progressed, my depression progressed until it took over my life and, unfortunately, my husband's life and my children's lives.

When I was finally diagnosed with major depression, I was 42 years old and my life was out of control. I was always angry. I cried for no reason. I forgot things, misplaced and lost things. I could hardly get out of bed each day. I felt like a total failure.

Antidepressant medications saved me. Along with therapy, medication gave me back my life. It gave my children back their mother. It gave my husband back his wife. For the first time in my life I have self-esteem, and I know what it

is to feel true happiness.
I was lucky. I had the resources to go
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around my insurance company and seek out a mental health professional who helped me find the right medication that worked best for me and who educated me on the risks and possible side-effects, not everyone is as fortunate.
As the "gatekeepers of treatment," insurance companies often direct diagnosis and treatment to primary care providers who are not trained mental health professionals and are not always knowledgeable and up to date on medications and their side-effects.
Without antidepressant medication, I would not be standing here today. Antidepressant medication is a critical and effective tool for fighting depression, yet fewer than half of Americans with depression seek treatment. For those that do, adding unnecessary warnings may scare them, their family members, and the doctors treating them away from their proven, prescribed treatment.
Access to mental health professionals and better monitoring and education of patients taking
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these medications about the risks and benefits of treatment would be preferable to any action that could negatively affect the millions of people who need treatment, putting them at risk of the very problem this Agency is trying to avoid, suicide.
Thank you.
DR. PINE: Thank you.
The next speaker is Jayne Richner.
MS. RICHNER: On August 16, 120 days ago today, our lives were shattered beyond any words I can express to you today. Our beloved 22-year-old son, Sean, was horrifically killed and we were brutally robbed. Sean had no history of depression. He had visited his primary care doctor just for general situational anxiety in which he was given a 90-day prescription of Celexa in a 10-minute office visit.
After being on these for approximately two and a half months, he could no longer sleep. His mind kept racing and thinking all the time, among other effects.
He went to his doctor, as a result of
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these feelings, four weeks prior to this death. His doctor recommended no further medication and said these are side-effects and they should resolve themselves in three to four weeks.
We and Sean trusted that the FDA and the doctors are educated and well-informed about these drugs and the risks and dangers in order to be able to prescribe these. We now know how wrong we were.

Without a doubt, we stand before you today knowing Sean was a victim of the withdrawal effects of discontinuing the antidepressant, Celexa, suicide by hanging in the middle of the night in our home.

At only 22 Sean had the world in his palms of his hands. He worked for almost two years in a high-tech company, my company. He has his car and his dream bike paid for.

He was pursuing a career as a firefighter. He was enrolled in an EMT paramedic program and was in the top of his class with one month left to go. The state trooper teaching his class is devastated by this and has awarded Sean

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all of his certificates.

Sean was also in training with the local auxiliary fire department and had just received his protective gear, which he proudly wore. He had taken the Firefighter Civil Service Exam in June. We just received his score result of 91 last month. Sean would have been excited and proud, although he knew he aced it when he took it.

Sean had it all going for him and he knew it. He was excited that he had a direction, and that it was all falling into place. He was articulate. He was outgoing and social with a sense of humor and a smile that drew everybody to him. He was athletic, played the guitar, and sang.

He openly loved his family, his future, and his friends -- who are all as devastated as we are knowing this is incomprehensible. Sean loved life.

Sean did not choose to end his life. That was done for him by the drug-induced fatal withdrawal effects of the antidepressant that he

0230

was prescribed.

A few nights prior to his death he appeared to be disconnected and then could be in and out of altered states. He jumped out of a second-story bedroom window and then requested that a friend stay over with him.

He was extremely restless and agitated as he slept and then awoke during the night and had to keep moving around. No one knew what was wrong. We now know this is referred to as akathisia. He was found kneeling at his bed with his hands clenched over his head.

When we found him, his feet were touching the floor. We can't imagine the psychotic state he must have been in. Without a doubt, Sean had no control over this and was overtaken by these drugs.

(Applause.)

DR. PINE: Thank you.

The next speaker is Nancy Sharby.

MS. SHARBY: Good morning. Thank you for allowing me to come. I am truly moved and very saddened by the story of the woman and the family who spoke before me, but I have a very different story.

I come here today from Boston, Massachusetts, but I really come from a farther place than that. I come from a place that has a long legacy of mental illness and suicidality.

In 1915, my great-grandfather walked into his kitchen, and while his family was eating dinner, he drank a bottle of lye. My grandmother's brother committed suicide; my grandmother attempted suicide; and my mother was suicidal. For all of them, there was no effective intervention nor effective treatment, but we are different.

I have two children with bipolar disorder, and I have depression myself. My daughter was diagnosed at 17, although she was sick for many years before that. My son was diagnosed at 19.

Both of them have told me that if it were not for my efforts of extensive advocacy and intervention for them, they would not be alive today.

My daughter has told me she is eternally grateful for interventions on her behalf, even though there were times when she looked at me and told me how much she hated me for dragging her to all of her clinicians.

Both of them have been hospitalized on numerous occasions as we attempted to stop their downward spiral into self-destruction. We are extremely fortunate that we have fabulous clinicians who are able to work with them and to prescribe effective psychotropic medications.

The only reason they are alive and thriving today is because of the integrated effects of family collaboration, my children's collaboration, and effective care by their care providers.

I can speak personally of the effects of depression on myself. It is not a matter of being sad or unhappy or sometimes feeling unmotivated. Depression takes you to another altered state where you aren't able to think, to remember, to make good decisions, or to express any joy in life. There is no hope that tomorrow will be any better than today. It disorganizes your brain.

Clearly, depression has a high personal cost, but it also has a high cost to society as well. As I mentioned before, there was high loss of work or productivity, there was decreased ability on disability claims, high health insurance

costs, and traumatically shattered families.

The good news is that depression is a treatable disorder, and there are many effective treatments available. However, no medication is effective for every person, and each medication is to be carefully calibrated to meet the exact needs of the individual who gets them.

I have to say in my family we have definitely needed to adjust medications. It can only happen when treatment is effectively monitored by the family, the care provider, and the patient alike.

Please do not set any barriers in place for effective treatment of patients who can benefit from drug rehabilitation.

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Thank you.

DR. PINE: Thank you.

The next speaker is Vera Sharav.

MS. SHARAV: Our organization disseminates credible information to challenge such reassuring documents as this report. I am overwhelmed to hear people worry about informing about risks. What is important is that the information in the black box is accurate.

In 1991, the FDA withheld evidence of suicides from the Advisory Committee. German documents revealed increased suicides in Prozac, so did FDA's own safety review. Confirmatory evidence from Pfizer and Glaxo were withheld from the Committee. FDA argued against warnings.

In 2003, it was the U.K. who issued the contraindicated warning against using any antidepressants in kids except Prozac. FDA did not issue a black box warning until Eliot Spitzer brought legal action against Glaxo.

Agency officials continued to obscure the scientific evidence with reassurances. They failed

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to acknowledge suicides such as Tracy Johnson, a healthy volunteer.

In May, Glaxo finally acknowledged that the suicide risk extends to adults. FDA's review is about damage control. It is designed to minimize and distort.

How did FDA reduce 16 suicides in 40,000 patients to 8 suicides in a 100,000 patients? Where did 4 Zoloft suicides and 13 attempts disappear? Shouldn't FDA analyze the very studies that have the most occurrences of these risks?

To exclude events which occurred during discontinuation periods and during dose tapering is dubious. That is when patients are at greater risk, and the label says so. The possibility that a five-fold, even a seven-fold increase risk of suicide can be described as "no effect" is unbelievable.

What the FDA presented to you is a reassuring interpretation of selected data by the very officials who have dodged the issue for 15 years claiming it is the condition, not the drugs.

What the FDA did not show you is evidence to support that SSRI safety for any age group or any indication. They are all at risk. They failed to provide you a complete SSRI data analysis.

They failed to provide you peer-reviewed critical analyses by independent scientists who have been proven right. FDA was wrong then; it is wrong now. Don't collaborate in this.

(Applause.)

DR. PINE: Thank you.

The next speaker is Kendrick Moxon.

MR. MOXON: My name is Kendrick Moxon. I am counsel to the Citizens Commission on Human Rights established in 1969 as a mental health watchdog.

After the first SSRI drug, Prozac, was approved by the FDA, CCHR began receiving complaints from consumers. In 1990, we submitted a petition on behalf of many of its victims to withdraw Prozac from the market.

In `91, the head of the statistical section of the FDA informed us that Prozac had the highest number of adverse event reports ever submitted to the FDA.

As of 1991, the FDA had received over 17,000 adverse reaction reports for Prozac including 60 deaths, nearly 500 cases of psychosis, and 991 suicide attempts.

In August `91, the FDA responded saying this was not unexpected for a drug that had been the subject of intense public interest. In other words, the FDA believed it was acceptable for a substantial percentage of consumers to attempt suicide.

The FDA stated it would convene a hearing to review all pertinent data on the relationship between the drugs and suicidality, but an honest and genuine review of relevant data did not happen.

CCHR lodged a complaint with the FDA because two of the 1991 committee members had conflicts of interest by receiving funds from Eli Lilly.

The FDA ignored that conflict of these two members and admitted that five other members had conflicts of interest and simply provided them waivers of criminal prosecution. Thus, at least 7 of the 10 members on that Committee had conflicts of interest that should have barred them from participating.

The panel acted in the interest of their

paychecks, not in the public interest. Seventeen thousand adverse reactions were brushed off as anecdotal, justification for misfeasance, which is still being used, Dr. Laughren.

Worse, every single one of these conflicted committee members in the `91 hearings voted not to change the labeling for the SSRI drugs. The three members who were not conflicted voted to strengthen the warning labels.

Let me repeat that. One hundred percent of the members who voted against a stronger label had conflicts of interest. One hundred percent of those not conflicted wanted to give consumers more knowledge.

I brought DVDs of CCHR's video footage of those 1991 hearings and I have provided copies for

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everyone on the Committee and for the media, if I wish them, to illustrate that nothing has changed.

You have again chosen three persons to whom you had to give conflict waivers of criminal prosecution for their admitted conflicts of interest.

Dr. Laughren's comment from the 1991 Committee, they felt no change was needed for SSRI labeling is most disingenuous. That Committee had a terminal case of conflict of interest and bias, and so does this one. It is clear that many more must die before impartial officials take the reins in this Agency.

(Applause.)

DR. PINE: Thank you.

The next speaker is David Shern.

DR. SHERN: Hi. I am David Shern. I am the president and CEO of Mental Health America, which was formerly known as the National Mental Health Association.

I joined Middle Health America or the NMHA on September 5, the first workday after Labor

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Day, giving up a tenured, full-professor position as a dean at the University of South Florida, the Florida Mental Health Institute.

I did that because of family experiences, my nephew having trouble ascertaining adequate care for some very serious behavioral problems he was having even though we knew all of the best people in the United States who were delivering care to children.

Out of a commitment to do more than I thought I could do as a professor and as a dean to sort of move science in to action, having my own family experiences as well as knowing many, many other people who have, I am deeply moved by all the stories that we are hearing today.

I am deeply moved by the people whose lives have been saved by pharmacological treatment

and by those families who have experience profound tragedies associated with that treatment.

For me the moral of the story, and many people have made this point as they have spoken today, is the importance of informed choices and

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good information for people.

It is also quite important for us I think to understand and act on the public health consequences of our decisions. This is a difficult calculus; it is not a simple calculus.

I am quite impressed by Dr. Mann's and Dr. Gibbons' work showing that a decrease in the use of SSRI following the black box warning, that the 22 percent decrease might be attributable to 200 excess deaths from suicide. It is very important that we balance this equation, and it is a very difficult decision.

I think that the data are reasonably clear that the availability of SSRIs has been clearly associated with a decrease in suicide. We look at ZIP code data with regard to the penetration of SSRI prescriptions.

We see that there is also an association between the availability or use of those drugs and decreasing suicide. The CDC's report of an increase after several years of decrease of suicide in adolescents has got to cause great pause.

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I don't envy you your decision. It is a very difficult one. On balance for me, the issues are raising the bar in terms of the quality of care that people receive. That is a resident theme which occurs in almost every testimony that we have heard today.

Informing the public about the possible risks and benefits for treatment, informing clinicians about that treatment and doing in a way that promotes the public health, I think on balance a black box warning for adults would not promote a public health objective.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Alison Malmon.

MS. MALMON: Good afternoon. My name is Alison Malmon, and I am the founder and president of Active Minds, Inc. Active Minds is the only national nonprofit organization dedicated to raising mental health awareness and supporting young adults at the peer level.

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We work with college students ages 18 to 25 on college campuses nationwide to improve awareness about issues in mental health, to educate students about available resources, and to increase the dialogue around the issues so everyone feels

comfortable getting the professional help they need and deserve.

In working with these students, the youngest group of the population you are looking at today and being a part of it, I wanted to be here today to represent the voice of young adults who find themselves in situations, transitions, and under stressors they have never felt before, to let you know to what extent they are suffering and emphasize the need for accessibility to all potential treatments to help them regain their lives.

To do this, I want to tell you the story of my brother, Brian. Brian was a brilliant, funny, and talented student in an Ivy League university, president of his a cappella group, sports editor of the school newspaper with a

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3.8 GPA.

In his senior year of school, when he was 21, he sought counseling from the school psych services. At that point we learned that Brian had been living in shame with serious depression since his freshman year.

The stigma, both internal and social, had overwhelmed him to the point that he kept his pain from everyone. He was terrified to admit anything was wrong, and he really didn't know what it was.

Eventually, Brian did seek help, but it was too late. He had lived for three years in college in total isolation and in the throes of depression.

When he finally sought the help, part of his treatment regimen did include psychiatric medications. The problem was that he had lived with his depression for so long and he had spiraled down so far that he died eventually of suicide from his illness, not from what was helping get him through it.

Many young adults first experience any

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symptoms of a mental health issue in this critical age of 18 to 24, the age when in fact most serious mental illnesses first present.

In a study done last year by the American College Health Association, nearly half of all students reported feeling so depressed they could not function, nearly half. One in ten reported having serious considered suicide.

Taking from the statistic offered by the U.S. Census that states that 17.6 million students are attending colleges or universities nationwide, this means that almost 9 million young adults are going through this world, through the best time of their lives, feeling so debilitated that they cannot function. Nearly 2 million have thought about taking their own lives.

This issue is much broader than the effects of antidepressants. These are students who are not even yet in the mental health system. In fact, anecdotally, most campus counseling centers will tell you that suicides that do occur on campus are primarily of students who are not in any sort

of psychiatric treatment at all. While you are weighing the benefits and risks of the psychiatric medications being presented today, keep this in mind.

DR. PINE: Thank you.

The next speaker is Ann Blake Tracy.

DR. TRACY: Ann Blake Tracy, Ph.D., head of International Coalition for Drug Awareness, author of "Prozac: Panacea or Pandora?" The last 17 years of my life have been devoted to researching, writing, and lecturing about these drugs.

In spite of that, two of my nieces in their early twenties, a decade apart, attempted suicide on antidepressants, the first on Prozac and the second just a month ago on Wellbutrin.

Due to time constraints, I refer you to my September 2004 testimony in my packet on the damaging effects of inhibiting serotonin metabolism, the very mode of action of antidepressants.

Impairing serotonin metabolism results in

a multitude of symptoms including suicide, violent crime, mania, and psychosis. Suicidal ideation is without question associated with these drugs according to medical research.

Rosie Meysenburg, Sara Bostock, and I have collected and posted 1,200 news articles documenting many exaggerated acts of violence against self or others at Drugawareness.org with a direct link to SSRIstorise.com.

Beyond suicidal ideation, we have mania or bipolar increasing dramatically. Antidepressants have always been known to trigger both as has the withdrawal of antidepressants.

According to "Pharmaceutical Business Review," in the last 11 years alone the number of people in the U.S. with bipolar disorders has increased by 4.8 million.

Dr. Malcolm Bowers of Yale found in the late nineties over 200,000 people yearly are hospitalized with antidepressant-induced manic psychosis. They also pointed out that most go unrecognized as medication-induced, remain

unhospitalized, and a threat to themselves and others. What types of threats from these manias?

Pyromania, the compulsion to start fires. Kleptomania, a compulsion to embezzle, shoplift,