

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE
CDER PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE
AND THE
FDA PEDIATRIC ADVISORY COMMITTEE

Monday, September 13, 2004

8:00 a.m.

Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

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Tana A. Grady-Weliky, M.D.
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PARTICIPANTS (Continued)

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Anuja M. Patel, M.P.H., Executive Secretary

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P R O C E E D I N G S

Call to Order and Opening Remarks

DR. GOODMAN: I wish to welcome you to this two-day joint session of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee, being held on September 13th and 14th here, at the Holiday Inn in Bethesda, Maryland.

I am Wayne Goodman, Professor of Psychiatry at the University of Florida, today wearing my hat as chair of the advisory committee. As you settle in, please take this opportunity to put into silent mode your cell phones and any other devices that emit sounds in the audible range of human beings.

Some of you may be surprised not to see Matt Rudorfer in this seat but we arm-wrestled for the position and he won.

[Laughter]

In all seriousness, his term has ended but we are fortunate to see him return as a voting consultant to the committee.

I have some official language to read to you. All committee members and consultants have been provided with copies of the background materials, from both the sponsors and the FDA, and with copies of letters from the public that we received by the August 23rd deadline. The background materials have been posted on the FDA website. Copies of all these materials are available for viewing at the FDA desk outside this room.

We have a very large table, a full house and important topic today so I would like to start with a few rules of order. Please speak directly into the mike when called on. We will be keeping track of individuals at the table who wish to speak and we will call upon them in order.

FDA relies on the advisory committee to provide the best possible scientific advice available to assist us in the discussion of complex topics. We understand that issues raised during the meeting may well lead to conversations over breaks or during lunch. However, one of the

benefits of an advisory committee meeting is that the discussions take place in an open and public forum. To that end, we request that members of the committee not engage in off-record conversations on today's topic during the breaks and lunch.

Whenever there is an important topic to be discussed there are a variety of opinions. One of our goals today and tomorrow is for the meeting to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Anyone whose behavior is disruptive to the meeting will be asked to leave. We are confident that everyone here is sensitive to these issues so understand that these comments are as a gentle reminder.

We look forward to a productive and interesting meeting. This is an unusual meeting in that we have two advisory committees represented here, Psychopharmacological Drugs Advisory Committee, chaired by myself, and the Pediatric Advisory Committee, chaired by Joan Chesney, to my left. We will now go around the table and have the

committee introduce themselves, starting on my right. Please indicate your expertise and affiliation. We will start in that corner, over there.

Introductions

DR. TEMPLE: Bob Temple. I am the Office Director, ODE I.

DR. KATZ: Russ Katz, Division Director, Division of Neuropharmacological Drug Products, FDA.

DR. LAUGHREN: Tom Laughren, psychopharm. team leader, in the Neuropharmacological Division.

DR. MURPHY: Dianne Murphy, Office Director, Office of Pediatric Therapeutics.

DR. TRONTELL: Anne Trontell, Deputy Director, Office of Drug Safety.

DR. FANT: I am Michael Fant, University of Texas Health Science Center in Houston. My expertise is neonatology and biochemistry.

DR. PFEFFER: Cynthia Pfeffer. I am a child psychiatrist at Weill Medical College of Cornell University, and I have expertise in

depression suicidal behavior in children and adolescents.

DR. FOST: Norm Fost, University of Wisconsin, Professor of Pediatrics, Director of the Bioethics Program and Chair of the IRB.

DR. ORTIZ: Irene Ortiz, University of New Mexico, Albuquerque VA. My expertise is in depression in the elderly.

DR. MALONE: Richard Malone, Drexel University College of Medicine, and my area is child psychiatry.

DR. NELSON: Robert Nelson, Children's Hospital of Philadelphia and the University of Pennsylvania. My expertise is in pediatric critical care medicine and ethics.

DR. PERRIN: Jim Perrin, Professor of Pediatrics, Harvard Medical School and Head of the Division of General Pediatrics at the Mass. General Hospital. I have shortened my expertise as being in general pediatrics.

DR. GRADY-WELIKY: Tana Grady-Weliky, Associate Professor of Psychiatry at the University

of Rochester School of Medicine and Dentistry. My expertise is in mood disorders and women across the reproductive life cycle and medical education.

DR. EBERT: Steven Ebert, Department of Pharmacy of Meriter Hospital and School of Pharmacy, University of Wisconsin, Madison.

DR. GIBBONS: Robert Gibbons, Professor of Statistics and Professor of Psychiatry and Director of the Center for Health Statistics at the University of Illinois, Chicago. I only do math!

DR. PINE: Danny Pine, child and adolescent psychiatrist, National Institute of Mental Health intramural research program. I am a clinical child psychiatrist.

MS. BRONSTEIN: Jean Bronstein, psychiatric nurse, Stanford University Hospital, the consumer representative.

DR. RUDORFER: Matthew Rudorfer, National Institute of Mental Health. My areas of expertise are mood disorders and psychopharmacology.

MS. PATEL: Anuja Patel, Advisors and Consultants Staff, Executive Secretary for the

Psychopharmacologic Drugs Advisory Committee.

DR. CHESNEY: Joan Chesney, the University of Tennessee, in Memphis, and Professor of Pediatrics, and my specialty is infectious diseases.

DR. MCGOUGH: Jim McGough, Professor of Psychiatry, UCLA. My area is child and adolescent psychopharmacology.

MS. GRIFFITH: My name is Gail Griffith and I serve as the patient rep. on this committee, and I would just like to take this opportunity to say why I am here. First, I am not a medical professional; I am a consumer. I have suffered from major depression since I was a teen. Second, I have a son who suffers from major depression and three years ago, at age 17, after he was diagnosed and placed on a regimen of antidepressants he attempted suicide by overdosing intentionally on all his medications. He nearly died. So, I know this illness. I know what it does to adolescents.

For the record, I would simply like to state that I have no professional ties to any

advocacy group or any patient constituency. I also wish to affirm that I have no ties to any pharmaceutical company, nor do I hold any investments in pharmaceutical manufacturers. My sole responsibility is to ensure that the interests of concerned parents and families are represented at this meeting.

DR. MARANGELL: Lauren Marangell, Baylor College of Medicine. I specialize in adult interventions in mood disorders, both unipolar and bipolar.

DR. ROBINSON: I am Delbert Robinson. I am from the Albert Einstein College of Medicine, in New York, and I specialize in psychotic disorders and anxiety disorders.

DR. LESLIE: Laurel Leslie. I am a behavioral developmental pediatrician at Children's Hospital, San Diego and my area of expertise is in children's mental health services research.

DR. IRWIN: Charles Irwin. I am a professor of pediatrics at the University of California, San Francisco. I am in charge of the

Division of Adolescent Medicine at the University, which is a multi-disciplinary program that cares for adolescents and trains large numbers of individuals caring for teenagers, and my research is in the area of risk-taking during adolescence.

MS. DOKKEN: I am Deborah Dokken. I reside in the Washington, D.C. Metro area. I do not have a specific institutional affiliation, and I have for several years been involved in parent and family advocacy and health care.

DR. NEWMAN: I am Thomas Newman. I am a professor of epidemiology and biostatistics in pediatrics at the University of California, San Francisco, and a general pediatrician.

DR. WELLS: I am Barbara Wells. I am a professor and Dean of the School of Pharmacy at the University of Mississippi. My expertise is in psychiatric pharmacotherapy.

DR. POLLOCK: I am Bruce Pollock. I am a professor of psychiatry, pharmacology and pharmaceutical sciences at the University of Pittsburgh. I head the Division of Geriatric

Psychiatry at the university.

DR. O'FALLON: Judith O'Fallon, Emeritus Professor of Biostatistics from the Mayo Clinic, with 30 years of experience particularly in cancer clinical trials but clinical trials methods.

DR. SANTANA: Good morning. I am Victor Santana. I am a pediatric hematologist/oncologist at St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. WANG: I am Philip Wang, Harvard Medical School. I am a psychiatrist and epidemiologist and those are my areas of expertise.

DR. GORMAN: Richard Gorman, a practicing pediatrician for 20 years in the Baltimore suburbs, Chair of the American Academy's Committee on Drugs, and representing the American Academy of Pediatrics at this table.

DR. MALDONADO: Sam Maldonado. I work at pediatric drug development at Johnson & Johnson. I am one of the industry representatives to this committee.

DR. MEHTA: Dilip Mehta, retired industry

executive and industry representative on the Psychopharmacologic Drugs Advisory Committee.

DR. GOODMAN: Thank you, all, for being with us these two days. Our session today is the second of two planned advisory committee meetings, convened to address recent concerns about reports of suicidal ideation and behavior developing in some children and adolescents during treatment of depression with a selective serotonin reuptake inhibitor, an SSRI, or other newer generation antidepressants. Our goal is to gather information from a variety of sources and perspectives to help us understand this complex situation, and ultimately to offer the best possible recommendations to the FDA.

I would like to thank the many groups, individuals and families that submitted written statements in advance of the meeting, many of which were quite informative as well as moving. A major portion of today's meeting will be devoted to a four-hour open public hearing during which dozens of people from around, and even beyond, the country

will have the opportunity to present their own personal or professional experiences and ideas about the relative risks and benefits of antidepressant medication in children and adolescents. Although the necessary consideration of the clock will permit only a short time at the microphone for each speaker, I can assure you that the committee welcomes and values input from all viewpoints and feels it is essential to our work that all voices be heard.

The committee's task is more difficult than usual. Our review is not confined to whether one agent is safe and effective based upon the corresponding clinical trials submitted to the FDA. We are faced, instead, with assessing efficacy and safety for nine drugs that represent more than one chemical class of antidepressants, all of which are already available on the market.

Although the cornerstone of the data under examination is derived from randomized clinical trials submitted to the FDA this time, following a reclassification of the adverse events, we find

ourselves turning to information from a wide variety of sources, in particular to inform ourselves about the drugs' possible benefits in this population. However, once we open our minds to consideration of data originating outside randomized clinical trials we rest upon a slippery slope in which variations in interpretation are introduced according to the weighting each member places on the merits of the source.

For me, the difficulty in assessing the balance between benefit and risk is multiplied by the nature of the adverse events under scrutiny. Psychiatrists grapple, for the most part, with illnesses that produce significant morbidity and more rarely mortality except from suicide. Nothing in my experience is more tragic than the loss of a child to suicide. To think that I might prescribe an agent that contributed to that outcome is unbearable. Equally unbearable is to think that I did not do enough to prevent it. This is the essence of the dilemma before us.

We may not have all the data we would

like, especially to assess long-term benefit. We can make recommendations about what research should be conducted, but we will be faced at the conclusion of business tomorrow to make recommendations based upon what we know at this cross-section in time. In deliberating on the safety of antidepressant treatment in children, let us not forget the toxicity of the underlying disease. Major depression remains an under-diagnosed, under-studied and under-treated serious disorder among many thousands of our nation's youth, leading to considerable suffering, disability and heartbreak in many families.

I believe that all of us in this room share the desire to alleviate the suffering from this disorder through the successful use of interventions that are made available to all those who need them. Despite the daunting task before us, I remain hopeful that with a fair and open-minded review of the evidence this advisory committee will constructively address the issues and ensure that interventions for this serious

disorder meet high standards for both effectiveness and safety.

Now I will ask Anuja Patel, executive secretary for the advisory committee, to review some of the ground rules for this committee and the public hearing.

Conflict of Interest Statement

MS. PATEL: Good morning. Before I continue, I would like to notify you of a correction on the roster attached to the agenda. The following consultants, Dr. Robert Gibbons, Dr. Matthew Rudorfer, Dr. Richard Malone, Dr. Tana Grady-Weliky and Dr. Irene Ortiz will be added to the roster. Amended copies of the roster will be available later this morning at the information desk outside this ballroom.

As you know, we have a very full open public hearing today, and in the interest of both fairness and efficiency we are running it by some strict rules. To make transitions between speakers more efficient, all speakers will be using the microphone and podium in front of the audience.

Each speaker has been given their number in the order of presentations and when the person ahead of you is speaking, we ask that you move to the nearby next speaker chair. Individual presenters and families have been allotted three minutes for their presentations. The one consolidated presentation has been given five minutes. We will be using a timer and speakers who run over their time will find that the microphone is no longer working. We apologize for the need for the strict rules, but we wanted to be fair and to give as many people as possible an opportunity to participate.

The public may submit comments after this meeting directly to the FDA's Division of Dockets Management. Instructions for submitting electronic and written statements are available at the registration desk outside this room. The docket will remain open until July 29, 2005. Thank you for your cooperation.

I would like to read the meeting statement into the record now. The following announcement addresses the issue of conflict of interest and is

made a part of the record to preclude even the appearance of such at this meeting. The topics to be discussed today are issues of broad applicability. Unlike issues before a committee in which a particular company's product is discussed, issues of broader applicability involve many industrial sponsors and products.

All special government employees and invited guests have been screened for their financial interests as they may apply to the general topics at hand. The Food and Drug Administration has granted particular matters of general applicability waivers under 18 USC 208(b)(3) to the following special government employees, which permits them to participate fully in today's discussion and vote: Jean Bronstein, Dr. Joan Chesney, Dr. Wayne Goodman, Dr. Lauren Marangell, Dr. James McGough, Dr. James Perrin, Dr. Bruce Pollock. In addition, Dr. Philip Wang has been granted a limited waiver that permits him to participate in the committee's discussions. He is, however, excluded from voting.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Infection Office, Room 12A-30 of the Parklawn Building.

In addition, Dr. Judith O'Fallon and Dr. Victor Santana have financial interest under 5 CFR, Part II, Sec. 40.202 that are covered by a regulatory waiver under 18 USC 208(b)(2).

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they may apply to each member, consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Dilip Mehta and Dr. Samuel Maldonado are participating in this meeting as industry representatives, acting on behalf of regulated industry. Dr. Mehta is retired from Pfizer and Dr.

Maldonado is employed by Johnson & Johnson.

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 product they may wish to comment upon. Thank you.

DR. GOODMAN: We will now proceed with a series of formal presentations that will bring us to 11:45 a.m. and then a 15-minute discussion before lunch. In the interest of time, I would like to ask my fellow committee members to restrict their questions after each presentation to issues of clarification only. There will be time, 15 minutes, for some discussion between 11:45 and 12:00 and tomorrow there will be a great deal of time for discussion and consideration of the questions before us. So, please, if you have questions about clarification, you can ask them after each presentation but restrict it to those kinds of issues.

With that, I would like to introduce Dr. Dianne Murphy, of the FDA, who will be followed by

Dr. Russell Katz, also of the FDA.

Overview of Issues

DR. MURPHY: Good morning and welcome to this very important discussion. Before we begin today's important deliberations, I would ask us to step back and see the broader context in which this meeting is occurring. I am going to spend a few minutes trying to describe that for you.

There are four points I hope you take from this short presentation. One is that the majority of medicines given to children in this country are prescribed off-label and have not been studied in all the pediatric populations in which they are used.

Second, because of new legislation and regulations since 1998, FDA has seen an increase in products that are used in children being studied in children.

Third, for the first 100 products, involving over 200 studies conducted as a result of the new legislation, FDA has found that approximately one-fourth of the time there was a

need to change the dose, a new pediatric-specific adverse event was described or the product was not found to be efficacious despite the fact that it was efficacious in adults.

Fourth, part of the reason we are here today is because we are finally studying the therapies that are being given to children. Children deserve the same level of evidence that is required for adults to determine that their use by them is safe, effective and properly dosed. They are a heterogeneous group who undergo rapid metabolic, hormonal, physiologic, development and growth changes in comparison to us, adults, who are rather static and tend only to deteriorate.

Over the last two decades FDA has actively supported, along with the American Academy of Pediatrics and many other groups, the efforts to encourage development of information and appropriate use of therapies in the pediatric population.

Very quickly, and this is important to understand, again, the context in which some of

this information has been brought to you, in the last decade we have made tremendous progress. In 1994 the agency published an approach that it hoped would help foster and encourage development of therapies that we be used in children. Congress passed legislation in 1997 which is referred to as the exclusivity or the incentive to develop studies on products that are being used in children.

In 1998 the FDA published the Pediatric Rule, which was an effort to say that if a sponsor is going to develop a product in adults and that same disease occurs in children, or condition, that product in most circumstances and certain conditions would be required to be studied.

We are going to go more into the 2001 adoption by FDA of Subpart D, Pediatric Ethics Regulations, and I wanted to bring up the Best Pharmaceuticals for Children Act, which you will hear referred to as BPCA, because it renewed the congressional legislation of '97 and is important in that, again, it is the renewal of the incentive to study products that are being used in children.

Another congressional legislative activity, the Pediatric Research Equity Act, in essence confirmed FDA's authority to require studies in children in certain circumstances.

In the last decade, particularly really since 1997, the FDA has issued over 290 written requests to sponsors asking them to study products in children because these products are being used in children. We have had submitted to us over 110 products, involving over 220 studies in children, and have now more than 76 new labels that have new pediatric information from these studies.

The major depressive disorders were included in the written requests that were issued, and written requests were issued for the products you see listed here, Prozac, Zoloft, Remeron, Paxil Effexor, Celexa and Serzone. Those studies were all conducted under this program or in response to this program.

This is a list of some of the programs and activities that are in place at FDA to help ensure the quality and ethical conduct of studies and the

approach to pediatrics. This is really focusing mostly on the drugs component of this. But there is, at the Commissioner's level, an Office of Pediatric Therapeutics. This was enacted by the Best Pharmaceuticals for Children Act in 2002 and first staff were hired last year. We now have in place an ethicist whose focus is pediatric ethics. You will hear a little bit more about the Pediatric Advisory Committee and Subpart D referrals in a minute. You just heard about the exclusivity process which has been important in making sure that trials do get conducted. I will spend a few moments at the end talking about disclosure requirements that are unique to pediatric studies that are conducted under exclusivity.

This is another meeting, actually in a long series of meetings that have occurred to ensure the scientific and ethical quality of activities involving studies that are being conducted in children. Since 1999, the Pediatric Advisory Subcommittee has had, including today's meeting, over ten meetings that have addressed over

ten scientific issues, three ethical issues and, in addition, starting last year, began having specific safety reviews of products that have been approved, again under the exclusivity provisions, so that all adverse events that occurred in the year after product was granted exclusivity were reviewed. Again, this is just to inform you of the ongoing pediatric activities that are occurring at the FDA, some of them.

The new advisory committee, I should say full Pediatric Advisory Committee is meeting for the first time today. It was chartered this year and is mandated to include patient and family organizations, and its mandated responsibilities include safety, labeling disputes and Subpart D referrals and general pediatric issues.

The first Subpart D ethics panel met this past Friday and will report to this committee on Wednesday. I will tell you a little bit more about that.

It is important to understand that Subpart D, which is part of the Common Rule, was those

extra protections for children applied to only federally funded activities until recently. In 2000, the Children's Health Act required FDA regulated products to be in compliance with additional protections for children that are embodied in the Subpart D of the Common Rule.

Subpart D is fundamentally a referral process. There is much more to it but it is a process for IRBs when they are unsure they can approve or under which regulation they should approve a study involving children. The Pediatric Ethics Subcommittee reports to the Pediatric Advisory Committee and this is a public process.

The disclosure of the studies that are conducted in children is distinct for studies that are conducted in children under the exclusivity provisions of BPCA. I mention this because it is unusual in the FDA if a product is not approved that those studies would be disclosed. However, we now have, again under BPCA, a requirement that within 180 days of submission of a pediatric study a public summary of the medical and clinical

pharmacology reviews will be posted. There are now 41 pediatric summaries posted at this website. Basically, you can go to the FDA page and get there by going to the Center for Drugs or pediatric summary\summary review.

The summaries of Effexor, Paxil, Serzone, Celexa, Zoloft and Remeron are available on the pediatric summary review site. As you know, and will hear, Prozac is the only antidepressant that is approved for use in children, and it is posted up on FDA's site for approved applications. That URL is provided for you here and in your handouts.

The new pediatric data has taught us that our knowledge of pediatric therapeutics is in its infancy; that we must study children if we are to understand pediatric-specific adverse events and reactions or if a product is going to work in children. The pharmacokinetics in children has proven to be more variable than anticipated. The submitted studies that we are receiving are teaching us that we need to know more about pediatric endpoints, pediatric trial designs and

how to conduct these trials, and that we will need to change some of our trials as we move forward. Ethical issues require reassessment from a pediatric perspective. Therefore, at this point no longer shall each child be an experiment of one in which not much knowledge is gained.

As we move forward, it will require our careful attention if we are to discover why children are behaving differently. If children are to be appropriately treated, we will need to know more than how to correct those things or describe adverse events. We are going to need answers to such fundamental questions as to why children react differently, what are the metabolic, physiologic events that are occurring that necessitate different dosing, or why is there a therapy that works in adults and does not work in children. Our public policy must be more knowledge to replace our ignorance. Thank you, and we look forward to your discussion.

DR. MARANGELL: Dr. Murphy, a quick question, when the FDA requests a study can you

specify methodology and assessments that you would like to see included?

DR. MURPHY: When FDA requests a study we do put in that written request the trial design, the number of patients, the adverse events--you know, under exclusivity all of that does go into the written request.

DR. GOODMAN: Thank you, Dr. Murphy. Now Dr. Katz?

Overview of Issues

DR. KATZ: Thank you, Dr. Goodman, and good morning. I would like to welcome you to this joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee.

As you know, we are here to present to you and to ask for your guidance in interpreting the results of our analyses of the relationship between antidepressant drug use and suicidal behavior in controlled trials in pediatric patients. This meeting is in follow-up to the meeting of these two committees held in February of this year. At that

meeting, as you recall, we presented to you and obtained your endorsement of our plans to perform these analyses.

At this point I would like to very briefly recap how we arrived to this point. As you know, we first became aware of a possible relationship between antidepressant drug use and suicidal behavior in pediatric patients in May of 2003 when, in response to our request for further clarification of their data, GlaxoSmithKline, the manufacturer of Paxil, submitted data to us that suggested such a link for that drug. As a result of this submission, the agency issued a public statement recommending that this drug not be used in pediatric patients with depression, and independently we asked all other manufacturers of antidepressant drugs to resubmit the relevant data from controlled studies with their drugs in pediatric patients.

Based on our review of this data, we issued a statement informing prescribers that there was a potential relationship between all of these

drugs and suicidal behavior, and that these drugs should be used with caution in these patients.

However, at that time we also noticed that the data submitted to us from the various companies was not reported to us in a form that would permit definitive analyses. Specifically, each company classified various behaviors as being suicide-related adverse events in their own idiosyncratic manner. This led to questions about whether or not these events were, in fact, suicide-related and, in addition, prevented meaningful comparisons between drugs in this class.

For this reason, we decided that an independent assessment of these possible events by experts in suicidology would be the most appropriate way to definitively answer the question of whether or not any, all or none of these drugs increased the risk of suicidal behavior in pediatric patients. Let me just add that by definitive analyses I mean analyses that make the best possible use of the available data.

It was at this time that we brought the

issue before you. At that meeting we presented you with our plans to submit blinded narrative descriptions of possible suicide-related events to a group of independent experts, to be coordinated by Columbia University, whose task it would be to classify these events as being suicide-related or not. Although no formal vote was taken, this committee fully endorsed this effort and agreed that the data in hand at that time did not permit definitive analyses to be done.

The committee also recommended, based in part on the data in hand but also, I believe importantly, on the basis of testimony from members of the public who had suffered the tragedy of loved ones who had committed suicide while taking these drugs, that the agency should ask sponsors of these products to warn prescribers that patients being treated with these drugs, especially at the beginning of treatment, should be closely watched for the emergence of signs and symptoms that might suggest a worsening in their clinical state.

Since that February meeting a number of

important things have happened. Based on your advice, the agency drafted, and all of the sponsors of these drugs have adopted, language in product labeling warning about the possibility of significant behavioral changes at the outset of treatment with these drugs in both pediatric and adult patients, and the prescribing community and the public have been informed of these changes.

Critically, this warning made clear that the possibility of worsening and a possible increased risk of suicidal behavior at the outset of treatment could not necessarily be attributed to the drugs because the data did not permit such a definitive conclusion. Nonetheless, it was considered appropriate and prudent to inform prescribers and patients and their families that changes in behavior could occur with the onset of treatment.

Also, the Columbia group has completed their task of reclassifying the potential cases of suicidal behavior and, importantly, we have completed our reanalyses of these data. As

promised at our February meeting, we are now ready to present to you the results of these analyses.

At this point I would just like to give you a brief overview of the agenda for today's and tomorrow's session. First Dr. Tom Laughren, of the Neuropharmacology Division, will provide you with a more detailed account of the regulatory history and events that have brought us here this morning. He will be followed by Dr. Diane Wysowski, of the agency's Office of Drug Safety, who will briefly present the results of some recently published epidemiologic studies relevant to this question. We have provided the committees with copies of these published materials. Although, of course, we consider our reanalyses of the controlled data to be the primary source of data on which your discussions and recommendations will be based, we thought it important to present at least briefly the available relevant epidemiologic data.

Next, Dr. John March, of Duke University, will present a brief report of the Treatment for Adolescent Depression Study, or TADS trial, a

recently completed trial that evaluated the effects of fluoxetine in adolescents with depression. As you know, fluoxetine is the only drug approved in the United States for the treatment of depression in pediatric patients and, as you will see, these data make an important contribution to our overall assessment of the problem before us.

Dr. Greg Dubitsky, again of the Neuropharmacology Division, will then present an overview of the design of the pediatric trials from which the data for our analyses were derived. This exploration is important because similarities and differences in design elements among these trials can have important implications for whether or not these data can be examined as a whole, or whether they must be considered separately.

Then, Dr. Kelly Posner, of Columbia University and the primary person responsible for coordinating the blinded reclassification effort, will present to you the methodology her group used to produce what we now consider to be the definitive data on which we have based our

reanalyses.

Because the reclassification of these clinical events was the critical activity on which all subsequent analyses and decisions will have been based, and because by its nature it involved subjective assessments of the primary data, we felt strongly that it was appropriate to ensure that the methodology used by the Columbia group could reliably and reproducibly yield similar results when applied by an independent group. For this reason, agency scientists performed such an independent reclassification of a percentage of these cases, utilizing the Columbia classification schema, and Dr. Solomon Iyasu, of the agency's pediatric group, will present the results of this independent audit of the Columbia process.

At that point, Dr. Tarek Hammad, of the neuropharmacology group, will then present the most critical results of his extensive reanalyses of the data as reclassified by the group of outside experts. These analyses look at the data for individual drugs, as well as across all drugs, and

will provide the data on which the committee subsequent discussions will be based.

Finally, the last formal agency presentation will be given by Dr. Andrew Mosholder, of the Office of Drug Safety. Dr. Mosholder's name is undoubtedly familiar to you. Dr. Mosholder was the agency reviewer who had, prior to the February advisory committee meeting, performed analyses on the cases as submitted, that is, the non-reclassified cases, and had concluded that these drugs did, in fact, increase the risk of suicide-related behaviors in this population. As you know, Dr. Mosholder did not present his conclusions at the February meeting, although the data on which his analyses were based were presented and we noted at that time that some in the agency had already reached a definitive conclusion on this question.

There has been since that meeting considerable public discussion and controversy related to the fact that Dr. Mosholder was not given the opportunity to present his conclusions at

that meeting. The reasons for our decision at that time were straightforward. As I have discussed today and as we have discussed publicly on numerous occasions, we had decided that at the time of the February meeting the data had not been submitted in a form in which we could reliably agree that the events described as representing suicide-related behavior did, in fact, represent such behavior. We, therefore, felt that conclusions reached on the basis of analyses that relied on these descriptions could no, in turn, be considered completely reliable.

We felt, and still feel, that presenting conclusions based on potentially unreliable analyses could have led to errors in either direction, that is, resulted in a conclusion that the drugs were dangerous when they really were not, or resulted in a conclusion that the drugs were safe when they were not. A mistake of either kind could have, in our view, disastrous consequences. For this reason it was, and remains, our view that these decisions must be based on the most reliable

analyses possible. Now that the definitive analyses have been done, however, Dr. Mosholder will present his own analyses and conclusions, with particular attention to a comparison between his results and Dr. Hammad's.

Following lunch we will hear brief comments from several of the pharmaceutical companies who have antidepressant drug products on the market, and the day will end with the open public hearing. A total of 73 members of the public have signed up to make statements. As you have heard and as in the February meeting, we will again need to limit the statements from the public, this time to three minutes per individual. We recognize that this is not much time and we apologize for the limit but it would be impossible for all those who wish to make statements to do so without imposing this limitation. We appreciate your understanding on this point and, as you have heard, anyone who wishes may submit written testimony to the docket.

Tomorrow the committee will discuss the

data you will have heard. We, of course, look forward to this discussion and in particular to your answers to the questions we have brought to you and which we have provided in your background packages. We are, in brief, interested in your views on our approach to the reclassification effort and, critically, whether you believe that the analyses establish that one or more of the drugs studied increases the risk of suicidality in pediatric patients. Importantly, if you do conclude that there is a signal for suicidality, whether for one or more of these drugs, we need to know what additional regulatory action, if any, you believe should be taken.

The results of our reanalyses are complex and their interpretation is not immediately obvious. They raise difficult questions, not only about the fundamental meaning of the results of the analyses for each drug, but also about the comparability of the various treatments and, therefore, whether it is appropriate to consider the drugs as a class for which any conclusion

reached should globally apply or whether the drugs must be considered individually. Further, the question of any further regulatory action is also a thorny one and must take into account the consideration of the lack of available effectiveness data for all of the drugs, except fluoxetine, although the absence of this effectiveness data is not easily interpreted either.

Because of the complex nature of the evidence and because of the extraordinary importance for the public health of the decisions that we need to make, we are turning to you, the experts, for guidance on these matters. We thank you in advance for your efforts.

DR. GOODMAN: Thank you, Dr. Katz. I would like to invite Dr. Tom Laughren to come to the podium.

Regulatory History and Background

DR. LAUGHREN: Thank you, and I would also like to welcome everyone to the meeting today. I am going to begin by briefly giving an overview of

events leading up to today's meeting. I am then going to talk about the key elements in the division's exploration and analysis of the pediatrics suicidality data. I will then spend a little time talking about our March 22nd public health advisory and the subsequent labeling changes that have now been implemented. Then I am going to spend a little time talking about the effectiveness data. I did this at the last meeting; I will do this again because I think it is important to have these data in mind since they are an important part of the context of this discussion about pediatric suicidality. Then I am going to quickly go over the questions and the issues for which we are going to be seeking feedback tomorrow. I think it is important that you have these questions in mind as you hear the talks this morning.

This slide lists a number of the people at FDA who have been involved in looking at these data. As you can see, these people come from various sections of the agency. It is a long list, and really the point of this slide is that we take

this matter very seriously and we have invested a lot of effort into trying to understand these data.

You heard earlier about the two laws, FDAMA and BPCA, that give FDA authority to grant additional market exclusivity for companies which do pediatric studies. The point of this slide is that most of the data that we are dealing with this morning come from these types of studies, in other words, studies that were done to obtain additional marketing exclusivity. However, we have also included in our analysis data from a ninth antidepressant drug, Wellbutrin, that was not studied for exclusivity. That was one study in ADHD. We are also including in our analysis data from the TADS trial that you will hear about in more detail later in the morning from John March, from Duke.

As Dr. Katz pointed out, this issue first came to our attention based on a review of the Paxil supplement. In that review, the reviewer noticed that events suggestive of possible suicidality were subsumed, along with other

behavioral events, under the preferred term "emotional lability." This led FDA to issue a request to the sponsor, GSK, to explain this coding practice. Ultimately, that resulted in a report to FDA, in May of last year, on pediatric suicidality with Paxil. As Dr. Katz pointed out, that report did suggest a signal of increased suicidality in association with drug use, particularly in one of three depression trials in that program.

What I am going to do in this slide is very quickly run through subsequent events that led us up to the February advisory committee meeting. So, in June of last year we issued a public statement cautioning about the use of Paxil in pediatric patients with depression. In July we issued requests to sponsors of eight other antidepressant products to ask them to give us the same kind of summary data that GSK had provided for Paxil.

In September of last year we held an internal regulatory briefing at FDA. The purpose of this was to brief upper management about this

signal. The two points that I took away from that meeting from the standpoint of the division's work were, number one, there was general agreement that it would be important to try and classify these events since many of them were not clearly related to suicidality and we felt it would be very important to do a rational classification. Secondly, there was sentiment that we ought to try and obtain patient-level data information, beyond the summary information, in order to try and explain differences among trials and between programs.

In September and October we began to get responses to our July requests. Also, in October we issued requests to sponsors for the patient-level data sets that I mentioned earlier. Also in October, we decided to go outside of FDA to get a classification of these cases accomplished. Then, again as Dr. Katz mentioned, in October we issued a second public health advisory, this time extending the cautionary language to all current generation antidepressants. Finally, in November

and December, having looked at the responses to the July request for summary data, it occurred to us that we may not have obtained all of the relevant events and so we sent additional requests to have a broader search for events that we would then try and get classified.

That brings us up to the February advisory committee that we held. At that meeting you advised us to basically continue with our analysis of the data but, in the meantime, to go ahead and make some labeling changes. In March of this year we issued a public health advisory announcing the changes that we had requested. In the meantime, the classification of the cases was ongoing by the Columbia group. Those were completed in June of this year. Then, in August of this year we completed our analysis of the pediatric suicidality data.

In this slide what I am doing is basically summarizing what I think is the major contribution of the division to this effort. Again, we went to a lot of effort to try to ensure completeness of

case findings, that we had a complete set of events to have classified. We then worked with Columbia University to have these events classified.

As an aside, I would like to mention that this effort, conducted by Kelly Posner and her group at Columbia and the very exceptional group of outside experts that they assembled to do this, represents a very substantial effort that has not only helped us to understand these data but I think will have implications for the field in terms of developing a standard approach to classifying these kinds of data, and also will lead to guidance document that, hopefully, will improve ascertainment for suicidality, which was a very significant problem in these trials.

Finally, the third effort that we were involved in was, again, in obtaining the patient-level data sets that allowed us to try and explore for confounding and effect modification, in essence, to try to explain some of the striking differences we were seeing in the signal across trials within programs and across programs.

As mentioned, at the February advisory committee you advised us to go ahead and strengthen labeling, in particular for monitoring for suicidality, while we were completing our analysis. We did this and we announced the request that we were making in a March 22nd public health advisory.

The changes in labeling that we requested have now all been implemented for the ten drugs of interest. I would add here that our plan is to extend the standard language to all antidepressants, not just the current generation and, in fact, that has already been done for some of these drugs. We are waiting to do it for the others until we work out the final standard language, which will be based on advice we get from you at this meeting.

What I want to do in this slide is to very quickly go over the labeling changes that have been implemented now. This slide focuses on the advice for clinicians who are using antidepressants for treating any condition really, whether in adult or pediatric patients. So, the advice is as follows,

first of all, we are asking clinicians to closely observe patients who are being treated with antidepressants for clinical worsening and for the emergence of suicidality, especially at the beginning of therapy but also at times of dose change.

Secondly, we are asking clinicians to consider changing the therapeutic regimen in patients whose depression is either persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Finally, we are also asking clinicians to observe for the emergence of other symptoms as well, for example, anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, and so forth. The idea here is that there is a belief, not really solidly empirically established but a belief that many of these events may represent precursors to emerging suicidality. So, we are also asking clinicians to be alert to these symptoms.

This slide focuses on advice for families and caregivers that also is included in labeling. We are asking those folks to also be alert to the emergence of these same symptoms and to report those symptoms to healthcare providers if they emerge.

Now I want to turn to briefly describing the efficacy data for the 15 short-term trials that we looked at in our review of these pediatric supplements. I am going to be focusing on primary outcomes in those trials. I also want to spend a little time talking about the difficulty in interpreting negative findings in this setting and again I want to note that although I am not going to be talking about the TADS efficacy data, you will be hearing about the TADS efficacy data from John March a little bit later in the morning.

This is kind of a busy slide but basically each row in this table represents a different trial. Again, there was a total of 15 trials. This is color-coded so you can separate the different programs. There were seven programs.

Paroxetine had three trials. The rest all had two trials. The column to look at is the far column where I have summarized the results on the primary endpoint.

Basically I have characterized the results as follows: Where the p value on drug versus placebo on the primary endpoint was less than 0.05, I am calling it positive. As you can see, that applies to the two fluoxetine trials and one of the citalopram trials. If the p value fell between 0.05 and 0.1 I am characterizing it as a trend. That applies to one of the sertraline trials and one of the nefazodone trials. If the p value was greater than 0.1 on that primary endpoint I am characterizing it as negative. That applies to all the remaining trials. So, basically what you have here is three out of 15 trials meeting FDA's standard for being positive.

The other point I want to make on this slide is that this represents FDA's view and I think it is a reasonable standard, however, it is not the only standard. To illustrate that, I want

to talk about two published papers, one for study 329, the paroxetine trial, a paper that was published by Keller in 2001. That paper characterized that trial as a positive study, the argument being that although it failed on the primary endpoint it succeeded on all the secondary endpoints. So, the authors of that paper considered it a positive trial and many in the community also considered that a positive study.

Secondly, there was a paper published on the two sertraline trials by Wagner et al., in 2003, that was based on a pooling of the two trials. Individually those trials did not make it but if you pooled them you got a significant p value. Again, many in the community view that as evidence of effectiveness of sertraline in pediatric depression. This does not meet FDA's standard but the point is that different folks have different views of the same data.

Now I want to talk a little bit about the problem of interpreting negative findings in this setting. First I want to turn to adult depression

trials for drugs that we believe work. Looking at trials that on face should work, about half the time those trials fail. If that failure rate can be extrapolated to the pediatric population, the expectation in two study programs and most of these programs were two study programs--the expectation is that three out of four times you would fail to get two positive studies. So, perhaps it shouldn't have come as such a surprise that many of these programs failed. On the other hand, the fact that the overall success rate, again according to FDA's standard, is only 20 percent success is clearly a concern.

Other factors to think about in looking at negative trials in this setting is, first of all, the history of antidepressant trials in pediatric depression. If you go back to the tricyclic era, there were 12 trials comparing tricyclics with placebo in this population. All of them failed. There are many interpretations of that. One, of course, is that these drugs simply don't work in that population.

Another might be that there is even greater heterogeneity in this population of patients captured under the diagnostic criteria for major depression than we see in adults. That would work against getting positive trials.

Another factor to think about is the somewhat unusual regulatory context in which these studies were done. Ordinarily, when companies do studies they only benefit if they get a positive trial. In this setting they would win in terms of getting exclusivity whether the trial succeeded or failed. I don't know whether or not that was a factor in the conduct of these trials but it is another thing to think about.

Finally, at the time that we issued written requests for these programs we were not routinely asking for phase 2 dose-finding studies as we are now. That, again, maybe a factor. It is possible that the dose was not right in some of these trials.

In any case, the bottom line in terms of efficacy is that I think there are plausible

reasons for failure to find efficacy other than the obvious one that maybe the drugs don't work. On the other hand, a very important point I believe is that even though most of these programs have failed to meet FDA's standard for approval, this is not the same thing as saying that we have proof that the drugs have no benefit. The drugs may have benefit that has simply not yet been demonstrated. On the other hand, the failure to demonstrate benefit clearly is a concern, especially when we have a risk, as we have now seen, of emerging suicidality. So, the burden is clearly on those who believe that these drugs do have benefit to show that benefit. Tomorrow I am going to talk a little bit about some possible designs for looking at longer-term benefits with these drugs.

Now what I would like to do is quickly move through the questions that we are going to be asking you to discuss and comment on tomorrow. Again, we think it is important that you have these in mind as you hear the presentations this morning.

First of all, we are going to ask you to

comment on our approach to classifying the possible cases of suicidality and our subsequent analyses of the resulting data for the now 24 trials--again, the additional trial is the TADS trial.

The question then would be do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients? If the answer to that question is yes, to which of these nine drugs does that risk apply? In other words, is this a class effect of all antidepressants? Does it apply to certain subclasses within this broader class or only to specific drugs?

If you believe there is a class risk or a risk that applies only to certain drugs, how should this information be reflected in the labeling for each of these products? What, if any, additional regulatory actions do you think we need to take?

Finally, again we would like you to consider what additional research might be needed to further delineate the risks and the benefits of

these drugs in patients with pediatric depression?

Thank you very much.

DR. GOODMAN: Thank you, Tom. I imagine people have questions but I want to try to catch up this morning to make sure that we have time for all the presentations. So, I will ask you to hold your questions and I would like to invite the next speaker, Dr. Diane Wysowski, who will be looking at data from different sources other than clinical trials.

Recent Observational Studies of Antidepressants
and Suicidal Behavior

DR. WYSOWSKI: Good morning. In this presentation I will be reviewing recent studies of antidepressants and suicidal behavior and briefly discuss their methods, results and limitations.

I reviewed two types of studies, ecological and patient-level controlled, observational studies. Ecological studies show increasing antidepressant use and simultaneous decreasing suicide rates. However, such correlations do not necessarily imply causality.

Findings of ecological studies can be merely coincidental. Numerous factors such as changes in risk factors, social and economic changes, more available counseling, changes in gun access and choice of a less lethal means of suicide in children and adolescents may coincide with decreases in the suicide rate in children and adolescents.

Ecological studies don't show which factor or factors are responsible for an observed trend. Furthermore, an increased relative risk of suicide with antidepressants in children and adolescents may coexist with a decreased suicide rate. To better examine causality, we turned to patient-level controlled studies, such as observational studies, in clinical trials.

For the rest of this presentation I will be focusing on two patient-level controlled, observational studies. The first is the Jick study that was published this July in The Journal of the American Medical Association. It is a matched case control design based on patient prescriptions and

diagnoses obtained from the United Kingdom's GPRD, the General Practice Research Database, for the period 1993-1999. The GPRD is a database of medical records from general practitioners of more than three million patients in the United Kingdom.

For this study subjects were 10 through 69 years of age. Exposures studied were the most widely used antidepressants in the U.K., amitriptyline, fluoxetine, paroxetine and dothiepin. Dothiepin was chosen as the reference category. From data on these antidepressant users, the investigators identified 555 cases of nonfatal suicidal behavior, defined as ideation or attempts. They identified 17 cases of suicide. From the base group of antidepressant users, the investigators matched the cases with more than 2000 controls who did not develop suicidal behavior. The researchers then compared the suicidal cases to the non-suicidal controls for initiation of each antidepressant.

Controlling for age, sex, calendar time and time from first antidepressant prescription to

onset of suicidal behavior, the range of relative risk for nonfatal suicidal behavior was 0.83 to 1.29 for the antidepressants compared to dothiepin. None of these risks were statistically significant. Paroxetine, with a relative risk of 1.29 and a 95 percent confidence interval of 0.97 to 1.7, had borderline statistical significance.

Similar results were obtained for those 10-19 years old. No statistically significant association was found between each antidepressant and completed suicide. No statistically significant association was found between stopping an antidepressant and nonfatal suicidal behavior.

The relative risk for nonfatal suicidal behavior and suicide were highest for patients first prescribed an antidepressant within 1-9 days, versus 90 days or more, before the suicidal behavior of the case in the same time period for the control. For nonfatal suicidal behavior the relative risk for antidepressant use within 1-9 days was 4, with a 95 percent confidence interval of 2.89 to 5.74. For suicide the relative risk for

antidepressant use within 1-9 days was 38, with a wide confidence interval of 6.2 to 231.

Reviewing the limitations of this study, the results are only as good as the GPRD data. There are concerns about possible missing data, possible incomplete ascertainment and misclassification of patients, and possible uncontrolled biases among the antidepressant drugs, such as selection by severity of depression. There were no interviews of cases and controls so medication compliance is not systematically known. There was no unexposed group, and the antidepressant risks are only in reference to the dothiepin group.

FDA asked Dr. Jick and colleagues to reanalyze their results with amitriptyline as the reference category. They kindly responded to our request, and asked that their interpretation of the results be presented verbatim to the committee. If the committee wishes to see these supplemental analyses I will be glad to present them in the question and answer period.

Other limitations of the study include the fact that suicidal ideation is a more subjective, softer diagnosis than suicide attempts and the risks were not examined separately. This was a study of mostly adults and there is limited information on children and adolescents.

Finally, the investigators excluded patients with a history of 11 other neuropsychiatric diagnoses, calling into question the representativeness of the patients compared with those in clinical practice.

Another patient-level controlled study examined the relationship between antidepressants and the risk of suicide attempt by adolescents with major depressive disorder diagnoses. The study was done by investigators at the University of Colorado School of Pharmacy and Medicine. Robert Valuck was the principal investigator. It was presented as a poster at the International Society of Pharmacoeconomics and Outcomes Research meeting, this past May.

It is a retrospective cohort study of paid

medical claims data from the PharmMetrics Integrated Outcomes Database of 70 managed health plans for the period 1995 through March, 2003. Paid claims data include health care provided in which costs are incurred, such as for prescriptions, doctor visits, emergency room visits and hospitalizations.

The investigators identified about 16,000 adolescents aged 12-18 with the first major depressive disorder diagnosis. They classified patients into cohorts by antidepressant prescription, those who received none over the entire follow-up period, which was the reference group, and those who received SSRIs, tricyclic antidepressants or other antidepressants within 30 days of diagnosis. They followed the cohorts for at least 6 months.

The researchers used a Cox proportional hazards regression analysis to control for some 14 covariates and to examine the multivariate relationship between antidepressant use and time to suicide attempt. The majority of patients, 78

percent, had no antidepressant filled in the 6 months after diagnosis; 15 percent had SSRIs filled within 30 days of diagnosis. And, 209, 1.3 percent, of the 16,000 patients made at least one suicide attempt in the follow-up period.

The investigators concluded that antidepressant treatment with any class of drugs did not increase the risk of suicide attempt. Antidepressant use for less than 6 months, compared with use for 6 months or more, was associated with a statistically significant 3-fold increased risk of suicide attempt. Females, those who received psychotherapy within 90 days of major depressive diagnosis, patients with substance abuse, schizophrenia or another mental health disorder, patients with more chronic diseases and those in the Midwest and West were independently at greater risk of suicide attempt.

Dr. Valuck and co-investigators recently expanded their study to include 24,000 eligible patients with a new diagnosed major depressive disorder. This expanded study is currently being

reviewed for publication. The researchers added a propensity matching adjustment to control for predictors of treatment and to achieve greater balance among the antidepressant groups. The proportion of suicide attempters, 1.4 percent, was about the same proportion as in their smaller study.

In this expanded study the hazards ratio for SSRIs compared to no treatment was 1.58, not statistically significant. The hazards ratio for tricyclics was not estimable due to small numbers and it was 1 for the other antidepressant category. The hazards ratio for multiple antidepressants was 1.43, also not statistically significant. The risk of suicide attempt declined with longer use of an antidepressant. Compared with patients having less than 8 weeks of use, those with equal to or greater than 6 months of use had a statistically significant decline in the risk of suicide attempt.

Concerning the limitations, the results are only as good as these paid claims data. There are concerns about possible missing data, possible

incomplete ascertainment and misclassification of patients, and possible uncontrolled selection biases by antidepressant group. There were no interviews of patients so we don't have systematically collected information on medication compliance. There are no data on the outcomes of the attempts. We don't know how many of the attempters died, and there is no information on suicides. Also, there is no information on individual antidepressants. There were differences in study results between the poster and the expanded study, although this is probably due to the larger size of the expanded study.

In conclusion, although most of the results for the individual antidepressants or classes of antidepressants were not statistically significantly associated with suicidal behavior, I do not believe that the Jick and Valuck studies completely rule out a possible increased risk of suicidal behavior with antidepressant use. The studies reviewed were in agreement in showing that the risk of suicidal events occurred statistically

significantly closer to diagnosis and onset of antidepressant treatment. The studies did not provide data about the characteristics of patients who did not respond to antidepressants or whose illness worsened with them. The studies had actual or potential methodological limitations.

I conclude that more definitive studies, perhaps large randomized, controlled trials of sufficient length, are needed concerning the risk of suicidal behavior and suicide as related to antidepressant use in children and adolescents. With so much at stake, children and adolescents, their parents and physicians and society in general deserve to know which therapies and which individuals work best for treatment of depression. Thank you.

DR. GOODMAN: Thank you very much, Diane. My preference would be that you present those additional Jick data tomorrow. I don't think we have time for it today. Would that be an agreement by the committee as well? So, I think we are in accord on that, if you could prepare to present

that data tomorrow to us. There is one question, yes, we will allow that.

DR. PINE: I am wondering if you could clarify in the Valuck 24,000 patient study, if you looked at the association in the less than 8-week treatment versus no treatment group. Did that confidence interval exclude 1? I mean, I saw that you gave less than 8 weeks versus prolonged treatment but I didn't see an odds ratio for less than 8 weeks versus no treatment.

DR. WYSOWSKI: I don't think that I have those data. I don't think that they did that analysis. Their results are still being considered for publication and we just got an abstract. You saw the poster in your package. Then, when they did the expanded analysis they only gave us an abstract of the results. So, we don't have a lot of detail on the expanded study.

DR. GOODMAN: Dr. Fost, you had a question also?

DR. FOST: One of the theories of why suicide behavior might be increased shortly after

prescribing is that the patients are at the worst then and that is why they are started on prescriptions. If that were true, one might expect to see increased suicidal behavior in the week or two before prescribing. Do either of these studies allow for that analysis?

DR. WYSOWSKI: I believe the Jick study did look at that. Actually, no--no, I don't see any information on that; it is just after.

DR. FOST: And the data set doesn't allow itself for that reanalysis?

DR. WYSOWSKI: Well, it may. I don't know whether either investigator has information on that.

DR. GOODMAN: I think that was an excellent question. Now I would like to invite Dr. John March, from Duke University, to present results from the TADS trial.

Brief Report on TADS Trial

DR. MARCH: Thanks, it is a pleasure to be here and I would like to begin the presentation by thanking the committee for inviting the TADS team

to present the TADS data, and also thank the FDA for the comprehensive and thoughtful way that it is approaching this question of enormous public health importance.

The TADS trial, the Treatment for Adolescents with Depression Study, is an NIMH-funded comparative treatment trial, and I am going to present efficacy and safety data from the stage-1 outcomes that were published in The Journal of American Medical Association several weeks ago. We have a detailed safety paper in preparation. We have a methods paper which has been published and a baseline paper which looks at the sample composition in press, and those of you who are interested in the TADS trial are referred to these papers for further information.

As I mentioned, this is a study funded by the NIMH, coordinated by the Department of Psychiatry at Duke University and the Duke Clinical Research Institute, the DCRI. It has had the benefit of oversight and consultation from numerous consultants, a scientific advisory board. The

NIMH, DSMB participants included 12 sites from around the United States. Lilly provided fluoxetine under an independent educational grant to Duke University, had no input into the design of the study, the conduct of the study, the analysis of the data or the preparation of the manuscript. My sense is that the major credit for this work, as for all of the research on which we base evidence-based practice, goes to the children and families who are willing to participate in research. Without their participation, we would have no evidence at all.

The overall objective of the TADS trial was to examine the effectiveness of medication and cognitive behavioral psychotherapy alone and in combination for the acute and long-term treatment for adolescents with DSM-IV diagnosis of major depression. The design of the trial was a balanced, randomized, controlled study that was masked by use of independent evaluators; four groups, placebo, cognitive behavioral psychotherapy, fluoxetine and their combination,

and the study involved 36 weeks of treatment, of which I am going to present the stage-1 data for the first 12 weeks of treatment. We also have a year of naturalistic follow-up and we have recently been funded to follow these youngsters out into young adulthood. That data will not be discussed today.

Now, it is important, in understanding the generalizability of the data, to know a little bit about the sample composition. The inclusion criteria included outpatients, both boys and girls age 12-17, with a DSM-IV diagnosis of major depressive disorder and an IQ greater than or equal to 80. Youngsters with severe conduct disorder or substance abuse, other than nicotine, pervasive developmental disorders, thought disorder, bipolar disorder, or history of suicidality or homicidality were excluded from the trial.

Because suicidality is the question at issue today, I thought it important to say a little bit more about these exclusion criteria, kids were excluded if they had a hospitalization within the

previous 3 months or if they were considered to be high risk, which meant a suicidal event of some sort within the past 6 months, the presence of active intent or plan, or if they had suicidal ideation in the context of a family which was so disorganized that we felt that even with the intensive monitoring in the TADS trial framework that it would not be reasonable to enter them into a randomized, controlled research study.

This was a moderate to moderately severely ill population. We had 439 kids, as you can see, randomized equally into the 4 groups. The total sample on the Children's Depression Rating Scale had a CDRS scale score of 60. That, again, is a mean score of moderate to moderately severely depressed, with a range from mild to severe depression. The T score for that mean score is 75. That means that these kids were more than 2 standard deviations out from normal with respect to severity of depression. The sample was multiply comorbid, as is characteristic of patients in the clinical samples. This was the first major

depressive episode for about 90 percent of the sample. Ten percent of the sample had had more than one depressive episode. The mean duration of major depression was 42 weeks. Again, over 50 percent of the sample was comorbid for another mental disorder, both internalizing and externalizing disorders; 14 percent of the sample had ADHD and half of those kids were on concurrent psychostimulant treatment.

So, unlike the industry-funded trials, the TADS sample is largely representative of patients who are treated in clinical practice with major depressive disorder. As you might expect, given the severity of illness and the pattern of comorbidity, these youngsters suffered significant functional impairment. This is the children's CGAS rating and you can see that the mean CGAS score was between 40-50, so significant functional impairment associated with mental illness in this patient population.

What did we learn in the trial? This is a take-home efficacy message. Four groups, again,

began at a CDRS raw score of 60. These are random regression analyses looking at the adjusted or predicted means at baseline, week 6 and week 12 of treatment. Actually, all 4 treatments showed significant improvement, a characteristic of major depression. The placebo group and the cognitive behavioral psychotherapy group were superimposed, one on top of the other. There is no additional benefit from receiving cognitive behavioral psychotherapy, either in the slope term or at the end point, over receiving placebo. There was significant benefit from fluoxetine alone, and the largest effect was associated with the combination condition. The combination condition beat the CBT condition and the placebo condition on all 4 efficacy measures. Fluoxetine beat these CBT on all 4 measures and placebo and placebo on 3 of the 4 measures.

If we look at the impact of treatment using effect size calculations, the mean of the control condition minus the mean of the placebo condition, divided by the pooled standard

deviation, the effect size for the combination was close to 1. This is a very large effect. For fluoxetine it was around 0.6, a moderate to large effect. For CBT there was no difference between CBT and placebo, effect size calculated relative to placebo.

If we look at response rates, defined as a clinical global importance measure rated by the independent evaluator of much improved or very much improved, 71 percent of the combination kids improved; 61 percent of the fluoxetine-treated patients improved; 43 percent of the cognitive behavioral psychotherapy treated patients and 35 percent of the placebo-treated patients improved. Combination statistically was no different than fluoxetine. CBT was no different than placebo. The two drug-containing conditions were superior to the two non-drug-containing conditions on responder analysis.

If we look at the effect size calculated as a derivative of the odds ratio of improvement for the active treatments relative to placebo for

the responder analyses, the results parallel the analyses on a scale or outcome variable, the Children's Depression Rating Scale. The effect size for combination was 0.8, almost 0.6 for fluoxetine, and about 0.2 for cognitive behavioral psychotherapy. So, again, clear superiority for the drug-containing conditions, with the largest effect reserved for the combination of medication management and CBT.

Now, of interest here are the safety outcomes from the TADS trial. Although we spent an enormous amount of time and energy on measuring adverse events, particularly measuring the impact of the treatments on the potential for harm, I think it is important to point out that the study did not have safety as a primary outcome. With 439 subjects randomized to 4 conditions, it is easy to see that for these outcomes the study is clearly under-powered.

It is I think important to separate ideation from behavior. Despite the exclusion, we had significant suicidal ideation in the TADS

sample. This is looking at the Reynolds Adolescent Depression Scale, item 14, and 7.5 percent of the sample exhibited a score of 4 or above which is the threshold for clinical investigation on the RADS. CDRS item 6, serious suicidal ideation, the kind of suicidal ideation that leads you to consider hospitalization, 2 percent of the sample met CDRS item 13 criteria for severe suicidal ideation. On the suicidal ideation questionnaire 2 measures, the SIQ flag which is to prompt clinical investigation, or elevated scores on any one of the items on the SIQ that would also prompt suicidal ideation, 29 percent and 10 percent of the sample respectively on these measures exhibited clinically significant suicidality. So, although suicidality was an exclusion criterion, there was plenty of suicidal ideation exhibited in the TADS sample at baseline.

Now, as expected, suicidal ideation occurred across all 4 groups taken in the aggregate. One sees here, looking at the CDRS item 13 score, in this case greater than 1, or SIQ score, SIQ flag greater than 31, significant

suicidal ideation at baseline. It came down at week 6 and was significantly reduced overall at week 12. This is the aggregated data across all 4 treatment groups.

Random regression analyses looking at between group differences on the SIQ, although it looks like these groups might be different at baseline, in fact there were no statistically significant differences on the SIQ in all 4 treatments.

One sees a different result than we found in the pattern for depression. This is placebo; this is fluoxetine; this is CBT and this is combination. The take-home messages here are three. First, as we saw in the previous slide, suicidal ideation improves with treatment irrespective of which treatment one gets. Second, fluoxetine and placebo are indistinguishable with respect to suicidal ideation, either with respect to the slope or at entry, indicating that fluoxetine, at least on average, is not provoking suicidal ideation. Finally, the only treatment

which separated from placebo with respect to reducing suicidal ideation was the combination of fluoxetine and CBT. So, here the combination offers a significant advantage over medication monotherapy.

Moving on to behavior, using a comprehensive adverse event monitoring procedure, we looked at the incidence of three kinds of harm-related adverse events. Harm-related events, the broadest category, were defined as harm to self. This could involve no suicidal ideation, ideation or attempt. Or, harm to others which required aggressive ideation or actual behavior involving harming another person or physical property. These events are subsumed one within the next. So, a suicide-related event, which is a subset of harm-related events, involves harm to self, either ideation or attempt. Then we had suicide attempts themselves. What differentiates harm-related events from suicide-related events is primarily one subject with aggression and 7 subjects, I believe, who exhibited self-injury

without ideation, primarily cutting.

These are the actual rates of harm-related and suicide-related events divided by treatment group. One sees that there is a larger number of harm-related events and suicide-related events in fluoxetine-treated kids relative to placebo-treated kids. The combination group is intermediate between harm-related and suicide-related events, intermediate between fluoxetine and placebo. The cognitive behavioral psychotherapy group was roughly comparable to the placebo group.

If you look at children who received drug, that is, combining the fluoxetine and the combination groups and comparing them to the placebo group, 10 percent, 22 of those fluoxetine-treated kids exhibited a harm-related event; 7 percent exhibited a suicide-related event; and the rates of these events overall were quite low, 7.5 percent of 439 kids, or 33 kids had a harm-related event, 24 of 439 kids, or 5.5 percent exhibited a suicide-related event.

I think it is very important as we move

through this discussion to understand that the base rates of these events are extremely low relative to the rates that we see for benefit.

If we look at the odds ratios calculated from the actual rate data, the relative risk is 1.5 for combination, 2 for fluoxetine, less than 1 for CBT. Those is calculated relative to placebo. For the collapsed category of fluoxetine and combination the relative risk is slightly greater than 2. This is the only statistically significant relative risk in which the confidence interval crosses 1. That is largely because these events are so rare so the power is quite low to identify these events. In fact, the power for detecting a 20 percent difference is about 10 percent.

For suicide-related events there are no statistically significant differences although, as you can see from the graph, the odds ratios pretty closely track the odds ratios for harm-related events.

The take-home message from this presentation actually is in this table--no, it is

in the next table. This is the table that looks at the suicide attempts in the trial. We had 7 of them out of 439 kids, or slightly less than 2 percent of the sample. Two fluoxetine-treated kids, 4 combination-treated kids, 1 CBT and no placebo-treated patients made a suicide attempt. There probably is an imbalance in randomization which may in part be responsible for this. There were more kids with an elevated SIQ flag randomized to the drug-containing than the non-drug-containing conditions so it is not clear what to make of this data.

Here I think is where the take-home message lies relative to safety. This is looking at the benefit/risk ratio using analyses for the number needed to treat and number needed to harm. What we see here is fluoxetine compared to placebo, in the first column; combination compared to placebo; and the collapsed category, SSRI versus no SSRI. The absolute benefit increase is calculated as the control, the experimental event rate minus the control event rate. So, it is the absolute

benefit increase for receiving the treatment. The absolute risk increase is calculated, again, as the experimental event rate minus the control event rate, that is, the risk increase attributable to the treatment over the placebo condition in absolute numbers.

The NNT and the NNH are the reciprocal of the absolute benefit increase and the absolute risk increase respectively, 1 over the absolute benefit increase or 1 over the absolute risk increase. These are defined as the number of patients for benefit that would need to be treated to find one patient who had benefit over the benefit occurring from the control condition or, in the case of the NNH, the number of patients who would need to be treated to find one patient who would be harmed over treatment with the control condition. So, it is a nice metric that combines both the absolute rate and the magnitude of the effect.

One sees clearly here that 27 percent of patients benefit from treatment with fluoxetine, with an NNT of 4 which is a large effect; 27

percent of patients benefit from treatment with combination, with an NNT of 3, again a very large effect; for SSRI versus no SSRI, combining the categories, 31 percent of patients benefit, again with an NNT of 3.

The absolute risk increase for a suicidal event with respect to fluoxetine is 4.7 percent as compared to placebo; 2 percent for combination over placebo; and 3 percent for the combined category. NNH is number of patients that you would need to treat with the active treatment to find one patient who would be harmed over the control condition of 21, 50 for the combination condition and 4 for the collapsed categories.

From a clinical point of view, these patients would be easy to pick out in a crowd, easily identifiable who is getting better and who is not getting better, active treatment versus control. These effects are so small and so uncommon that one could not possibly pick out patients who would be harmed by the medication versus patients who would commit these

suicide-related event behaviors with placebo treatment. If you calculate the NNT to NNH ratio looking at benefit to risk, one sees clearly here that the benefit tilts in favor of the treatment, and particularly the combination treatment.

So, we conclude that the combination of fluoxetine and CBT is the most effective treatment for adolescents with major depression. Fluoxetine alone is effective but not as effective as the combination of the two treatments. CBT alone is less effective than fluoxetine and not significantly more effective than placebo. We also conclude that placebo is acceptable in randomized, controlled trials of adolescent major depression and, in fact, is essential for looking at the adverse event outcomes, at least in this study. Suicidality decreases substantially with treatment. The improvement in suicidality is greatest with the combination and least for fluoxetine alone. Fluoxetine does not increase suicidal ideation. Suicide-related adverse events which are uncommon may occur more often in fluoxetine-treated

patients. CBT may protect against suicide-related adverse events in fluoxetine-treated patients.

Taking both risk and benefit into account, the combination of fluoxetine and CBT appears superior as a short-term treatment for major depression in adolescents.

Now, the most practical clinical trialist, the kind of trial models that are used in other areas of medicine--cardiology, oncology, infectious disease for example, would much prefer a large simple or practical clinical trial in 2000 subjects to a meta-analysis of 10 under-powered subject trials. So, it is our sense from looking at the FDA data and also the TADS data that we have a significant signal for drug treatment relative to suicidality but the evidence is not conclusive. In fact, a definitive study has not been done and we would, as a field and as consumers of this information, much benefit from a placebo-controlled, practical clinical trial comparing fluoxetine to another SSRI, perhaps sertraline or citalopram. This trial could be run

easily on the child and adolescent psychiatry trials network, which is a clinical trials network that we are now putting in place to run these kinds of trials in the pediatric population. Thank you.

DR. GOODMAN: Thank you, John. My first question is will you be here tomorrow?

DR. MARCH: No.

DR. GOODMAN: Oh, you won't? That may affect my subsequent questions because I am sure, besides myself, there will be a number of questions for you. I don't know if we have time to take them all right now. I wonder if there is any other option, Anuja. What time do you leave today, Dr. March?

DR. MARCH: Noon.

Committee Discussion on TADS Trial

DR. GOODMAN: I am going to ask a question. My understanding in looking at your results is that on the categorical measures of response fluoxetine is superior to placebo. However, if you look at a comparison of the mean scores on the CDRS fluoxetine is not superior to

placebo. Is that correct?

DR. MARCH: The slope term on the random regression analysis for the CDRS, the p value was 0.08 for fluoxetine versus placebo. Fluoxetine was statistically significantly different than CBT but not placebo.

DR. GOODMAN: So, from a standpoint of FDA, if this trial had been submitted to the FDA and you didn't have the CBT group, it seems to me that it might be classified as a negative study.

DR. MARCH: It would have been classified as a negative study using the CDRS as the primary endpoint, the slope term.

DR. GOODMAN: Do you have any comments about the methodology or outcome measures we are using and whether we are using the most appropriate ones in your opinion?

DR. MARCH: Well, I think it is actually a very important question. If you look at the fluoxetine outcomes on the predicted endpoint, the week 12 endpoint on the CDRS predicted by the CDRS slope, on the clinical global improvement measure

dichotomized and on the Reynolds Adolescent Depression Scale fluoxetine was statistically better than placebo. It was simply a near miss on the slope term, which probably relates to the way the random regression analyses handle standard errors. So, my sense of the story that the data is telling us is that fluoxetine--and also if you look at the effect size calculations--the story the data is telling is that fluoxetine is an effective treatment and it would be a mistake to consider this a negative trial. On the other hand, the technical definition used by the FDA would require that the study be considered negative.

DR. GOODMAN: Dr. Perrin?

DR. PERRIN: On the other side of the equation, you made comments that the sample was somewhat different from some of the trials that have been sponsored by industry. Could you be a little bit more specific about what the differences are, and how they might have affected the results, and what are the implications for meta-analyses of these studies?

DR. MARCH: I think it is a very important question, and we have a paper that is in press in The Journal of Child Medicine Psychiatry, the "orange journal," which describes the TADS sample in some detail and compares the TADS sample to epidemiologic samples and to treatment samples, both on the pharmacotherapy side, primarily the industry data sets, and also the cognitive behavioral psychotherapy trials, of which there are 13 published at this point. In general, our sample is not substantially different from either the epidemiologic or the treatment seeking samples, with the caveat that we are slightly sicker and slightly more comorbid, particularly relative to the CBT samples.

So, given that the range of depression goes from mild to severe and half the sample is comorbid, there are plenty of patients in the data set who resemble the mildly ill patient all the way up to the severely ill, multiply comorbid patients. So, I think the result of the TADS trial is generalizable to the total sample.

With respect to meta-analyses, it would be better to have a very large sample including all these variations, but by combining the data sets one gets a better picture, I believe, of the total variation in the patient population than simply using the industry data sets which tend to exclude the more complicated and clinically ill patients.

DR. GOODMAN: Dr. Newman, did you have a question?

DR. NEWMAN: Normally when you use a continuous outcome you have greater power than when you dichotomize. I assume that is why you specified that as the endpoint at the beginning of the trial. A reason why you might not is that the medication helps maybe a majority but actually harms a minority and then you could actually see that if you dichotomize the percent to improve is statistically significantly greater in the fluoxetine group but the mean may not be significantly greater because there are some people who are harmed and they drag the mean down, whereas they have no effect on the dichotomized variable.

Did you look to see whether there was evidence that the variation in the standard deviation in the effect size differed between the two groups and might have been greater with fluoxetine?

DR. MARCH: That was actually the point that I made, that the standard errors are larger in the fluoxetine-treated group than in the combo or the placebo--

DR. NEWMAN: Actually, not just the standard errors but the standard deviation, meaning that, in fact, there are some people who are harmed by it and that diminishes the apparent benefit when you average.

DR. MARCH: It would be impossible to look at the standard errors or the standard deviation and make a judgment about harm because there is a fair amount of variability data point to data point which is intrinsic to the disorder. Some patients get better; some patients deteriorate.

We do have in the safety paper a whole set of analyses looking at shifts, which I am not confident enough in to have wanted to present

today. We will try to examine what percentage of patients are getting worse with respect to ideation and behavior, and how that relates to treatment classification and also how it relates to other adverse events like mania activation, anxiety disinhibition and so on. I think the secondary paper is going to shed a fair bit of light on these questions.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I have two questions. One is were there any differential dropout rates in the samples? This also relates to the question of compliance in the different treatments. My last question is these were intent-to-treat analyses?

DR MARCH: All very good questions. The analyses are all intent-to-treat. Although I didn't present the data, if we look at observed cases analyses, those who were still on their assigned arm at any given assessment point or completer analysis, the results are exactly the same. About 10 percent of the kids in each treatment overall dropped before the week-12 data

point. Another 10 percent were what we call prematurely terminated. That is, for ethical reasons. They received an out of protocol treatment at some point during the first 12 weeks of the study. There were no statistically significant differences across treatment groups in either the rate of dropping out or the rate of receiving an ancillary treatment, that is, a premature termination.

You will see this afternoon when FDA presents its analysis of the TADS data that the odds ratios for being harmed by receiving fluoxetine are greater than we presented, or I presented this morning on behalf of the TADS team. That is because the FDA data set excluded those kids who were prematurely terminated and received another treatment. That actually represented two kids in the placebo group and that, in turn, inflated the odds ratios in the FDA results versus the TADS results. So, there is some method variance in there which accounts for the differences between the two findings.

DR. GOODMAN: Dr. Gorman?

DR. GORMAN: Does analysis of your data set allow interpretation of the time of onset of treatment to behaviors that we are studying today?

DR. MARCH: That is a very good question and, in fact, one that we will address in the secondary paper. I can tell you that the majority of the events occurred within the first 6 weeks but not within the first 2 weeks. But I don't have that data presented in slide form so I can show it to you, but it will be in the safety paper that we are currently preparing.

DR. GOODMAN: So you don't know what the differential rates are between the groups at this point, particularly between fluoxetine and placebo?

DR. MARCH: In terms of time?

DR. GOODMAN: Yes, in terms of the early events.

DR. MARCH: My general impression, looking at the data, is that the fluoxetine events occurred early and the placebo events occurred later, which is kind of what you would expect given what we know

about the compounds. But I wouldn't want to cite chapter and verse or have you base your decisions based on that because we haven't completed the final analyses of the data.

DR. GOODMAN: Dr. Rudorfer, you will be the penultimate questioner.

DR. RUDORFER: If I can go back to the characteristics of the patients for a moment, we will be looking at a number of studies that were submitted to the FDA by various sponsors, and it seems to me that the TADS inclusion criteria go beyond DSM-IV in terms of length of illness and degree of dysfunction in various spheres of life. Could you comment on that?

DR. MARCH: Sure, it is a very good question. That is, the exclusion criteria included requirements that were designed to ensure a stable baseline. So, we required at least six weeks of mood disorder symptoms that crossed two or three contexts--home, peers in school--which, of course, are not required in the DSM-IV criteria. This was done in part to minimize the chance of a placebo

response and to ensure that we had a sick patient population that would be both ethical to randomize and would offer some opportunity for the combination treatment to separate from the two monotherapy conditions.

I think we actually designed a very good experiment, and looking at a 35 percent placebo response rate did exactly what we had intended to do. But in that sense, this population is sicker perhaps than what is seen in the industry data sets and certainly sicker than what is seen in the CBT data sets on average.

DR. GOODMAN: I will permit two final questions and that is it, one from Dr. Pine and then Dr. Fant.

DR. PINE: I want to return to the first question from Dr. Goodman as far as how this study would be evaluated from an FDA perspective. My sense from reading the paper is that there were two primary outcome measures and three analyses, and two of the three were positive so that the CGI analysis done categorically was positive, the CDRS

analysis done categorically was positive, and it was only the third analysis, the CDRS continuous measure, that was not positive.

So, my take on that from an FDA standpoint of, you know, do the primary outcome measures make it or not is that it would be closer to positive than negative. Do I have that right?

DR. MARCH: You have it partially right. There is a CDRS slope analysis, and whether that is positive or negative depends on whether you treat the intercept term as random. I mean, there is a fair amount of method variance on a subtle level that can tilt these things one way or the other when it is a near miss. There is a CDRS endpoint analysis based on the predicted or marginal mean. There is a categorical analysis, logistic regression, and there is a self-report scale which was included, the Reynolds Adolescent Depression Scale, which was included because the CBT literature relies heavily on patient self-report. Three of those four measures, all but the CDRS slope analysis, were positive for the

fluoxetine-placebo comparison. The CDRS slope analysis, again, was a p value of 0.08, a near miss.

So, I think the take-home message is actually in the effect sizes, not in whether you are looking at p values or not. Clearly, combination and fluoxetine have larger effect sizes, meaningful effect sizes relative to placebo as contrasted to CBT.

DR. FANT: For the sake of the study I know it was necessary to exclude certain patients to optimize the conditions for the study, but I think in real-world practice a lot of the patients who were excluded would be patients who would be prescribed medication under various conditions. Is there any reason, from your standpoint or perspective, to think that that population of patients may be at a different risk for fulfilling suicidal attempts, ideation, and carrying it through to the ultimate result, or may be affected differently by the medication than patients that are not excluded from the study?

DR. MARCH: That is a very good question. That is, is there some issue to believe that there would be a differential treatment response in patients who would be excluded, particularly excluded for harm to self or others, as compared to the TADS sample of patients? I don't know of any a priori reason to believe that there would be a differential treatment effect relative to the TADS sample. I do think it is quite clear from the treatment and epidemiologic literature that they would be at higher risk for adverse harm-related outcomes but whether they would be more at risk than, say, the TADS sample patient I don't think we know. My guess as a clinician is probably not.

We are actually doing an NIMH-funded study called the Treatment of Adolescent Suicide Attempter Study, in which we are comparing a medication algorithm to cognitive behavioral psychotherapy to the combination--no untreated control condition obviously in this sample--to try to understand something about treatment for this particular patient population precisely because

they have been excluded from these other trials, and we need additional data on their care. So, that trial is now under way and should be completed in the next couple of years.

DR. GOODMAN: Thank you very much, John. The final question that I will take the chairman's privilege to ask is do you have data that you haven't presented yet on long-term outcome based on this trial?

DR. MARCH: The final subjects in the trial are out in a naturalistic follow-up window so that 36-week data is in the can, but that data set has not been cleaned and locked yet. We expect it will be cleaned and locked and ready for analysis in the spring, and we hope to have that data in press by this time next year.

DR. GOODMAN: Thank you very much, John.

DR. MARCH: Thank you.

DR. GOODMAN: I would like to ask our next speaker to come forward, Dr. Greg Dubitsky.

Characteristics of Pediatric Antidepressant Trials

DR. DUBITSKY: Good morning. You just

heard about the TADS trial from Dr. March. I would like to now go on and briefly summarize the other studies that were included in the FDA's primary analysis of suicidality.

I do want to emphasize that my review and this presentation are really descriptive only. I am not going to touch on efficacy outcomes or safety outcomes. The discussion of the risk of suicidality in these trials will be presented later this morning by Dr. Hammad.

The study pool, again excluding the TADS study, consisted of 23 placebo-controlled studies which were conducted between 1984 and 2001. Each study was done with one of nine different antidepressant drugs and studied patients with one of five different diagnostic indications; major depression, obsessive compulsive disorder, generalized anxiety disorder, social anxiety disorder or attention deficit disorder.

These studies all had some features in common. They were all randomized, double-blind, placebo-controlled. They utilized a parallel group

design and a flexible dosing regimen.

I did prepare a handout to go with this talk which should be in your packets, at least for the advisory committee members. It consists of two tables which summarize some of the design characteristics of these 23 studies. Table 1 has some basic study information, to include the diagnostic indication, the age range that was studied, number of patients by treatment group, the duration of double-blind treatment, and the dose range that was used in the particular study.

I would like to point out though that I don't intend for everybody to read this and memorize it; this is really for reference for later this morning when you hear about the analysis of these trials.

The second table in the handout includes some information on screening and exclusionary criteria. Some of the studies used very extensive diagnostic screening. I have indicated those in the table. I have also indicated information on whether there was a placebo lead-in, and also

whether certain exclusionary criteria were employed in the various studies to include whether people were excluded who had a history of treatment resistance, current suicide risk, history of a suicide attempt, bipolar disorder, or family history of bipolar disorder.

My review of these studies did include a number of other variables. I have listed in these two tables the most relevant ones but in my review that is on the Internet I do describe some other characteristics which you might be interested in, such as the location and number of sites, whether stratified randomization by age group was utilized and other exclusionary criteria such as homicidal risk or the presence of psychotic symptoms.

There were a few notable differences between these studies that I would like to point out. One study with Prozac, HCCJ, was a very small study. It was the smallest of the 23 studies, with only about 40 patients and it was terminated early.

Only one of the 23 studies included an active control arm. That was study 329 with Paxil

in major depressive disorder. That included an imipramine control arm. The others only had a placebo control.

Two of the studies did include inpatients as well as outpatients, the Celexa study, 94404, and Wellbutrin, 75.

Last, I did want to point out that three of the studies did use a rather extensive diagnostic screening of the patients, much more so than the other studies, Prozac studies X065 and HCJE, and Paxil study 329. Those three studies were done in major depressive disorder.

One other difference involves the treatment options after patients completed the acute phase of double-blind treatment. This was quite variable across the trials. In eight studies there was a taper of acute treatment before discontinuation. Seven other trials just abruptly discontinued treatment, and there was no provision for continued treatment. Five trials did allow for continuation of open-label treatment, and in three trials patients could continue double-blind

treatment.

However, this was also very variable within trials. For instance, in Paxil 329 responders could continue double-blind treatment but non-responders were tapered off treatment. This variability in the follow-up treatment following the acute phase made it very difficult to do any analysis of suicidality-related events post double-blind treatment.

I would like to point out that none of these studies was specifically designed to assess suicidality. Suicide attempts and ideation were detected only through routine safety monitoring, that is, through treatment emergent adverse events and through suicide-related items on various depression scales, such as the HAM-D and the CDRS. One problem with this is that often descriptions of possibly suicide-related events were rather vague or incomplete and often made it difficult to reach a classification.

I have no specific conclusions since this is really a descriptive review and overview of the

studies. I think one of the important questions that arises from this information though is whether any of these differences in design characteristics could contribute to any observed differences in suicidality risk that we observed across these studies. That is a question that will be addressed later this morning by my colleague, Dr. Hammad. So, that is all I have.

DR. GOODMAN: Thank you for being concise and providing us with an outstanding handout for our reference. We have one question. Dr. Rudorfer?

DR. RUDORFER: Thank you. Could you clarify, of the 23 trials how many were submitted in response to the pediatric exclusivity rule?

DR. DUBITSKY: I don't have the exact number. I believe most of them were but some of them were submitted well before pediatric exclusivity took place or came into effect. I don't have the exact number off the top of my head.

DR. GOODMAN: Dr. O'Fallon?

DR. O'FALLON: Asking the question in a

somewhat different way, the data that you have for this reanalysis, does any of that data come from outside, beyond the data that was submitted to the FDA? That is, were you able to go in and obtain data from studies that were never submitted to the FDA for approval or whatever?

DR. DUBITSKY: Well, to my knowledge, there was one study that had not been submitted as part of an efficacy supplement or an approval package. The other ones, I believe, were. Dr. Hammad actually requested data sets for all these studies. Correct me if I am wrong, but I believe we had relatively complete data sets to allow reasonable analysis for all these studies.

DR. O'FALLON: But I am asking whether there are, as some are claiming, studies that were done but were never submitted to the FDA. Are there any of those data here, if they exist?

DR. DUBITSKY: There are some studies that are not included in this analysis, but those are mainly open-label continuation studies of the acute studies. Also, there were a number of pediatric

pharmacokinetic studies but I think for obvious reasons we didn't include those in the analysis. But, to my knowledge, I think we have everything.

DR. GOODMAN: Dr. Laughren, do you also want to respond to the question?

DR. LAUGHREN: I think I can respond to that. The vast majority of these programs were submitted under pediatric exclusivity so the companies were required to submit every scrap of data they had as part of those supplements. The only trial here that was not submitted as part of an application, in terms of a company trial, was the ADHD study for Wellbutrin. The other study that we have included safety data for is the TADS trial and, of course, that was also independent. But those are the only two trials of the 24 that we looked at that were not submitted as part of an application.

DR. GOODMAN: Dr. Marangell?

DR. MARANGELL: How many of the studies excluded family history of bipolar disorder?

DR. DUBITSKY: Let's see, actually I think

I have that in table 2. I don't know the number off the top of my head. It looks like about ten of the studies excluded a family history of bipolar disorder.

DR. MARANGELL: Thank you.

DR. GOODMAN: Dr. Perrin?

DR. PERRIN: You are saying basically that the extensive diagnostic screening occurred only in three studies, I believe. Is that right?

DR. DUBITSKY: I am sorry?

DR. PERRIN: The extensive diagnostic screening occurred only I think in three studies--one of the points that you made. Does that give us some information about the potential diagnostic heterogeneity and also raise questions about whether entrance into these studies of children, ages 7-17, might not have had MDD in the MDD studies? My last related question is, since I am not a psychiatrist at all, what do we know about the ability to distinguish bipolar disorder from MDD in the 7-17 year-olds?

DR. DUBITSKY: Well, it is true that in

looking across all 23 studies, those three studies did stand out as far as using more extensive diagnostic criteria. I believe that it certainly is possible that we might have more confidence that those patients did actually have the diagnosis under consideration. Whether that is actually true or not, I don't know and I don't know any good way of figuring that out.

I am not a child psychiatrist so I can't answer your last question about the ability to diagnose. I understand it is very tricky though.

DR. GOODMAN: Thank you again. I would like to ask Dr. Kelly Posner to come up to the podium to present. Dr. Posner is from Columbia University and she will be talking to us about the reclassification of the clinical trials data according to suicidality.

Classification of Suicidality Events

DR. POSNER: I would like to start by introducing my expert work group from Columbia that included myself, Dr. Maria Oquendo, Dr. Barbara Stanley and Dr. Madelyn Gould. Dr. Stanley and Dr.

Gould are here with me today. Our statistical consultant was Mark Davies.

Why was reclassification needed? The problem is that the field is challenged by a lack of well-defined terminology and common language to refer to suicidal behavior, and this was reflected in the lack of standardized language used in the 25 trials in question. That is why there was difficulty in interpreting the meaning of all of these reported adverse events that occurred in these trials. So, AEs that should have been called suicidal may have been missed and there may have been AEs that were inappropriately classified as suicidal.

Here are some illustrative examples of the difficulties in adverse event labeling in the field. I want to make sure to note that these labels have nothing to do with the labels the sponsor gave these events, but just original investigators at the site. Again, they are extreme examples just to reflect the problem.

You see the first one, it says patient

attempted to hang himself with a rope after a dispute with his father. Investigator did not consider this event to be a suicide attempt but called it a personality disorder in this 10 year-old patient.

The second one is one we have all heard a lot about. The patient is reported to have engaged in an episode of auto-mutilation where she slapped herself in the face, called a suicide event. Then, the patient took 11 tablets impulsively then went to school--called a medication error.

So, how do we address this problem? Well, a common set of guidelines needed to be applied and we needed to look at the data consistently across trials using research-supported definitions and concepts that had reliability and validity. We also needed to broaden the range of adverse events that we were looking at. This was for two reasons. The first one is to avoid bias in readings. We wouldn't have wanted the expert raters only to have had what the sponsors had identified as possibly suicidal. Also, to identify suicidal events that

may have been missed.

So, what was included in this broadened range of events? Of course, the events originally identified by the sponsors as possibly suicide related, all accidental injuries which included accidental overdoses, and serious adverse events which includes life-threatening events and all hospitalizations.

Why did we need experts in suicide? Well, you all heard about the limited information provided in the narratives, particularly frequent lack of stated suicidal intent. So, only experts in suicide would have allowed for inference based on details of behaviors and related clinical information.

This is the list of our very distinguished international panel of experts. I will just read their names very quickly, Drs. Bautreais, Brent, Brown, Van Herringen, King, Mazark, O'Carroll, Rudd, Spirido and Miller.

So, what was the Columbia classification? I want to move to this slide because it goes

through the definitions which I will just go through briefly. Suicide attempt, of course, which is defined as a self-injurious behavior associated with some intent to die. Intent can be stated or inferred by the rater. It is important to know that no injury is needed.

Then there was preparatory actions towards imminent suicidal behavior. So, the person takes steps to injure himself but is stopped by self or other, anything beyond the threshold of a verbalization but not quite making it to a suicide attempt.

Then we had self-injury behavior, intent unknown. These are cases where we know there was some self-injury but we don't know what the intent was. So, the associated intent to die is unclear and cannot be inferred.

Self-injurious behavior with no suicidal intent is the next category. That is where, again, we know there was deliberate self-harm but there was no intent to die so behavior is intended to affect other things. This is what we think of

self-mutilation typically.

Suicidal ideation was the next relevant category, which can be passive or active thoughts, passive thoughts of wanting to be dead or active thoughts about killing oneself.

Then we had all the other categories. That is essentially one rating, anything other than deliberate self-harm or something suicidal. That could include accidents, psychiatric events or medical events.

Finally, we had not enough information, which meant that there was insufficient information for a rater to be able to say whether or not there was some deliberate self-harm or something suicidal.

The scheme is laid out conceptually here for you. I think it helps make a little more sense of it. The blue boxes refer to what you will hear later as the FDA's primary outcome. These are ratings that are considered definitively suicidal, suicidal behavior and suicidal ideation. You see codes 1, 2 and 6. Suicide attempt, preparatory

actions and ideation. The next are non-suicidal events, all the other events and the self-injurious behavior without suicidal intent, and then indeterminants. The green boxes are what will be referred to as the sensitivity analysis, things that could have been suicidal but there is no way to know.

So, what was done? The classification methodology involved, of course, choosing the expert panel who had expertise in adolescent suicide and suicide assessment, based on reputation and publications. They had no involvement in industry youth depression trials in question, and no expert rater was employed by Columbia University.

We had a training teleconference to review classification parameters, then training reliability exercise to ensure appropriate application of classifications. All case narratives were blinded to any potentially biasing information, and I will review that in a minute. There was random distribution of 427 events to 9

expert raters. Each case was independently rated by 3 raters. Each rater received approximately 125 events to rate, and any group of 3 raters shared only 5 cases. All ratings were reviewed for quality assurance and identification of non-agreement cases. Consensus teleconferences were held for any disagreement cases, and there was double data entry for quality assurance.

Now, what was the consensus process I referred to? If ratings did not have unanimous agreement, then a consensus discussion was held. Each case was discussed by the three raters involved only. Discussion of each case was led by an expert other than those originally assigned the case. The goal of the discussion was to reach 100 percent agreement. If 100 percent agreement could not be reached, the case then became indeterminate. Sometimes the original majority opinion did not always end up as the final consensed classification. In other words, if there was a minority rating, sometimes that ended up being the final outcome.

Now, what was rated? Blinding of event narratives to avoid bias included--we received the narratives from the FDA blind to all potential drug identifying information. This included drug name, company sponsor name, patient identification numbers, whether they were on an active or placebo arm, and any and all medication names and types because there could be associated treatments that might bias somebody or tip them off as to what drug was being talked about and, of course, primary diagnosis. We also did some additional blinding of potentially biasing information which included the original label of the event given by the investigator or sponsor and serious or non-serious labels.

Rating guidelines--how was the classification scheme applied? We wanted the experts to apply concepts using their clinical expertise and judgment; to use their experience to integrate clinical information and infer when appropriate. We wanted them to have a reasonable certainty in order to commit to a rating, and

rating was based on what was probable, not what was possible.

The guidelines for intent inference involved inferring if something was clinically impressive, and I am going to give you an example of that in a moment, or using two smaller pieces of clinical information. The clinical information that could inform inference of intent included clinical circumstances. That could be method used, number of pills; past history of suicide attempt; past history of self-injurious behavior or self-mutilation; and family history of suicide or suicide attempts.

Now, here is a case example of inferred intent, what we call clinically impressive circumstances. This is the first time you are actually seeing one of these real narratives. In this case clinical impressiveness actually overruled stated intent, so you see the subject attempted suicide by immolation. Her siblings doused the flames immediately. She was left with minor burns on her abdomen and on her left

shoulder. The subject admitted she was angry with her parents for going away and leaving her alone at home because she was fearful. The subject admitted that she had acted impulsively and had not intended to kill herself.

Here are more examples. This is another example actually of clinically impressive circumstances which was ultimately called a suicide attempt. It is also important to know that we had no idea what the sponsor ratings were but both these cases were consistent with what the sponsor had said as well.

This case involved a 16 year-old who claimed to have ingested 100 tablets of study med after a fight with her mother. The patient informed her mother. The mother brought her to the ER. The patient reported feeling shaky. Emergency room physician said she was slightly tachycardic with a pulse of 100. The tox. screen was negative but the patient did have some illness and she stayed in the ER until she was asymptomatic, and then was later admitted to the psych. unit.

Another example of a suicide attempt, a patient age 17 took an overdose of 20 tablets. In the father's opinion the overdose was 5 tablets. The patient didn't have any symptoms of an overdose, not even nausea, but it was classified as a suicide attempt, of course.

More overdose examples. You see in this first example there were 113 tablets and it exemplifies how medication types were blinded so you see all the different numbers there. Then, the next one is patient aged 15, impulsively slit her wrist following an altercation with her mother. Finally, age 17, attempted suicide by taking 8 tablets after a fight with her father, whom she considered harsh and rejecting.

Now, these are examples of self-injurious behavior, intent unknown. So, this is where we did some harm but we just don't know why. A patient aged 10 had superficial scratches, left arm, scratched herself with scissors. That was all the information that was there essentially.

Patient, aged 14, ingested or simulated

ingestion of 2-3 cigarettes. The patient was reported as feeling tired and playing a theatrical role. Subject, aged 9, reported he had ingested 4 of his brother's tablets on a dare. Finally, patient, aged 10, swallowed a small amount of after-shave lotion while angry. It is hard to know what to make of those without information.

Examples of preparatory actions, age 16, tried to hang herself and was prevented from doing so by her family. The next case, age 18, a voice commanded him to jump from the roof. Although he went up, he did not jump. Next one, age 10, held a kitchen knife to her neck while alone but did not cut herself. Event was not witnessed. Finally, a patient, age 18, was noted to be hostile, hopeless and helpless and had written suicide notes. As I said, anything beyond a verbalization was considered a preparatory action, including writing a suicide note.

These are good examples of self-injurious behavior, no suicidal intent. In the first case the patient stated there was increased family

tension. She made superficial cuts on her wrist with an Exacto knife. The patient and mother reported the cuts weren't deep and they looked like cat scratches. Patient adamantly denied any suicidal gestures or intent. She stated she only wanted a release and that cutting and hitting her legs offers her a release.

The second case, denied suicidal thoughts. The first time she cut herself was age 16. She stated she did it for attention. Today her cutting was more spontaneous. She reported that cutting gives her a good weird feeling.

So, what were the results? This slide just refers to what we are talking to in our results, or referring to, and there were 427 events but some patients had more than one event so we ultimately, in the reliability data, used 378 cases. We employed the same severity hierarchy that the FDA used. So, we just took the most severe event for cases that had multiple events.

Expert rater consensus--only two of 427 cases had no agreement among the three raters. So,

each rater had a different rating in only two cases. Fifty-nine cases had agreement among two of three raters, and those had to go to teleconference. There were no cases in which consensus was not able to be reached during the teleconference and they, of course, had that option.

Now, discordant cases between the sponsor and Columbia classifications, there were 40 out of the 427 cases in which the sponsor and the Columbia classification differed. Twenty-six new cases were identified that had not been identified by the sponsor as possibly suicide-related. There were two new cases of self-injurious behavior without suicidal intent that had been labeled something other than deliberate self-harm, and 12 cases were originally called possibly suicidal and were changed to something other than possibly suicidal.

Here it breaks it down for you further. Of the 26 new possibly suicide-related events, one was a suicide attempt; one was a preparatory act; 13 were ideation events; four were intent unknown

acts; and seven were not enough information to say whether there was deliberate self-harm.

Here is an example of one of the newly identified suicidal events. This is a preparatory act. The patient, age 11, held a knife to his wrist and threatened to harm himself. The patient was hospitalized with an acute exacerbation of major depressive disorder. The reason we have this is because, as I mentioned before, every hospitalization is a serious adverse event so that is why this preparatory act was caught.

The events that were changed from suicidal to something other included two changed to psychiatric; one changed to an accident; and nine changed to self-injurious behavior with no suicidal intent. Again, our famous example, a patient reported to have engaged in an episode of auto-mutilation where she slapped herself in the face. The event resolved the same day without any intervention.

These are actually the kappa, the agreement between the sponsor and Columbia. So,

Columbia's classification of possibly suicide-related and the sponsor's classification of possibly suicide-related, the kappa was 0.77. You see in the 2 X 2 table that the numbers correspond to the numbers that I just went through with you.

Now, if you want to look somewhat more specifically or at least what we think is more specific, we did a comparison of what Columbia said was definitively suicidal and what the sponsor said was possibly suicidal, and the kappa was 0.69.

Here are the reliability results of the ratings with the nine expert raters. The median ICC was 0.86 and what the FDA will refer to as the primary outcome variables, you can see the numbers here, suicide attempts is 0.81; preparatory actions, 0.89; suicidal ideation, 0.97.

Where do we go from here? We need to improve our adverse event reporting for suicide-related events by developing consistent terminology; developing guidelines for classification of suicidality so that adequate information is provided by the clinician;

utilization of research assessment tools, what questions to ask, how to ask, and what measures aid this; finally, hopefully, that will lead to improved, more valid identification and documentation of suicidality.

DR. GOODMAN: Thank you very much. Dr. Chesney?

DR. CHESNEY: Thank you. This is a little bit of thinking outside the box, but we heard at the February meeting a number of examples of homicidal behavior. I wonder if, in your speciality, homicidal behavior is ever identified as being self-injurious primarily to affect circumstance or to affect an internal state.

DR. POSNER: No, that did not represent any of those self-injurious, no suicidal intent ratings. So, the classifications that you are referring to, internal state and circumstance, are not synonymous at all with the cases that had homicidal ideation or any kind of aggressive behavior. It doesn't mean that it couldn't be looked at in another analysis but it wasn't

represented in these cases.

DR. CHESNEY: I guess my more general question, I just wonder in the bigger question, homicidal behavior outcome is bound to be bad and self-injurious, and if it is just another factor that we should consider in this whole picture. Thank you.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Do you know how many of the events led to hospitalization and how it breaks down in terms of your classification?

DR. POSNER: Dr. Laughren, do you know?

DR. LAUGHREN: I don't have that figure off the top of my head. There were a substantial number of events leading to hospitalization, I believe somewhere in the ballpark of maybe 40 percent. I don't have the exact number. It was a common outcome.

DR. POSNER: It is important to know that we were very narrowly just looking at obtaining the most appropriate label for the particular event in question, and we didn't have any of the surrounding

information or follow-up information in this particular piece of the project.

DR. GOODMAN: Dr. Wang?

DR. WANG: I have a question. Do you know how many of the sponsors originally submitted reports that were categorized as serious? The reason I am asking is to get a sense of how many cases may not have been originally reported. I know you had these serious cases sent to you for adjudication, just to check in case there were cases that were being missed in what the sponsors were reporting, but did you look as to how many cases were not considered serious by the sponsor, jut to give us a sense of how many may be sort of out there in the non-serious pool?

DR. POSNER: Again, we were blinded to sponsors' classifications throughout the entire process. I don't know if somebody from the FDA can answer that question for you.

DR. LAUGHREN: Again just a ballpark figure, I think it is probably somewhere in the vicinity of maybe 65-70 percent. But you have to

understand that a designation of serious is a judgment that is made by the sponsor fairly subjectively. I mean, there are criteria for regulatory serious. It is fatal, life-threatening, seriously disabling, leading to inpatient hospitalization. But even though, you know, that on face appears to be fairly definitive, sponsors in many cases, in my view, made the judgment that if it was considered to be suicide-related it was, by definition, serious.

So, if you look at many of the narratives that were classified as serious, I think no reasonable person looking at those would consider that, in a common sense notion, as a serious event. But the point is that that designation--how that judgment was made varied from sponsor to sponsor. So, you know, some of them classified many more of the events as serious than other sponsors. But the answer to the question is that overall roughly two-thirds of these events that were included in the analysis were designated as regulatory serious.

DR. GOODMAN: Ms. Griffith?

MS. GRIFFITH: I have a question about cutting specifically. It seems to me that most of the examples of cutting fall into self-injurious behavior, intent unknown or self-injurious behavior with no intent. I am just curious as to are you confident that the reporting that you received and reviewed actually got to whether or not there was intent or no intent, and how subjective is the reporting likely to be?

DR. POSNER: Again, as you can see, cutting is a method that is used both in suicidal behavior and self-injurious behavior without suicidal intent. If you remember the conceptual scheme, there was the category self-injurious behavior, intent unknown, because cutting can be used both ways. I forget the exact number but there were 20-something cases in which they cut but we don't know if it was suicidal or not. That is why we had to come up with a category just to categorize and deal with that issue. The FDA will point out that the included that in the sensitivity analysis so just in case all of those were

suicide-related events, they have those numbers.

DR. LAUGHREN: If the question you are asking were the narratives lacking in detail, they absolutely were. These were not by any sense complete descriptions. Ideally, many more questions would have been asked when these events occurred to help flesh them out. That is why it was necessary to use inference as one approach to try and get at intent because intent was not included for the vast majority of these.

DR. POSNER: Which is why only experts in the field could have been able to infer from the surrounding information. The narratives were limited with respect to suicidal intent often but there was significant surrounding information for the expert raters to be able to infer from in many cases.

DR. GOODMAN: Thank you, Dr. Posner. I would like to welcome Dr. Solomon Iyasu, from the FDA, who will be presenting what I think is a vetting of the sample to establish reliability and validity of the classification system.

OCTAP Appraisal of Columbia

Classification Methodology

DR. IYASU: Good morning. I am going to be speaking about the appraisal that we did regarding the classification scheme of Columbia University.

In my discussion today I will give you a brief background and then give you what the objectives of the FDA audit or appraisal were. Then I will describe briefly the methods that were used and also present the results of the audit and, finally, discuss the limitations and the strengths of the methodology and give some conclusions regarding our appraisal.

I just want to make clear that the objective of the FDA appraisal of the Columbia methodology was really to assess how reproducible or reliable the methodology is. The objective was not to assess the validity of the methodology or the scale as we cannot really test it against a gold standard which is not available right now. So, I just wanted to make sure that the audience

understand that this is really to assess reliability.

Just like Columbia, we reviewed all the sponsor-submitted event narratives. They included all the original ones as well as the subsequently requested narratives. The FDA team also reviewed a computerized line-listing of these event narratives and from the review we drew a sample from those that were appraised or rated by Columbia.

In our methodology we grouped the event narratives that were submitted into four predefined strata, and then we selected event narratives from the various strata via a stratified simple random sampling scheme. We over-sampled for difficult to classify and reclassified events.

Stratum 1 is defined as events reclassified by Columbia to non-suicidal or other events. Stratum 2 was defined as events newly identified or classified by Columbia as possibly suicide related or other categories. Stratum 3 is events that were difficult to classify as defined as events with discordant initial independent

ratings by the Columbia reviewers. Then the last stratum was events that are the straightforward cases that were concordant among all reviewers in the Columbia rating.

We had 64 sample records out of 423. You notice that it is only 423 because some events were in active control and were not included in our review, unlike the Columbia group. We included 2 events in stratum 1. We over-sampled and took one-third each from stratum 2 and 3, and then from the last stratum, which were the straightforward cases, we only sampled one-tenth.

This slide just shows how collaborative this process was. There was a planning group that included individuals from the Division of Pediatric Drug Development and the Division of Neuropharmacologic Drug Products, and then the Office of New Drugs. Clinical reviewers who served as independent reviewers of the case narratives included two individuals, pediatricians, from the Office of Counter-Terrorism and Pediatric Drug Development, and then from the Division of

Neuropharmacologic Drug Products one pharmacist and one other psychiatrist. None of these clinical reviewers had previously been involved in the review of any of these narratives or the trials. We had a consensus process, similar to what Columbia did, that was facilitated by a psychiatrist who was also not previously involved in any of the reviews.

Basically, we wanted to replicate the training that was given to the Columbia reviewers so we had Dr. Kelly Posner provide a similar two-hour teleconference training to all the review team regarding the suicidality scale.

Each sampled event was randomly assigned to three of four reviewers for independent and blinded review. Therefore, each reviewer had 48 events to review, and we received a total of 192 reviews from the four reviewers that we had. Reviewers were similarly blinded to treatment assignment, sponsor, diagnosis and also to the final Columbia ratings.

The planning group also wrote a memo

outlining the procedures of the review to all and provided this to the audit team members. Reviewers were not allowed to discuss the events among themselves or with colleagues during the independent review period. However, we did allow reviewers to call Dr. Kelly Posner to clarify the classification scale or to obtain clarification on the scale, but no discussion of specifics of any case was allowed during this process.

We also required reviewers to record on the rating form if they consulted with Columbia during the review process. For recording the ratings, we used a modified and pre-coded rating form which is shown here. The only difference is that this is pre-recorded and includes all the 12 event categories. At the bottom of the form is where they would indicate if they did consult with Columbia.

The reviewers and the rating scores were returned to me in sealed envelopes and these were key-entered into an Excel database. Then we identified the discordant ratings and then these,

similar to the Columbia group, were taken to a consensus meeting which was facilitated by a Board certified childhood and adolescence psychiatrist who was external to the Division of Neuropharmacologic Drugs, who was actually from the Division of Scientific Investigations. This individual had not been previously involved in the review of these records, as I mentioned before.

The final consensus ratings were again entered into an Excel database and compared to the final Columbia ratings. Then, finally, discordant ratings between FDA and Columbia were discussed by teleconference basically to understand the reason for the differences.

How did we assess the concordance of ratings among FDA reviewers, as well as between FDA and Columbia? With definition of concordance for categories 1 through 3, 6 and 10 and we required that there be an exact match between the two reviewers. Then, for categories 4, 5 or 11, which all describe essential self-injurious behavior with no suicidal intent, we considered them as

equivalent rating. We didn't need to differentiate between these three. Lastly, categories 7, 8, 9 or 12, essentially other categories, non-suicidal and non-self-injurious behavior, are considered equivalent rating.

What were the results? Among the FDA reviewers, of the 64 that were rated, 47 were concordant among the three reviewers. We had 17 that were discordant. These were taken to the consensus meeting and, similar to Columbia, we also arrived at consensus ratings for all 17 events.

Once we got the final ratings by the FDA reviewers for the 64 sampled events, then we compared them to the final Columbia ratings and 57 out of the 64 were concordant, which gives us an agreement rate of about 89 percent, with a kappa of 0.84. We did look at the discordant ratings, which were number 7. We assessed severity hierarchy to sort of analyze where the ratings differed. In general, compared to Columbia, the FDA audit team classified six out of the seven events with a higher severity score than Columbia, and one event

was a lower severity. I must point out that three of the six that were rated higher were events that were classified as not enough information or other, so not really pertinent to the suicidality events.

I will point out now the limitations. In this audit neither the quality of the narratives nor the clinical source material for the narratives were evaluated. Secondly, the validity of the Columbia classification method was not assessed as this was not the objective, and there is also no gold standard to compare it to.

The strengths are that despite the differences in expertise and experience between the two groups of reviewers and the short time line that we had for training and review, and finally, more importantly, intentionally over-sampling is difficult to classify events for review, we achieved a very high level of concordance between the reviewers.

Therefore, from this activity we concluded that the Columbia suicidality classification methodology is robust and reproducible when used by

a non-expert group to classify a similar group of events.

Finally, I would like to acknowledge the team of auditors who participated in this review from OCTAP, DNDP, DSI and OND, and also I would like to acknowledge the contribution of Kelly Posner in terms of the training and classification scales. Thank you.

DR. GOODMAN: Thank you very much. I would now like to take a short break. I am sorry, I missed somebody who had a question.

DR. PERRIN: Thank you. I just wonder whether you know whether the five or six discrepancies between the Columbia review and the FDA review might have been highly represented among the cases that were considered cutting in the last presentation, or were ones that were reclassified by Columbia as non-suicidal from the original industry reports.

DR. IYASU: Well, there were seven discordant ratings, as I mentioned before. Three of them were classified by the FDA reviewers to a

10, which is not enough information, from a category that was other. So, if you look at the severity hierarchy it sort of went towards the more severe hierarchy because 10 represents not enough information; not sure whether there is deliberate self-harm or self-injurious behavior. So, when you are not sure you put them in that category.

In the other cases, I actually have a slide to show the cases that were discordant. I talked about the cases where not enough information was classified from a 12 and 7. But for those that were important, critical elements in terms of the suicidality event, there were four and the FDA group rated one as a suicide attempt from a Columbia group that was self-injurious behavior, intent unknown. Then there was a second one, self-injurious behavior according to the reviewers, and a 10 which was not enough information from Columbia. Finally, there was a suicide ideation versus psychiatric.

But we don't consider this to be critical in terms of numbers because the objective was not

really to test the validity of one classification as opposed to another one. It was really to test how reproducible it was so we are not really making a statement as to which one really measures suicidality.

DR. POSNER: The final case that you didn't talk about, the negative severity bias, was one in which your raters called it self-injurious behavior, intent unknown and we called it a suicide attempt--

DR. IYASU: Exactly.

DR. POSNER: --which was the only suicide attempt and we rated it as more severe. I think, you know, it is just worth noting all of them.

DR. IYASU: Yes, that is right.

DR. GOODMAN: Thank you. I wish to remind the committee members not to discuss any elements of today's presentations among yourselves during the break. We will reconvene promptly at eleven o'clock so that doesn't give you much time to get back here for a very important presentation by Dr. Hammad.

[Brief recess]

DR. GOODMAN: Anuja Patel has some clarification points for tomorrow's agenda.

MS. PATEL: We have been receiving a lot of inquiries regarding the times for tomorrow's meeting and I just want to clarify that the Federal Register Notice does state that the meeting will begin promptly at eight o'clock in the morning, and it is scheduled to end at approximately 5:00 p.m. tomorrow. If you look at the agenda, it is pretty much deliberations for tomorrow. There is no saying whether we will end earlier or not. So, if you are making flight arrangement plans, I do encourage you to go ahead and make your arrangements for after five o'clock just to be safe. So, I just wanted to make that clarification for tomorrow's agenda. Thank you.

DR. GOODMAN: I am hoping that, at the current rate, we will be able to break for lunch at 12:15. So, that is my intermediate goal this morning.

I would like to introduce our next

speaker, Dr. Hammad, from the FDA, and this is one of the key presentations before the committee this morning, involving a reanalysis of the clinical trials data following the reclassification of suicidality.

Results of the Analysis of Suicidality in Pediatric
Trials of Newer Antidepressants

DR. HAMMAD: Good morning, everyone. I am here today to share with you the results of our analysis of suicidality in pediatric trials of antidepressants. These are the elements that I will cover in my presentation. After a brief statement of our objective, I will describe the data that we requested and then I will give you the highlights of the findings before I go over some of the limitations of the current investigation. Then I will give you an overall summary of the findings.

Our objective was to investigate the relationship between antidepressants and pediatric suicidality based on the adverse events reported, as well as the suicidality item scores in pertinent depression questionnaires. So, it is important to

keep in mind that we will be dealing with two different sets of outcomes, and I will draw your attention to that again at the transition.

First, our data came from 25 clinical trials in nine drug development programs, in addition to the TADS trial. Here is a list of the drugs and number of trials involving each drug. At first glance you will notice that there are differences between the available trials for each drug, which have an implication actually for our ability to observe the event of interest.

Here are the indications that these trials were conducted in. As you can see, the majority of trials were done in depression patients. Two trials were excluded, one because it was a relapse prevention trial and the other was simply uncontrolled. So, we ended with 23 available trials in addition to the TADS trial. All trials were comparable in design. They were all parallel, controlled trials.

Although trials started in the '80s, I think one trial or two, the majority were conducted

in the late '90s and TADS was, of course, in '04. The duration of treatment ranged from 4-16 weeks.

In the next section I will focus on the findings first for outcomes based on the adverse events, the ones that you see here. I will go over them in detail. Then, the ones that were based on the suicidality scores.

That is the first set of outcomes. These are four outcomes that we examined; these are the main outcomes we examined. The first outcome we called suicidal behavior and it included cause 1 and 2 from the Columbia classification. You can see here the details of what 1 means and what 2 means. As you notice, this will stay up all the time so you will be able to have a chance to go back and see what everything means.

The second outcome was suicidal ideation. It includes code 6. You have 33 events here and 45 events here. Putting them together, we came up with outcome 3, which was the primary focus of the analysis. This is simply the combination between number 1 and number 2. It had codes 1, 2 and 6.

So, it ended up with 78 events.

The so-called outcome 4, to construct that we added two more types of events, code 3 and code 10. Just to remind you, code 3 meant suicidal injury with intent unknown, and code 10 meant there was some injury but there was no information to help determine what the intent was. So, this is sort of considered the worst-case scenario and it was used in the sensitivity analysis for the primary outcome. The reason we chose this as a primary outcome--it was chosen a priori--is because it is the most pertinent and the one least likely to be subject to dilution because of misclassification.

I will take you step by step over the events from the time that we sent them to the Columbia group. We sent them 427 adverse events. We ended with 260 that were coded as "other" that are not really pertinent to the analysis. Don't be surprised by the magnitude of the number. The reason is because we cast a very wide web to start with to be able to capture every possible event.

So, we ended with 167 potential events with those particular codes.

Those events boil down to 141 unique patients because many patients had more than one event. Among those, we chose the most severe events. For example, if a patient had an event that was coded as 6 and an event that was coded as 4, then this particular patient would be labeled with the most severe event.

Among those, we ended up with 21 that were not eligible. The eligibility here is determined by when the event occurred. If it occurred within the double-blind period, then we considered it eligible. If it was outside, then it was not eligible. So, we ended with 120 eligible. Among the eligible, we had 109 that were pertinent, that were suicidal related. You notice what is missing from here are codes 4, 5 and 11 which are self-injury but the intent is known not to be suicidal. So, they were not pertinent to the analysis. We ended up with 109. You notice a few discrepancies between some of the numbers because

it depends on if we are looking in the window or outside the window. So, don't worry about the few discrepancies here and there.

I showed you on the previous slide how we ended up with 109 events. These 109 events were not exactly the same events that the sponsor reported initially. So, in this light, I will walk you through the disposition of the sponsor original events. We started with 115 possibly suicide-related events as reported by the sponsor. Now, we took out 11 because they were not pertinent. Just to remind you, being pertinent or not had to do with how it was coded by the Columbia group. So, they were coded as non-suicidal. The 15 were taken out of consideration because they were not eligible. Some of them were suicidal but they were not within the double-blind period. So, we ended with 87 pertinent events. To those we added 29 new events from broader search and classification. However, only 22 were pertinent. Others were not pertinent to the analysis. So, we ended up with 109 events.

Before I go on with the results, this is a list of caveats that I would like to draw your attention to because they have important implications on the interpretation of these findings. There is always the possibility of a chance finding because we are dealing with post hoc analyses with multiple outcomes, complicated by having many sub-analyses. So, keep in mind that there is always the possibility for a chance finding.

It is also difficult to compare across drugs, unfortunately, because of the low power of individual trials and the differences in the databases among the trials, which is the point I mentioned earlier for each drug. So, it will affect our chance of observing the event of interest. In addition to this, there is the potential role for differences in the level of ascertainment of events and completeness of narratives between trials or between development programs. Mind you, the sponsor actually is the one that puts together the narratives based on the

case report form so you would expect to find some variability here also.

Having said that, I will go on with the rest of the analysis. The investigation followed a standard approach for examining the effect modification and confounding in the variables that we asked for. First, the effect modification--this was slightly harder to do but by modification I mean that the effect of the drug is actually modified by another variable. For example, if the drug was more risky among the males versus females, then the gender variable modified the effect of the drug and this would have important implications if it was true.

Before I go on, it was difficult to figure out if there was interaction or not, so my approach was to look if there was any inconsistent finding across the trial when I stratified by the variables of interest. As you can imagine, we have very small numbers of events. But that is in this particular outcome. Other outcomes had more events.

The variables that I focused on were the age group, gender and history of suicidal attempt at baseline. But none was found to meaningfully impact the risk estimates so there was no effect modification to report so I am not reporting any.

In examining the confounding we were concerned about the possibility of perhaps some randomization failure at baseline. So, there might be some randomization failure that might be responsible for the observation we have because we have very few events. So, if this was true, then adjusting for these imbalances would have made a difference in the risk estimate.

We examined several variables, at least 17 variables, but the exact number of variables differed between trials because some trials had missing information about some variables so it was not exactly the same number of variables for all trials. Again, none was found to meaningfully impact the risk estimates and I am not going to present any. I think the purpose of these two slides is to show you the process that we went

through.

In the next section I will go over suicidal behavior or ideation which, again, are codes 1, 2 and 6, by drug. I will do it drug by drug. Then, at the end of that section I will give you a summary of all the drugs in one table so you can have a snapshot of the whole picture.

I will start with Celexa. I ordered them alphabetically. This graph has a lot of information so I would like to take a minute to orient you with the graph. First, this section will have the name of the outcome that we are trying to evaluate. In this case it is suicidal behavior or ideation. In the upper corner, here, we have the name of the drug and the indication of the trials. Here it will give you the modeling approach. The value of this section is to know the study number. It is sort of redundant, you again have the indication and the drug name. This section will draw your attention to the actual relative risks, risk ratios, with the confidence intervals. This section gives you the percent

weights which reflects the relative contribution of each trial of these two, for example, for the overall estimate of risk. So, this trial had more weight in getting the overall estimate. This actually is a standard approach for meta-analysis, and it takes into consideration both the sample size and the number of events.

Just as an example for how to read the graph for this trial, that is the number of the trial, 94404. The size of the box, if you notice, is slightly larger than this one because this reflects the percent weight. So, all you need to do is just look at the graph and get a lot of information.

Notice that the relative risk is more than 1. For those who are not familiar with relative risk, it is simply the ratio of the risk in a drug over the risk in the placebo group. As you can imagine, if it is 1 then the risk is equal. So, if any relative risk is 1 it would fall on this red line. It will not be red in other graphs but I made it here to emphasize it. Now, if you see the

trial estimate on your right-hand side, this means the drug is worse. If you see it on the left-hand side, that means the placebo is worse. So, in this case, this is saying that the drug is slightly worse in one trial and not exactly the same in other trials. So you can see immediately the divergent results.

Now, one last thing to keep in mind is that this is just an estimate and that is why we provide the confidence interval. It sort of reflects the amount of information we have and simply means that if we are to repeat this trial or the sampling process 100 times, 95 percent of the time the true effect of the drug will be somewhere between these two extremes. So, it is important to put keep in mind that this is just an estimate.

I will move on with Paxil. It will be much quicker. With Paxil, notice that all the trials are on your right-hand side, which means that all of them have a relative risk of more than 1. Overall it is 2.65, but the confidence interval is just at 1, the lower limit. Notice here that

this graph contains all indications. Later on in the summary I will separate the depression-based trials and non-depression trials.

For Prozac this graph shows you the results I have in my briefing document. As you can see, there is not much going on in all the trials, and the overall estimate is almost 1.

But after I finished my report we received information from the TADS trial and, as you can notice here, I am only using two arms of the four arms that you heard about this morning, only the Prozac and the placebo because these were the two arms that were really blinded. Again, the events were sent to the Columbia expert group and we ended up with 9 events total in the Prozac group and 2 events in the placebo group. So, I ran the analysis again and I added the TADS trial. Note that based on these numbers the TADS trial is the only trial that you have in all the 24 trials that has a confidence interval that does not include 1. It has a considerably different picture than the sponsor-conducted trials. As you can imagine, the

overall the risk will increase.

Zoloft had three trials, one in OCD and two in depression. As you can imagine, when we take the OCD from the consideration, the overall estimate will actually be different; it will be higher.

For Effexor we had four trials, two in anxiety and two in depression. The two in anxiety did not have anything going on, but the two in depression really had the highest estimate in all the trials, and overall actually represents the only overall for a drug that does not include 1.

This is kind of a busy slide but it gives you a snapshot of the whole picture so I would rather have it on one slide instead of giving it to you on two slides. I will try to orient you with this slide. This gives you the overall relative risks of suicidal behavior or ideation by drug. This column has the brand name alphabetically. The first group is SSRI. The first column here shows you the results in the depression trials and the last column shows you the results in all

indications in all trials, regardless of indication.

For example, let's take Celexa. You will notice that the numbers here and there are the same. That is because Celexa only had two depression trials. It did not have any non-depression trials. Luvox did not have depression trials but it had one OCD trial. So, this really gives you a snapshot of all the findings in all the drugs whether by being a depression trials or overall.

Notice that Paxil did not change much. Prozac did not change much whether you look at depression alone or depression and other indications. Zoloft, as I told you, if you take out the OCD trial the overall estimate slightly increases. Then, Effexor, if you take the MDD trial it is considerably increased actually whether you actually just focus on the depression or overall. Both estimates do not include 1 in their confidence interval. Remeron, again is the same because it had one trial with depression. We did

not have any events in with Serzone, so nothing is reported here. Wellbutrin did not have a depression trial and it did not have an event in the only trial it had, which is ADHD.

The overall observation here is that all relative risks were more than 1 but, of course, as I mentioned earlier, there is always the possibility for a chance finding because, as you can see, the majority of numbers really overlap and they include 1 in their confidence intervals, except for Effexor.

One thing that you observed in the slide I showed for drug by drug is that we observed differences between trials even within the same drug within the same development program. So, we tried to examine some of the trial design attributes to try to understand where these differences come from. But none was found to consistently explain the observed differences in the risk estimates between trials whether within or between development programs. For example, you might find a trial that excluded placebo

respondents and had a signal, and also find a trial that actually included those and also had a signal. So, there was really no consistent pattern. So, there is a chance that what we are observing is due to some attributes that we have not captured, like how rigorously the trial was actually implemented and how closely the investigators were actually following the instructions of inclusion and exclusion criteria, and so on.

Now, every time you lump things we might lose some valuable information. So, after I did the overall analysis for suicidal behavior or ideation I did an analysis for the components of all outcomes which you can see on this other slide as outcome 1 and outcome 2.

This is again a slide which gives you an idea of what is going on in all the drugs that have events. First, again this just shows you the drug name. Here is the relative risk of the suicidal behavior alone; then suicidal ideation alone; and then I repeated again the combination for ease of comparison. If you notice, for example, with

Celexa the behavior was slightly more frequent in the drug but the ideation was slightly more frequent in the placebo group. But if you look at the combination you find that there is a slightly diminished signal if you compare it to the first outcome, which is the suicidal behavior. It is slightly more when you look at ideation. So, it really depends on what outcome you really can trust more. Perhaps you can say that behavior is more readily captured and that ideation is something that might be missed. However, the first three drugs are showing this pattern. When you go to Zoloft, for example, it reverses itself and you have more ideation in the drug group than the behavior. Anyway, of course, all this can just be due to chance findings because everything is actually overlapping but I thought you might be interested in knowing what exactly is going on behind the scenes of a combined outcome.

The sensitivity analysis, as I mentioned, we actually added three events coded 3 and 10 to the pool of codes already in suicidal behavior or

ideation, 1, 2 and 6 as the sort of worst-case scenario. I have here the results, again, all trials, all indications and just SSRIs in depression trials. As you can see, there is not much difference between 1.95 and 2.19. All the confidence intervals did not include 1, which means they were all significant. Again, perhaps there is some difference here but it still did not meaningfully change our perception that there is risk going on.

This is a different way to look at the risk estimates. We actually also did an analysis by the risk difference that is different from the way we just presented. The analysis of risk difference estimates the absolute increase in the risk of the event of interest due to treatment. It is simply the risk in that group minus the risk in the placebo group. The overall risk difference for SSRIs in the patient trials ranged from 2-3 percent, actually 2 percent for outcome 3 and 3 percent for outcome 4. So, that is the range that we have here.

This can be interpreted as out of 100 patients treated we might expect 2-3 patients to have some increase in suicidality due to short-term treatment because what we have is just a short-term treatment, and that is beyond the risk that occurs with the disease being treated.

Now, this is a different section now. We are moving to the outcomes based on the suicidality scores, which is totally different from the one that I just presented so far. There were two outcomes. One is worsening of the suicidality score and it was simply defined as an increase in the item score of pertinent depression questionnaires relative to baseline, regardless of subsequent change. Emergence was defined the same, except that the patient had a normal baseline score.

As you know, these questionnaires are actually collected regularly as part of the efficacy judgment. We are only capturing here sort of the subscore that is pertinent to suicidality.

For worsening, again, the same approach

was used as for effect modification and confounding, and here we had a considerably larger number of events, but again none was found to meaningfully impact the risk estimate.

This graph shows you all the trials that we have, and simply shows that there is not much going on overall. It is almost 1, the relative risk. There are only 3 trials that have some suggestion that there might be some signal going on there. Interestingly, these trials also show the signal with the other set of outcomes.

Now, the emergence--just to remind you, they are identical, except this one which required the patient to be normal at baseline. Again, effect modification and confounding were examined but none was found to meaningfully impact the estimates.

Here the same picture holds. In the majority of trials there is nothing going on, except for a few trials that have a suggestion of a signal and, again, those trials show the signal in the other set of outcomes and here the overall was

really not consequential.

I did many other analyses, as you can see in my briefing document. But in the interest of time I am not including them in my presentation. I tried to focus on the highlights of the findings, and none of what I did present changed the conclusion about the risk. But I will quickly go over the other list of things that were done and I can answer any questions about those.

I also did another sensitivity analysis examining the effect or the modeling approach. I also did an analysis of the co-called completers analysis in which I stratified by discontinuation and I looked at the signal within those that discontinued and compared that to those that completed the study.

Also, I did the time-to-event, both survival curves, and I estimated the hazard functions for all the SSRIs put together. I am sure a question will come up about the timing of the events. The finding of Dr. Jick's group did not hold. There was no initial increase in the

risk and chances that their finding was confounded by indication.

I also did some preliminary look at the so-called activation syndrome. The issue was raised at the last AC. Then I did some post hoc power analyses to just show why none of the trials really had power to detect a signal on its own or even within the same drug. So, I can share with you any of these if you have any questions.

Anyway, before I conclude, I have a very few slides left. The limitations, again just to recap what I said before, what we are dealing with here is post hoc analyses with multiple outcomes that in addition involved many subanalyses, therefore, caution is warranted in the interpretation of the findings.

As you saw, there were observed differences between drugs but the differences in themselves are no a limitation but our ability to tease out where these differences come from is the limitation. They can be due to chance findings because most of the confidence intervals actually

overlap. They can be due to true differences so, in effect, there is no class effect. Also, they can simply be because we don't have much opportunity to observe the outcome. Because the database sizes are different, they can simply reflect differences in the level of ascertainment of events and completeness of narratives. As I mentioned earlier, the sponsors put together the narratives so there might be some differences there. Also, there might be some differences in the trial design attributes that we were not able to capture or quantify.

Now, just a quick reminder that we are dealing here with short-term exposure and we don't have any information on the risk beyond 16 weeks. It might increase; it might decrease. It is very difficult to extrapolate.

Medication non-compliance might have influenced the occurrence of the events of interest. However, the determination of non-compliance was suboptimal in the way it was defined and the way it was assessed actually. Some

companies did it post hoc; some had pre-planned it in the protocol. It was very difficult to really get hold of ascertainment of the non-compliance.

Again, after everything is said and done, it is important to know that the observed rate of suicidality associated with the use of antidepressants might not reflect the actual rates among patients in the general population. Because we are dealing with volunteers we have the volunteer bias. We have the whole logistics of conducting the trial, the very close care for example that patients take and the detection bias that can result from that. So, it is important to appreciate this issue.

Most trials were conducted with a flexible dosing scheme, eliminating our ability to examine the dose effect. So, none was examined.

Now to give you an overall summary of the findings, the broader search for adverse events in various drug development programs and the blinded classification process identified many new events and also eliminated several events that were not

appropriately classified. It is important to note that there were no completed suicides.

The next point is that many individual trials had a relative risk of two or more for suicidality and some confidence intervals of overall estimates did not include 1. I think the key here is not really the statistical significance, because of the caveats I mentioned, as much as the consistency. You can see most of the trials falling on your right-hand side of the graph, which means that there is some suggestion of signal coming from many trials even though none of them was really significant perhaps.

The next point is that the sensitivity analyses did not yield a meaningful difference in the evaluation of the estimated risk. This gives more confidence in the finding that we might really be dealing with some real finding.

None of the examined covariates was found to be an effect modifier or to meaningfully impact the risk estimates as a confounder. But, mind you, this might be simply a function of power because

there might be some slight imbalance but the sample size is not large enough to really detect it or detect its effect.

Among the examined trial design attributes, none was found to consistently explain the observed differences in the risk estimates between trials. But I believe they can partially perhaps explain some of the differences, as I am sure you saw in my briefing document.

My last point is that no signal was observed in the outcomes based on the suicidality scores, unlike what we saw with the adverse events.

I have like 70 backup slides so if you have any questions, feel free.

DR. GOODMAN: Thank you, Dr. Hammad. I am sure you will be here tomorrow so I would ask the committee members to limit your questions to clarification because we will have an opportunity to ask additional questions tomorrow as we deliberate over the questions that are posed to us. With that in mind, Dr. Marangell?

DR. MARANGELL: It doesn't appear that you

included family history of bipolar disorders.

DR. HAMMAD: No.

DR. MARANGELL: How come?

DR. HAMMAD: This was an attribute of the trial. It is not patient-level data so what I have is that this trial did this or didn't do that and none of the actual attributes explain any of those differences anyway. So, the non-inclusion was because they were not patient-level data; they were trial-level data, and it really did not make much difference. You can see that some excluded and had a signal and some did not exclude and still had signal.

DR. GOODMAN: Dr. Leslie?

DR. LESLIE: I just wanted to make sure of the SSRI alone analyses and the activation syndrome analyses, if we can do that tomorrow. Since one of our questions is to think about these drugs as a whole versus certain classes versus specific medications, I just want to make sure we can do that.

DR. GOODMAN: Dr. Perrin?

DR. PERRIN: As I understand it, the nefazodone sample, which is about 450 kids in the MDD trials, has zero events noted. Can you help us understand why that might be true, and what might be different about those trials and those sample selections compared to the other trials?

DR. HAMMAD: I have not reviewed the actual protocols of the trials. That is something that Dr. Rabitsky did so perhaps he can comment on that tomorrow.

DR. GOODMAN: Dr. Gibbons, do you have a question?

DR. GIBBONS: First, I think you have done a great job. Apparently getting four degrees in your lifetime was a good benefit! I have a couple of general questions and lots of specific questions which I will hold for tomorrow. But the most general question is this, most of your analyses focused on the relative risks, which really in some ways goes away from the idea of using the patient-level data and using patient-level characteristics or covariates.

Now, I think you have done a very nice job of conditioning on things using stratification, but the analyses, even though in some sense are similar for the time-to-event, the survival kinds of analyses which do make use of the individual patient-level data--it seems to me those would be much stronger because they adjust for time at risk. The relative risks ignore the differential time--a study was conducted for the differential time that an individual within a study participated, whereas that is exactly the time-to-event analysis. So, I would just like your general comments on that.

DR. HAMMAD: The first thing was to actually make sure if there was any imbalance in the exposure time between trials, and I did not find much difference in the actual time for every trial between placebo and intervention. In spite of that, I realized that the time-to-event can answer other questions, other than taking into account imbalance between both. That is why I did it both ways actually. They are giving more or less similar conclusions. I didn't see that there

was that much difference in conclusions whether we looked at it as relative risk or as time-to-event analysis.

DR. GIBBONS: Just one follow-up question to that, one of the things you see throughout your analysis is that if you condition on prior history of suicide attempts or ideation, what you find is that the effects tend to go away. So, the development of new suicidal effects or worsening of suicidal effects shows absolutely nothing. When you conditioned on prior history the risk ratio went down to 1.2 essentially for those people who didn't have a prior history. What is your sense of this kind of what you bring to the table and then the effect of the drug?

DR. HAMMAD: I think this actually draws our attention to the fact that when you are dealing with a patient that is at higher risk to start with you might expect the drug to be--I don't want to be more risky because quantitatively the difference is not significant, the difference you are referring to. There is some trend towards that but if you

actually look at within trial you find that it goes both ways. Sometimes it is more in those patients; sometimes it goes the other way. So, I don't think actually there was much meaningful--that is why I used, if you noticed, the word "meaningful" difference. I don't think this particular covariate, which I believe is the single most important risk factor, plays much of a role in modifying the risk estimates.

DR. GIBBONS: Thank you.

DR. GOODMAN: Dr. O'Fallon?

DR. O'FALLON: I am interested in the missing data essentially. That is the thing that is bothering me all through this retrospective analysis. There are two issues that I am concerned about. One of them is how many of the patients had, in essence, missing follow-up? I mean, they disappeared from the study and, therefore, they could have had an event that was never observed or recorded. What percentage of missing data disappeared? I know you talked about last follow-up carried forward and that sort of thing in

your analyses.

DR. HAMMAD: Not in my analyses.

Actually, I don't have information in my database about the lost to follow-up. However, we did something that is sort of similar that sort of talks to the same idea. When I stratified by discontinuation, those that end up as discontinuing without us really capturing them, you would expect that among those who discontinued, because we know they discontinued--among those the signal would be greatly diminished. They would look as if nothing is going on--

DR. O'FALLON: Yes.

DR. HAMMAD: --but when I stratified by that, as a matter of fact there was a tendency for the majority of trials to observe a signal among those that discontinued, which simply sort of means that those that have events usually discontinue but it sort of allayed anxiety about the fact that we might be losing or missing information.

DR. O'FALLON: Yes, but I am still worried about the fact that there are some that could have

dropped out and then had an event and it was never recorded. So, you may be missing events.

DR. HAMMAD: Sure.

DR. O'FALLON: The other part of it was that I am concerned about the timing of events with respect to dose changes. I realize, again, with the retrospective analysis you may not have the information in your database, but that is one of the issues here, whether the events are occurring in connection with a dose change of any sort, and can you get at that or not with your data set.

DR. HAMMAD: No, we can't. The issue of the non-compliance, as I mentioned, is to some extent similar to dose change. I mean, it doesn't matter who changed it, the physician or the patient decided not to take it. I don't think we can capture that, unfortunately.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: I understand that on the Paxil trial 329 there was an active control. I think it was imipramine. Could you tell us was there a difference between imipramine and Paxil in

terms of--

DR. HAMMAD: No, I have not compared it to Paxil actually.

DR. GOODMAN: Could you repeat the question, please?

DR. ROBINSON: The Paxil trial 329 had another active antidepressant as a control and I believe that was imipramine, and I was asking if there had been any comparison of the effects of Paxil and the imipramine cell.

DR. HAMMAD: I did not do a formal comparison but if you look in my review, on page 101, you will see that there were two events in the active control and four events in the SSRI and one event in the placebo in this particular trial, with the sample size almost identical. So, it gives you an idea that it was about half of the ones observed on Paxil but double the ones observed on placebo.

DR. GOODMAN: Dr. Santana?

DR. SANTANA: Based on your expertise in this area, and I confess that I am not a behavioral scientist, can you give me some general sense, if

you look at these outcomes in adults are the relative risks for these outcomes the same when these drugs are used, or is this a universe that is particular to pediatrics, based on the data that you know of?

DR. HAMMAD: No, I am not aware of any data that actually looked at this particular question among adults.

DR. GOODMAN: You said that you have not examined those data in adults?

DR. HAMMAD: No, I don't have that.

DR. GOODMAN: Is there somebody from the FDA who can respond to that question? Tom?

DR. LAUGHREN: Yes, the adult data have not been looked at with the same level of scrutiny. But there are a couple of things I can tell you. First of all, this issue first came to our attention with Prozac back in the early '90s, and based on reports, from spontaneous reports of suicidality events in association with Prozac, the company went back and looked at all their controlled trials for Prozac, looking at them in

two different ways.

One thing they looked at are the item scores, roughly the same thing that we did here, and they did not find any signal for excess risk on the item scores, as we did not here. They also looked at event data and they did not find any signal with event data either.

Now, they didn't go back and try to reclassify the events in the same way that was done here. But subsequent to the Prozac experience, all subsequent NDAs for all antidepressants were looked at in the same way. The companies did an item analysis and they looked at their own event data, using their own approaches to classification. With all these subsequent NDAs, we have never seen a signal for excess suicidality, either looking at event data or looking at item data.

In addition to that, we now have a much larger database for completed suicides in adult data that we are currently looking at. Based on the analysis that we have done to date, we have not seen a signal for excess completed suicides in a

very large adult database. I mean, this comprises I think 240 trials, over 40,000 patients. But, again, none of these data in terms of event data, short of completed suicide, have been looked at with the same level of scrutiny for adults.

DR. GOODMAN: Tom, let me follow-up to that question. When you say that there has never been a suicide signal, I take that to mean a greater rate in the drug versus placebo group. What is the denominator there? How many studies are we talking about in adults?

DR. LAUGHREN: Again, this has only been looked at by individual programs so it is however many trials exist in the different databases, and generally, you know, we are talking about--this is ballpark again, I don't have the numbers in front of me but generally we are talking about anywhere from probably 4-10 trials per drug. So, it has been looked at within individual programs. It may, in fact, be larger than that if you include trials for indications other than depression. You know, I am just giving rough estimates here. So, it has

not been looked at across programs the way we have looked at it here for the pediatric data--complete suicides has been but not the event data or the item data.

DR. GOODMAN: One final follow-up question, from me at least, on these data, I don't imagine that you have stratified in the adult data by age, such that you would look at whether there is a relatively increased risk of suicidality in the younger adults versus the older.

DR. LAUGHREN: I don't believe that has been done. Again, these NDAs came in over a period of 10-12 years. I don't recall that being done.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Just a quick question for Dr. Laughren, the 40,000 database that you spoke of, was that what was published in the Kahn report in The American Journal of Psychiatry, 2003, or has this been published?

DR. LAUGHREN: No, I believe it is a larger database than Kahn included in his analysis that was done several years ago. So far it has

only been published in abstract form, a little over a year ago. It is an analysis that we are still working on but basically so far we have not seen a signal.

DR. POLLOCK: Thank you.

DR. GOODMAN: Dr. Rudorfer?

DR. RUDORFER: Yes, I have a question/comment for both Dr. Hammad and Dr. Laughren. It seems to me that one issue that we are up against that is unique here, unlike the adult data, is the relative dearth of positive efficacy in these trials so that the Celexa data that we just saw are particularly interesting because, as I understand it, those are the only set of studies where there is one positive efficacy trial and one negative. As I understand the suicidal risk ratio, there is an inverse relationship so that the study that was done in the U.S. and showed positive efficacy had a suicidal risk ratio less than 1 and the study that was done in seven different countries--we can talk about that tomorrow--and had negative efficacy result

showed a suicidal risk ratio greater than 1.

So, I wonder if there is any way we have for working around that issue, namely, if we are up against a couple of dozen studies that maybe were not done very well, or not done very seriously, or were not done in the right people, and then we are looking at adverse effects but in the context of a drug that is not doing what it is supposed to be doing.

DR. GOODMAN: Was that rhetorical?

DR. RUDORFER: That was the comment.

DR. GOODMAN: Well, thank you very much.

Dr Pfeffer?

DR. PFEFFER: You gave us relative risks and the confidence intervals very rarely reached 1. What would be the power or the size of samples necessary to show the effects with more assuredness?

DR. HAMMAD: I have one in my backup slides that I can share with you.

DR. NEWMAN: While he is getting that, could I make a comment?

DR. GOODMAN: Okay.

DR. NEWMAN: When you have randomized, double-blind trials the main thing that you worry about is lack of power. Most of the errors will leave you being unable to show a difference. So, it is relevant I think to look not just at the confidence interval but what the p values were for these estimates when you pool all the trials together. That is what I was just doing with my spreadsheet. I don't know if Dr. Hammad did that or not, but for the confidence interval that is furthest from 1 the p value is about 5 times 10

-5.

So, the probability that these are chance findings is very, very low. The confidence intervals are far from 1, at least for the outcome that is most impressive.

So, I think to think that these are chance findings is not a viable explanation, even given the number of subgroups and even given the differences in the trials. Most errors will be in the other direction, will be false negative. This also addresses what you have on the slide but if

you calculated the p values for the difference between the risk ratios and 1, you know, the p values for the pooled estimates.

DR. HAMMAD: No.

DR. NEWMAN: Well, I can share my spreadsheet. Just from the confidence intervals and the width of the confidence intervals you can do that.

DR. HAMMAD: No, I didn't do that. I thought the confidence interval gives you more information.

DR. NEWMAN: Yes, well, I disagree. I think if you are talking about chances and explanation, how low the p value is, is actually very relevant and something that most people around the table can understand, and they are very low.

DR. HAMMAD: But they are not equivalent to each other actually. So, you might have two confidence intervals that hardly overlap and then the p value is not significant, or the reverse. So, I thought that the confidence interval would give you more information, that is all.

Back to your question, it actually depends on the incidence in the placebo group. The red is assuming an incidence of 1 percent in the placebo group and the blue is assuming an incidence of 5 percent in the placebo group. So, for example, if you want to design a trial to be able to detect a relative risk of 3 or more, then you would actually need around 200 patients per group here and around 800 patients per group there. So, it depends on your assumptions of how many events would occur in your placebo group. And, one of the limitations in this particular effort is the great variation even in the rate in the placebo group. So, it would be hard to really plan for the future, but that is your range.

DR. GOODMAN: Dr. Pine and then Dr. Gorman, and those will be the last questions for the speaker.

DR. PINE: I wanted to return to the summary by Dr. Laughren and ask two questions about it. It sounded like a meta-analysis of 40,000 patients as opposed to a bunch of individual

studies, I just wanted to confirm that I understood that correctly, that you were talking about a global meta-analysis, number one.

Then, number two, I notice that you started your comment by stating that those studies have not been looked at with the same level of detail as the studies and analyses that have just been presented, on the one hand. On the other hand, I wondered if the level of review was comparable to kind of the first-pass review from the pediatric studies where there appeared to be a signal on more fine grade analyses. Was that meta-analysis comparable to the initial pediatric one or not?

DR. LAUGHREN: Let me again distinguish between the analysis that is focusing on completed suicides in adults. That is a very different matter from the analyses that the individual companies did, looking at either event data or item data. I would say, in answer to one of your questions, that probably the quality of the analyses looking at event data and item data were

comparable to the initial data that we got from Paxil in that sense. But, again, none of those data have been reclassified using the more critical approach that we have used for these data, but probably comparable to what we have seen for Paxil, and from that standpoint may have some validity, the fact that we never saw anything in any of those trials.

The adult completed suicide data--Tarek can speak more to that than I can, but that is a completely different thing. That is something that we have done based on data that we have obtained from companies and a relatively small number of completed suicides. I think the total number of completed suicides in that 40,000 patient database is only about--what?--30, Tarek?

DR. HAMMAD: Around 30, yes.

DR. LAUGHREN: Would you characterize that as a meta-analysis?

DR. HAMMAD: Yes, it is because we had a couple of hundred trials that were all pooled together, but the analysis was not the trials; it

was the actual patients. So, it is slightly different. And, there were only eight trials that were actually positive--not positive, that had some event in one of the arms. All other trials did not have anything at all. So, it is sort of controversial to take findings from eight trials and pool them with others and then try to get a conclusion. But even with those eight trials, our statistical group did a review and they found no signal, even focusing on those eight trials alone.

DR. GOODMAN: Dr. Gorman?

DR. GORMAN: This question is motivated by trying to answer some questions for the agency tomorrow. When you looked at the relative risks of the suicidal scores that were used, you found them to be not predictive of the behaviors that you may be observing. But we don't generally think of screening tests or predictive tests in terms of relative risk; we usually think of them in terms of sensitivity and specificity. Can you reanalyze your data for us to see if these scores actually predict the behaviors you then observed?

DR. HAMMAD: I have this in my review. I did a sort of clustered relation between the two types of events regardless of the treatment between the worsening and between outcome 3, which is the primary focus. In some trials there was a significant association; in some there wasn't. So, in some trials it was predictive to some extent; in some trials it wasn't. But the word predictive implies that one is occurring before the other and we don't have this exact timing associated in the data.

DR. GORMAN: I was more interested in the patient-level data. Were the ones that actually participated in behaviors that were ranked in outcome 3, in fact, predicted by the screening tools that we use?

DR. HAMMAD: But this assumes that you know the outcome occurred and then you have the screening tool before it, but we don't know that. The finding is not in my database.

DR. GORMAN: Thank you.

DR. GOODMAN: Thank you, Dr. Hammad. We

look forward to further interrogation of the data--not you but the data--tomorrow.

DR. HAMMAD: Thank you.

DR. GOODMAN: Now I am pleased to introduce Dr. Andrew Mosholder, from the FDA.

Comparison Between Original ODS and Current DNNDP
Analyses of Pediatric Suicidality Data Sets

DR. MOSHOLDER: Thank you very much.

[Applause]

Thank you. I was asked to present a brief comparison of the original analysis done in the Office of Drug Safety with the current analysis that Dr. Hammad just presented. I will present that and then I will touch on two or three additional points that were covered in the March consult document that is in your briefing packages that weren't really part of the analysis we just heard, just to supplement that. So, during this talk I will refer to the ODS analysis as the original one that I completed, and then the Division of Neuropharmacological Drug Products analysis as the one that Dr. Hammad just presented

to you.

This is just to orient you to the ODS analysis. It was the same trials as in the DNDP analysis, with the important exception that the TADS data has been added to the DNDP analysis. The events were determined from the responses to the July, 2003 data requests. Dr. Laughren mentioned these requests earlier, but just to amplify on that, last July the agency asked all the sponsors of the drugs in question to essentially reproduce the analysis that GlaxoSmithKline had done for their Paxil pediatric trials. This involved basically two components. One was an electronic search of specific terms in the adverse event databases for those trials, then followed by a manual review of all the serious adverse events in those trials. These were the data that I used for the ODS analysis.

I chose to emphasize the sponsor identified suicide-related events, that were identified by the means I just described, that were also classified as serious adverse events and I

will show you the exact definition of that in a moment. This, of course, predated the Columbia University reclassification.

There are some differences in the analytic methods. This just gives a brief summary. In the ODS analysis person-time was used as the denominator rather than the number of patients. The post-treatment window for including events was 30 days versus 1 day in the DNDP analysis. Events during down-titration I included in the ODS analysis. Also, in the Mantel-Henzel calculations Dr. Hammad's analysis employed a correction for zero cells, whereas my method did not.

To give you an overview of the data set for the analysis, there was a total of roughly 2200 drug-treated patients and 1900 placebo-treated patients. This yields a total exposure of about 407 patient-years for drug, almost 350 patient-years for placebo. Just to remind people, patient-year is a unit of exposure. It is a cumulative measure so that it could be represented by one patient receiving the drug for a year; two

patients receiving a drug for six months; 12 patients for a month, and so forth.

As we have heard, one of the limitations of these data is that they are all short-term trials so that there is no implication that there is any year-long treatment data here. In neither treatment group were there any completed suicides. Then, there was a total of 74 sponsor-defined suicide-related events with drug; 34 with placebo; and then a subgroup of those, 54, were serious and 24 for placebo were serious.

This slide gives the definition of seriousness. It has already been mentioned this morning but, basically, if the event is fatal, life-threatening, involves hospitalization, is disabling or is a congenital defect it is considered to be a serious event according to the FDA regulations. Now, in this case the events would fall under these two categories since there weren't any completed suicides, as has been mentioned, and the other two categories aren't relevant.

Each sponsor determined whether the adverse event was serious, and that is routine in the conduct of clinical trials. I will show you the comparison between the outcome that I emphasized, which is serious suicide-related events, to the Columbia University outcome 3, as we see over here, which is the suicidal behavior/ideation. The reason for concentrating on seriousness was to eliminate some of the events that were of questionable clinical importance, such as superficial self-cutting or the girl who slapped herself. Cases like those were not part of the serious events by and large.

So, this gives the comparison for those two categories. For the ODS serious suicide-related events there was a total of 78, and 61 of these were also eventually classified by Columbia University as definitive suicidal behavior/ideation. Of the remaining 17 cases, 13 were considered self-injurious behavior with unknown intent, which is over here. So, they were not part of outcome 3 essentially because the

intent was unknown. Then, conversely, for the Columbia University category--and this is ignoring the time following double-blind treatment so that this is a somewhat higher number because events occurring after treatment discontinuation are being shown here--there was a total of 95 in that category.

As I said, 61 overlapped with the previous category. There were 18 new cases disclosed by the expanded search algorithm that you head about earlier. Then, there were 16 sponsor-defined suicide-related events which did not meet criteria for seriousness so that they were not included in the ODS analysis but they were considered to be definitive suicidal behavior/ideation by the Columbia University team.

First I am going to show the results of relative risk for both analyses, and first for individual drugs. These are the drugs for which both analyses were able to calculate a relative risk. Just to orient you, first of all, let me point out this is a logarithmic scale because some

of the confidence limits are quite broad here. Then, I have highlighted the value of 1 here to remind you that values above 1 indicate a risk with drug and below 1 indicate a protective effect of the drug. For the ODS analysis the values are on the left and the DNDP are on the right.

First of all, we see that just in general the new relative risks from the DNDP analysis fall within the confidence limits of the previous results. So, from that standpoint there is agreement. Then, if you look at particular cases, some are similar; some are a little different. For sertraline the value decreased just slightly--let's see, this is 2.5 to 1.5 based on the addition of a single placebo case. For paroxetine, 2.2 versus 2.7. Venlafaxine actually showed an increase, 1.8 to 5 and the confidence limit, you see, just touches 1. Fluoxetine in both cases is just below 1. However, with the inclusion of the TADS data you see that the new relative risk for fluoxetine is 1.5. Then, for citalopram, 2.5 versus 1.4.

Next we are going to look at some

groupings of trials. First, on the left are SSRI major depressive disorder trials. Again, the value here, 1.9; the new analysis, 1.4. The confidence limit extends below 1 in this case. But then, again, with the addition of the TADS data the relative risk is 1.7. Then, for the category of all trials the relative risk is 1.9 versus 1.8. Then, with the addition of the TADS data, just below 2. You see in all cases that the confidence limit excludes 1.

That concludes a brief overview of comparison of the two analyses. I just wanted to touch on three additional topics. First is the incidence rate difference analysis. Secondly, and this has already come up in the discussion, there is one case in which we have direct comparison to adult data, and that is for paroxetine. Finally, a little bit of data on treatment discontinuation events.

This is an analysis of rate differences. This is a little different from what you have been seeing. Again, the events are per patient-year

but, of course, as I said, there is no implication that patients received the drug for longer than the short-term trials. Here I have highlighted zero because, as you realize, a value above zero would indicate a risk of the drug because it is drug minus placebo. A value below zero would indicate a protective effect of the drug. This is actually statistically a rather crude method. This is a simple totaling of the data for each drug's clinical trial database.

But with those things in mind, we see first of all that the pattern is that in every case here for the individual drugs, except for fluoxetine, the risk difference is positive, indicating an excess rate on drug compared to placebo. For fluoxetine I did not have the TADS data so one would expect, as we have seen with the addition of that data, that the fluoxetine risk difference would likely be above zero as well. For fluvoxamine there were no events. Unlike the DNDP analysis, there was one event for nefazodone, giving us a positive value.

So, for the individual drugs, those you see, the confidence limits are rather broad. For the set of all MDD trials the rate difference is about 0.09 events per patient-year. For all trials it is somewhat lower. Taking this one as the worst case, that translates to one excess serious suicide-related event for about every 12 person-years of treatment with the drug. In summary, this is just a slightly different way to look at the same data set.

This is a summary of the analysis that GlaxoSmithKline did in which they applied the same search algorithm to their adult clinical trial database that had found the signal in the pediatric trials. First of all, I need to point out, of course, that these events are not reclassified. These are simply the sponsor-defined suicide-related events. These are, again, rates per patient-year. There are a couple of things to point out. First of all, if we look at the placebo rates we see, first of all, that in major depressive disorder compared to all indications the

rate is a bit higher, and that is true for the pediatric group as well. That is not unexpected, given the association of suicidality with major depressive disorder which is being diluted in the larger pool of trials with other indications.

Secondly, we see that actually the placebo rates comparing adult and pediatric data sets are actually rather comparable, similarly for the MDD trials, not too dissimilar.

Third, we notice that for the adult trials the rates between drug and placebo are really not that discrepant. That could, of course, mean that some drug-treated patients are getting worse and others are getting better but there is no net imbalance. Also, I should point out that, of course, these trials are not designed to measure impact on suicidality because, as we know, most suicidal patients are excluded from these studies. But be that as it may, there doesn't seem to be much discrepancy in the rates for the adult studies.

However, for the paroxetine pediatric

trials that is not the case. You see that there is an excess for the MDD trials, and also in the larger pool of all trials which did reach statistical significance. So, it is not perfect data but I think it suggests, at least to me, that there could be a difference between the pattern of these events for pediatric patients and adults.

Finally, this is just to look at the possibility that drug discontinuation plays a role. These are going back to the serious suicide-related events now. This is all trials, all indications. As you recall, in the DNDP analysis events were included up to one day after the end of double-blind treatment. Here that is extended out to up to four weeks. This shows the pattern. We see that there is sort of this cluster here in the first week. In fact, all those occurred within the first four days of treatment discontinuation.

It may not be projecting real well, but paroxetine accounts for the largest number. Five of the nine events were in the paroxetine trials. Not too much is really seen in the subsequent

weeks. Again, it is just a suggestion. This is not perfect data but suggests that there may be some phenomenon happening early in the period after treatment discontinuation.

In conclusion, both the original ODS analysis and the current DNDP analysis indicate an association of suicidal adverse events with antidepressant drug treatment in this set of short-term placebo-controlled clinical trials.

Thank you.

DR. GOODMAN: Thank you very much. Any questions? Dr. Rudorfer?

DR. RUDORFER: Thanks. Andy, a question about your discontinuation data, did you get the sense, or could you tell from the data whether there were discontinuation issues during the course of the trial? I mean, some of the data we have seen suggest that in some of the trials adherence could have been a problem and I am wondering, particularly with paroxetine which you showed was being problematic after the end of the trial, if a child in the study is taking the drug only

intermittently wouldn't they be exposed to repeated discontinuations?

DR. MOSHOLDER: Yes, of course, that is true. I think that has been hard to capture in the clinical trial data though. I think in some cases patients were discontinued by the investigator if they admitted to not having taken their medication in several days, but that might not always be the case. So, it is very hard, at least in the data I looked at, to really get a sense. It was much easier to look at what happened when double-blind treatment was known to have been discontinued.

DR. RUDORFER: Right. Just as a follow-up, I am wondering if that could play a role in the difference you noted between the pediatric and the adult data for paroxetine, that is, if medication use is more continuous in the adult samples than in the pediatric ones.

DR. MOSHOLDER: That is a hypothesis. I don't know if there is any data that directly compares compliance for pediatric and adult patients. I think we know that compliance could

always be better, wherever one looks, but whether it is really worse in the pediatric group or not--I think people suspect that but I know if that has been documented.

DR. GOODMAN: Dr. Fant?

DR. FANT: Yes, I was struck by your fluoxetine data when you included the TADS trial, you know, showing more concern than the previous trials had shown, and it really makes me wonder, with the inclusion of children with other coexisting comorbidities and other medications on board, whether or not this may be pointing to a subset of kids, maybe in a distinct minority but who may be at higher risk for potential adverse events related to these medicines. It is just a comment.

A question, when you looked at the TADS data, when you included that, did you look at all of the kids who were given the drug or did you split it up into how they looked when they were given the drug alone or given the drug plus CBT?

DR. MOSHOLDER: I think I have to defer

this to Dr. Hammad who gave me those results so I could include them here.

DR. FANT: Since CBT seemed to suggest perhaps an enhanced effect on efficacy.

DR. HAMMAD: In my presentation I actually mentioned that I did not include CBT patients. The two arms were excluded because they were not really blinded. I only included the blinded ones.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: I was just going to mention that before the TADS data came in one of our explanations for why Prozac might have been different is that it is not so easy to discontinue with its several week half-life. Now that the TADS data seem to go in the same direction, the discontinuation hypothesis seems less strong.

DR. GOODMAN: Dr. Gibbons?

DR. GIBBONS: In your person-time analysis how did you handle people who had multiple events?

DR. MOSHOLDER: I took the first event.

DR. GIBBONS: So, they counted just once?

DR. MOSHOLDER: Right. I believe Dr.

Hammad took the clinically worst event; I took the first event. As a practical matter, that didn't involve large numbers.

DR. GIBBONS: Great!

DR. GOODMAN: Dr. O'Fallon?

DR. O'FALLON: In your discontinuation data, is there any chance that in that week-1 group there are people who were discontinued because they were doing badly? In other words, are these people who went all the way to the end of the planned analysis and then had an event? I mean, you are looking at this event in the week after they discontinued therapy. Were they the ones who completed the therapy or were they possibly having their therapy discontinued because they weren't doing well?

DR. MOSHOLDER: Yes, I don't have the numbers on that to break it down by whether they were prematurely discontinued or completed the intended length of treatment. I believe it is a mixture of both but I can get you those numbers.

DR. GOODMAN: Last question?

DR. PINE: Yes, I found the direct comparison of the data for paroxetine in the adults and children very helpful, and I was wondering if that was volunteered by the company or was there a specific request and, if the latter, are there plans to do comparable analyses for other agents?

DR. MOSHOLDER: Well, by way of answering, I can say it is included in my March memorandum and it was a submission that actually I believe went to another regulatory agency which FDA was copied on. As far as whether neuropharm. is asking other sponsors, I will defer to one of the people from neuropharm. for that.

DR. LAUGHREN: Yes, we don't have any current plans to do this in terms of adult data. Since we have this fairly large database with completed suicides which, after all, is the event that is of greater interest right now we are focusing on that.

DR. GOODMAN: Momentarily we will break for lunch. Before we do so, this is the last call for registered open public hearing speakers to sign

in. We are going to reconvene and, hopefully, be seated and ready for presentations by 1:15. We have three presentations that need to be given before we begin the public hearing at 2:00. For the benefit of the committee members sitting around the table, there are reserved places for you at lunch in the restaurant in the lobby. A final reminder once again, we are not to discuss matters that are germane to our deliberations during our break.

[Whereupon, at 12:26 p.m., the proceedings were adjourned for lunch, to reconvene at 1:15 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. GOODMAN: We are about to hear three presentations from representatives of the pharmaceutical industry. We are going to get started with the presentations. Our first speaker is representing Forest Laboratories.

Sponsor Presentations

Citalopram and Escitalopram Product Safety Data

Forest Laboratories

DR. JONAS: Good afternoon. My name is Jeffrey Jonas, and I am the vice president for the central nervous system therapeutic area at the Forest Research Institute. Thank you for allowing me to address you today.

I will be presenting some new analyses today based on our three studies of pediatric major depression. Two of these studies you have already seen involving citalopram. Another involves a recently completed study of escitalopram, the S-isomer of citalopram which we believe to be the active component, also in pediatric major depressive disorder.

I will be presenting an analysis of the SREs, presenting an integration of these three studies. Then I will discuss our Lundbeck study, European Union study 94404 which was conducted by our licensor, Lundbeck, and talk a little bit why we think this study is distinct from our other studies and, indeed, from most of the other studies under consideration today. Finally, I will be concluding with some exploratory analyses, looking at some alternative explanations for SREs, in particular, an examination of activating adverse events and a look at responder analyses of patients with and without serious suicide-related activities and events.

As I mentioned, there are three completed placebo-controlled studies in pediatric major depressive disorder, two with citalopram and one with escitalopram. The citalopram studies are MD-18, which was a U.S. study looking at children and adolescents, conducted in outpatients in the United States. The second study is a European Union study, 94404. This is a study of adolescents

only that enrolled both inpatients and outpatients.

The escitalopram study, MD-15, studied children and adolescents and in most respects was similar in design and implementation to the U.S. citalopram study MD-18. This study was recently completed. The safety data were just recently submitted to the FDA, in May, and the efficacy data were completed afterwards, sometime in June, and then submitted to the FDA. We will be presenting integrated analyses for this study with our other two studies, but I should point out that the SREs were not reclassified by the Columbia group.

The escitalopram study was an 8-week, double-blind, flex-dose study, basically conventional design. It studied patients with DSM-IV major depressive disorder. Of note, patients who were at high risk for suicidality were excluded and this study studied only outpatients.

I will be focusing on safety today but I just want to highlight the efficacy results of these three studies. Study MD-18 in citalopram was a positive study utilizing as its primary endpoint

the CDRS-R. Study MD-15 also had the same endpoint. This was a negative study. I should note, however, that recent analyses have shown clear trends in the adolescent subpopulation in MD-15. Also of note, both of these studies had similar decreases in the CDRS-R of about 22 points, the differentiating feature being the placebo response in MD-15 which was largely driven by the placebo response in the children's group. Study 94404 utilized the K-SADS and this was a negative study.

This slide now shows the SREs for the three studies combined. The middle row shows you the data for MD-15 which is the recently completed study in escitalopram. We analyzed the study using the FDA-provided algorithms that were used in the other studies for the analyses we have been discussing today. In the study there were three SREs, two in placebo and one in escitalopram. None of these was categorized as SAEs.

As you can see here, for both the U.S. studies the risk for an SRE was greater in the

placebo group than in the escitalopram group. The reverse was true in the European Union study. Overall, however, the risks for placebo or active treatment are roughly comparable when all three studies are combined.

This slide depicts that in terms of relative risk. As you can see, the confidence intervals all cross unity and, again as you can see for the U.S. studies, the relative risk for an SRE is greater for the placebo patients rather than patients on active drug, and the reverse is true for patients in the 94404 study.

Dr. Hammad, in his report, did comment that in most respects our European study was dramatically different or differed in almost every respect from our U.S. studies. So, we spent a little time looking to see if we could understand some of these differences.

We think the most important differentiating features involve the inclusion and the exclusion criteria utilized in the U.S. and the E.U. studies. This slide shows some of the major

differences. For example, inpatients could be enrolled in the E.U. study. I should point out that most of these inpatients were complex psychiatric cases with many psychosocial stressors, many coming from dysfunctional families, many on multiple medications. In addition, patients could have recent psychiatric hospitalizations, even suicidality, could be included in the study, and patients with a history of suicide attempts, even a recent one, could also be included. About 15 percent of the patients in the European study were inpatients. About a fifth had a history of psychiatric hospitalization and about a third had a history of a suicide attempt.

Few other studies of the studies we have looked at today had these features. In addition, the complex nature of the inpatients may have made it hard to have successful randomization balance in these studies. In particular however, we think the features of including inpatients and patients with significant psychiatric hospitalizations may have been a major differentiating feature of this study

from the other studies we examined today.

We, therefore, did a somewhat straightforward analysis and simply looked at relative risk in 94404, excluding the patients who had a history of hospitalization or who were inpatients at the start of the study. As you can see, when you do this analysis the risk for SREs is similar between placebo and citalopram.

Looking at the relative risk, we now see an analysis that in some ways makes these three populations and three studies comport more closely to each other. Here you see that overall the relative risk for an SRE is greater for placebo than for drug.

If one accepts the possibility that medication may not be the only factor or a factor in inducing SREs, one must look for other explanations. One common theory is that patients experience activating adverse events in association with SSRI treatment. This has been postulated also in relationship to other therapies but today we are speaking about SSRIs. In particular, there is a

theory that SSRI treatment induces early stage AEs that, in turn, are precursors to SREs. As a corollary, there is some clinical theory, I would say, that patients sometimes have to get worse to get better, and that is, patients who are responding to treatment undergo an energizing effect that may be confused or may be heralded as an activating adverse event--so-called getting worse to get better.

Regardless of how we postulate the role of AEs, we thought this was worthy of examination. So, we cast a broad net at looking at AEs in our studies in order to make sure that we basically subsumed any adverse event that might be considered to be activating.

This slide presents the risk data for the three studies. As you can see, overall there is not very much difference between active therapy and placebo.

We also conducted other analyses looking at activation adverse events. We looked at the pattern of onset and we found no difference between

drug and placebo. We also noted that the large majority of patients who have AAEs do not go on to develop SREs. Conversely, if one looks at patients with SREs, we found that if one looks for close proximity of AAEs to the SRE there is very little difference between the drug and placebo groups. Taken as a whole, we found no preferential relationship between AAEs and medication therapy.

This slide shows the relative risk for developing AEs in drug versus placebo. As you can see, in the two U.S. studies the relative risk was actually greater than in the European study, 94404, and we found this to be an interesting finding. You may recall that the signal for SREs in the U.S. studies was weaker than in the 94404 study where the risk of SREs was felt to be greater for drug treatment. This is not what one would expect if one thought that SREs were associated with AAEs. As a result, we feel that there is not very good data in our data set to suggest a relationship between AAEs and SREs.

Finally, we explored what we thought was

perhaps a more parsimonious explanation for SREs, that is that patients who develop SREs are simply patients who are not responding to therapy, whether they are being treated with drug or placebo. We hypothesized that SREs were simply associated with the course of depression, exacerbation of depression or clinical deterioration rather than associated with medication treatment.

We conducted a series of analyses to look at this question. The one I am going to show you now compared the course of response in patients with and without SREs using the change from baseline in a primary efficacy measure. the K-SADS.

This is the data from study 94404, looking at all the patients who had SREs. There are a number of points to make. First, there is good separation between the groups. However, the groups here are patients with and without SREs. The top two lines represent patients who had SREs; the purple, patients on placebo; the blue, patients on citalopram. This is an LOCF analysis and I should point that if you plot this with the OC analysis

the curves are virtually the same. Approximately 50 percent of these patients went on to completion, likely, of course, because these patients could be hospitalized in this study even during the course of the study.

If you look at this slide, this suggests to us that it is lack of response that may be responsible for the development of SREs, regardless of treatment group, rather than a distinct effect of medication.

We have done a number of other analyses looking at this theory and some of them are still in development. However, if you look, for example, at the patients in this study who were classified by the Columbia group as having SREs, of the nine patients on citalopram with SREs, none met protocol-defined endpoints for response. In the patients on placebo, there were five. Only one met protocol-defined criteria for response. Considering that in this study both the placebo group and the active treatment group had protocol-defined measures of response at 60

percent, we think this is an interesting difference and we, again, think that these data suggest that it is exacerbation of depression, regardless of the treatment group, that may play an important factor in the development of SREs.

In conclusion, we found that the numerical rate of SREs in the two U.S. studies was lower in active drug groups versus placebo. In the E.U. study, when one corrects for patients who might not have been included in the U.S. studies, this removes the signal for SREs from that study.

We found no evidence overall of an increased rate of AEs in the active drug group relative to placebo, and really no evidence suggesting that AAEs were etiologically related to the induction of SREs.

Finally, our data suggest that patients with SREs were typically poor responders whether they received placebo or active drug. Thank you very much.

DR. GOODMAN: Thank you.

DR. MCGOUGH: Did you elicit your

activating AEs by structured interview or rating form, or was it simply open-ended questioning?

DR. JONAS: The AAEs in the European study had a questionnaire and we actually got our AAEs by searching the data strings for the preferred terms in the studies.

DR. MCGOUGH: How about in the U.S. studies? Was there a structured rating to elicit--

DR. JONAS:: No, in the U.S. it was spontaneous.

DR. MCGOUGH: Because there is good work that shows that you get under-reporting of AEs if you don't have a structured instrument.

DR. GOODMAN: Dr. Fant?

DR. FANT: Your second conclusion or summary point is that patients with SREs are typically poor responders, suggesting that it had more to do with their non-responsiveness than the drug itself. Based on your data, can you exclude the possibility that there is something about the makeup of those patients that the introduction of altered chemistry might predispose certain

behaviors in those particular patients?

DR. JONAS: We looked to see--

DR. FANT: --which may coexist with non-responding in general.

DR. JONAS: We looked to see, when we did these analyses and, as I say, some of these are still ongoing, whether or not there were any differences between the groups in terms of pattern, onset and so forth, and we just found none. It simply looked as though this was a pattern that was common to patients whether they received placebo or drug. So, we had no clue, for example, of any prognostic factors that might herald this. if I am answering your question.

DR. GOODMAN: Thank you very much, Dr. Jonas. Our next speaker will be representing Pfizer Pharmaceuticals.

Sertraline Use in Product Population:
A Risk/Benefit Discussion, Pfizer, Inc.

DR. ROMANO: Thank you very much. My name is Steve Romano. I am the therapeutic head for psychiatry in our worldwide medical organization.

That is not the name you see on your agenda.

Charlotte Kremer is a colleague of mine. The title there though is mine.

What I am going to be talking about today briefly is sertraline use in the pediatric population and I am going to talk a bit about a risk/benefit discussion. Of course, I also want to say that I appreciate the opportunity to address this joint committee.

There are some critical points I think that are worthwhile considering in the assessment of risk/benefit for any antidepressant for use in pediatric patients and adolescent patients with MDD. Clearly, MDD is a very serious illness. It affects many children and adolescents in the U.S. and is associated with suicidal behavior. Unfortunately though, physicians have limited approved treatment options for pediatric patients with MDD. Pfizer believes that the risk/benefit of antidepressant use in pediatric depression should be assessed on an individual product basis, and this is for a number of reasons.

Antidepressants do differ with regard to chemical structure, pharmacological profile, pharmacokinetics, adverse events and discontinuation symptom profiles, and I think that all of them may potentially translate into a differential effect in the real world. Also, in support of this, as a result of the studies reviewed in the FDA analysis, they do vary from drug to drug. We believe that approaching this issue as a class effect might jeopardize or at least fail to highlight potential beneficial treatments for children or for some children and adolescents with MDD.

The suicide-related behavior in MDD in the pediatric population is a huge medical concern and a public health concern. It is the third leading cause of death in adolescents 15-19 years old. The annual present prevalence rate of MDD in children is roughly 2-3 percent but about 2-3-fold that in adolescents. The diagnostic criteria, as we all know, clearly clarify suicidality as a part of the disorder itself and that is clearly captured in our

diagnostic nomenclature, DSM-IV for instance.

In one study, it is important to note that suicidality in depressed children and adolescents, at the time of study entry was quite significant, in fact, about 1/10 individuals had a previous suicide attempt and up to 66 percent, or about two-thirds of the patients, actually had a previous history of suicidal ideation. I say this because I think the latter may very well complicate our ability to evaluate suicidal ideation in clinical trials. It is frequent and it is very difficult to assess the intent. Suicide attempts are a much clearer manifestation of potential suicidality.

We are now shifting to the Pfizer sponsored placebo-controlled trials. These are the trials done in pediatric patients with sertraline. As you can see, there are approximately five studies. The three studies I am going to talk about are the first three, a study in OCD and two studies identically designed in major depressive disorder. Those are the three studies that have contributed to the analyses that you are going to

review today, or have reviewed to this date.

The last two studies, one a PTSD study that is being conducted in response to a pediatric request, and the last, a non-IND OCD study, are both continuing and are blinded so they have not contributed to any events that you are going to see in any of the analyses and I am not going to talk anymore about those today.

What I do want to point out though is that all of these studies include both children and adolescents in the age range of 6-17. There is, by the way, and it is worth noting one NIMH-sponsored study that Pfizer has provided sertraline to, and it is not so dissimilar from the TADS study that was reported this morning. It is called the POTS study and it is looking at OCD patients. We do understand from communication from John March, and this is personal communication, that there were no events in any of the arms of that study that looked at CBT, sertraline, a combination as well as placebo, and that is a randomized trial. That has been submitted for publication but is not yet in

press. That was not a Pfizer sponsored study. I just share that for completeness.

The main discussion today, obviously is in MDD but I do want to show you that, in fact, we have met the rather rigorous criteria for a regulatory submission and an indication in OCD in children. This just shows that in our study, the ITT analysis, LOCF, change from baseline to endpoint. We did show a robust difference, a statistically significant difference between drug and placebo for OCD. We have been on the market for OCD and have had an indication in OCD since 1997.

Turning now our attention to the studies in major depression, we used the CDRS as the primary outcome measure and the primary efficacy analysis was a change on scores from baseline to endpoint in the ITT population, the LOCF analysis. As you can see, in both individual studies, study 1001 and study 1017, neither study showed a robust separation from placebo although, as Dr. Laughren pointed out this morning in his summary of all the

trials, study 1001 on the primary analysis of the change score on CDRS did show a trend of 0.8.

But, interestingly, we did have an a priori defined analysis which was a pooled analysis of those two identically designed trials, and that was also reported in an article by Wagner in JAMA about a year ago. In that particular pooled analysis, in fact, we showed separation from placebo on both the primary outcome measure of the CDRS change score, as well as on the responder analysis, the categorical analysis of those patients who met a greater than 40 percent change in CDRS at endpoint.

Now, I think the interesting point to highlight is really when we look at this data, why is it that we are not seeing a more robust or significant difference between drug and placebo in pediatric patients with depression? In other words, it doesn't mirror that which we see in adults. And, I think this slide is somewhat helpful in clarifying, at least for the sertraline database, what might be contributing to that.

This is looking at the placebo-controlled

pediatric MDD studies with sertraline, but at this case we are looking at the CDRS responder rate, the categorical analysis. I have it divided, on the left for children and on the right for adolescents. I think the important point here is that the placebo response in both children and adolescents is quite high but it is even more significantly elevated in children. We did include children in all of our trials and in both MDD studies. So, as you can see, there was a separation in the adolescent subgroup. This is a post hoc subanalysis. There is separation on this particular indicator of improvement--there is not, but both placebo and drug showed significant improvement on both subgroups.

Just for completeness, you saw the presentation of the item 13 score this morning in previous presentations, this is just to highlight that item 13 of the CDRS, which is suicidal ideation score, did improve in patients with major depression in our sertraline clinical trial database from baseline to endpoint. As you can

also see though, there is no significant difference between active treatment, in this case sertraline, and placebo but both groups showed improvement from baseline to endpoint. I think the fact that children can get in, present for their illness and actually get treated and are seen on some regular basis does impact on a child's outcome.

Let's move specifically to talk about the events of suicidal attempts and suicidal ideation. None of what I am showing you is new. This is in the briefing documents and was included in the analysis that the FDA and Columbia have done. I think it is also important to point out that the FDA analysis is consistent with the Pfizer analysis. In other words, no events were relabeled or significantly changed. They did not find new events. So, this really is consistent with the analysis that was done by both FDA and Columbia.

What I want to show now is suicide attempts first. We feel strongly that we need to look at suicide attempts separately from suicidal ideation. Suicidal attempts are a much clearer

and--it is a much clearer indicator of suicidality. As you can see here, for patients in the MDD trials as well as the patients in the OCD trial the rate for suicide attempts was quite low. In fact, it was exact in the case of subjects experiencing these events in MDD. We had two patients in the MDD trials who received sertraline and reported an event that was classified as a suicide attempt. We had two subjects in the placebo group, although one of those subjects contributed two events of suicidal attempt. But the incidence rate based on the subject numbers is the same and as you can see by the confidence intervals, they overlap zero. There is no difference. In the OCD study there were no events in either the placebo group or the sertraline group and in the combined, as you can see, we are showing the exact incidence. Looking at suicidal ideation, again, in this case this is a very common adverse event and it is quite difficult to assess intent around suicidal ideation. So, we really do feel it is worth looking at them separately and not combined. Again, as you can see

here for MDD and OCD, there was a relatively low rate of events across these studies. In the MDD studies, again, we were looking at the pooled analysis of those two MDD trials. There were three patients on sertraline for a rate of 1.6. There were no patients on placebo that experienced the event of suicidal ideation during the course of those MDD trials.

In the OCD trial, which was a 12-week short-term trial, we see that there were no events in the sertraline group but one event out of 95 patients in the acute phase of that particular trial. As you can see, neither in MDD nor in OCD or for sertraline or placebo was there a statistically significant difference across the groups, and that is true also for the combined analysis.

Now, one of the issues that has arisen as being very important to consider is, is there a temporal association between the onset of a particular event, like suicide attempt or ideation, and the initiation of double-blind therapy or

titration of drug during the course of the study. This is looking at all the cases of suicidal ideation and suicide attempt for sertraline and for placebo in our trials, both the MDD trials and the OCD trial, so for those three trials.

As you can see, if you look to the far end, the last column, day of event, the day of double-blind therapy, in fact in sertraline-exposed patients none of these events occurred in the first week or two of exposure to drug, and there was no pattern of response that was based on changes or titration of drug during the course of the therapy. For placebo, there were two patients in the first week and a half, one in depression and one in the OCD trial, where the event was associated with initiation of treatment but in this case, of course, we are looking at placebo.

So very importantly, there was no specific pattern in time of event. It was fairly random. There was no association between time of event and dose increases. I think more importantly as well, when we get down to the narrative level most of

these events were actually associated with some psychosocial stressor or precipitant that was captured.

In summary, for the placebo-controlled pediatric studies with sertraline we can say that sertraline is effective and safe in the treatment of pediatric OCD, and we were granted that indication about eight years ago. The a priori pooled analysis of the sertraline clinical studies in pediatric MDD did demonstrate a statistically significant effect on the CDRS but, admittedly, the benefit relative to placebo was modest. The effect size was relatively low, and there was a high placebo response, as I showed you previously. That was primarily driven in the subpopulation, children ages 6-11.

There were no completed suicides in any pediatric study with sertraline. You are well aware of that. There were also no statistically significant differences between sertraline and placebo in placebo-controlled studies of MDD or OCD with respect to suicide attempts, as I just showed

you, or suicide ideation. Again importantly, no temporal association was seen between onset of double-blind therapy or dose increases and suicide-related events, either suicide attempts or suicide ideation.

So, just to highlight the points that we really think are very important to consider are the fact that this is a very serious illness; that physicians really do have limited approved treatment options for the treatment of pediatric patients with MDD; and that the risk/benefit of antidepressant use in pediatric depression should really be assessed on an individual product basis for the reasons I mentioned earlier. Again, I think it is worth underlining that approaching this issue as a class effect might jeopardize or at least limit the likelihood of clarifying some benefit in some population of patients with MDD in the pediatric group.

Lastly, I just want to highlight a position of Pfizer's, we currently feel that class labeling for monitoring during treatment with

antidepressants accurately reflects the risk of suicidality in adult as well as pediatric patients. We think that such labeling should be applied to all medications indicated for the treatment of depression and simply not just to the SSRIs or SNRIs, and I think we heard earlier from Tom Laughren that that may, in fact, be a consideration of the FDA's as well.

We also feel that if the FDA does consider a label change necessary that product specific labeling would be most beneficial to prescribers and patients. I guess an example of that might be the inclusion of specific event rates of suicide-related behavior for the placebo-controlled clinical trials, and perhaps the best place for that would be in the adverse section of the label. We do this for other dimensions of tolerability like weight, for instance, and that has been very helpful to our prescribers and I think it might actually clarify potential risk as well as a possible benefit in some patients treated with sertraline. Thank you.

DR. GOODMAN: Thank you, Dr. Romano.

Questions from the committee? If not, I would like to proceed with our next speaker who will be representing Wyeth Pharmaceuticals.

Wyeth Pharmaceuticals

DR. CAMARDO: Good afternoon. I am Dr. Joseph Camardo. I am head of medical affairs for Wyeth, located in Pennsylvania. Wyeth developed and has marketed venlafaxine, brand name Effexor, since 1994 and I want to start by expressing my appreciation for the opportunity to speak before the committee.

As we have heard today, mental illness, including depression in pediatric patients, is a complex medical condition and it is associated with the risk of suicide. More than two million children and adolescents in this country suffer from depression in one form or another. Physicians need to treat individual children and they have cautiously used the newer antidepressants, including venlafaxine, even though most are not indicted in the pediatric population.

Wyeth has never labeled or recommended venlafaxine for such use but we, and other manufacturers, have conducted clinical studies of antidepressants in children. However, despite all of our research efforts many of the drugs that have been very beneficial in adults have not been proven to be effective in clinical studies in pediatric patients. The studies of antidepressants in children have shown an apparent increase in suicidal thoughts and possibly suicidal attempts which is a concern for us, for the patients, for the parents and for the physicians. Thankfully, no child committed suicide in any of these studies. It is important that we learned about these effects and now we need to make use of this information that is the subject of this meeting. I want to take just a few minutes to describe Wyeth's point of view. The first is that we should make use of this information that was gleaned from these studies and provide this information to physicians. In our pediatric clinical studies there were increased reports of hostility and suicide-related

events, such as ideation and self-harm. We, at Wyeth, updated our label and we provided our pediatric safety information to over 450,000 healthcare professionals in 2003 in a "dear healthcare provider" letter.

Studies with other antidepressants, carried out by other pharmaceutical companies in pediatric patients, have shown similar adverse events. As an industry, we should continue to provide safety information broadly and in a consistent way to physicians, and the information should be similar for all antidepressants.

Second, although the FDA's and the Columbia University's cross-study analyses were done carefully, one cannot conclude that a difference among the drugs has been demonstrated. This is largely due to limitations inherent in the various study designs, and I think you heard a lot about these caveats from Dr. Hammad already. The reviews, by necessity, included post hoc analyses with multiple outcomes and no statistical corrections. They are complicated by the lack of

statistical significance for many of the subanalyses. This increases our level of uncertainty. So, we have to exercise caution if we try to draw definitive conclusions about the true relative risk of these events.

Also, these trials were designed for efficacy and were not sufficiently large to detect differences in the less frequently reported events. Moreover, the studies did not include a direct comparison of one antidepressant with another. There was insufficient commonality among the studies to make valid comparisons. For example, the studies we venlafaxine did not exclude patients with treatment resistance, history of suicide attempt or homicidal risk, but some of the trials with other medications did exclude these patients. Therefore, while we recognize that there were larger risk ratios reported for venlafaxine than for some other products, we do not, on the basis of these observations, believe it is appropriate to advise that a physician could apply special precautions for one antidepressant and not the same

special precautions for another.

Third, it would, in our opinion, represent good medical judgment to allow physicians to use these products in pediatric patients if they believe the products to be necessary, and if they determine that other ways of treating depression are unsuccessful. Companies should provide warnings. Prescribers should be fully aware of the risks and fully capable of identifying and managing suicidal thoughts, hostile behavior and suicide attempts. The parents should be well informed of these risks as well in order to recognize the emergence of these symptoms.

Let me summarize our point of view.

First, we should continue to provide information to physicians about what we have learned in our studies about suicidal thoughts, suicide attempts, and we need to emphasize the need to be vigilant.

Second, the information we provide should be consistent for all of the antidepressants since the data do not allow us to distinguish among them for the appearance of this particular risk.

Third, we should keep these products available to physicians to use when needed, according to their expert judgment, because depression in children is a complex, serious problem and it may be extremely difficult to treat.

I want to thank you for giving Wyeth the opportunity to present our position.

DR. GOODMAN: Thank you very much. Any questions? Yes?

MS. GRIFFITH: I appreciate the time you took, and I don't mean to pose a hostile question to you but as a parent, looking at the data that Dr. Hammad gave us, it is so dramatically different, the presentation for effects and the overall risks of suicidal behavior and ideation. I mean, it wasn't just a couple of points difference, you know, 8.84 as opposed to 1.37 for Celexa; 2.15 for Paxil. I am not a clinician but that would alarm me as a parent and I don't quite understand how you excuse a result that is so dramatic.

DR. CAMARDO: I purposely acknowledged the risk, and your question is not at all hostile,

first of all, and we in fact believe that notification of the risk is critically important to any physician who is trying to use the product. I don't want what I said to be misinterpreted as not being forthcoming about the risk and the differential risk observed. I just am recommending that we be cautious about treating one drug as so dramatically different from another that you could apply a warning or precaution in one case and not in another case when we have seen that one trial can be different another; one condition, such as anxiety, could be different from depression; and sometimes the differences in the way the studies were done may lead to differences in the outcomes. So, I think we just need to be careful about believing that we have distinguished between the drugs on the basis of magnitudes of effect that might be suspicious when you look at them carefully.

DR. GOODMAN: Dr. Fant?

DR. FANT: Could you just reiterate the comment you made about differences in exclusion

criteria in your studies and some of the other studies with the other drugs? If I am remembering your comment correctly, and validate this for me, I think you said you included kids who potentially had more problems that were excluded in other studies.

DR. CAMARDO: I am actually basing what I say only on the basis of what I know about our own studies. In fact, Dr. Hammad outlined in his review some differences between different studies, and that information is only available to me from that review. But having said that, we did include, for example, children who had not responded to other antidepressants. I don't know if that is true in the other studies or not. We have included in the venlafaxine studies children who actually may have had a previous suicide attempt. Our only exclusion criteria were if the child was considered to be a high risk of suicide. So, I only know a little bit about those.

DR. FANT: Now, if you went back and excluded those kids in your group and reanalyzed

the data using different exclusion criteria, how would the risk look?

DR. CAMARDO: I don't know the answer to that question. It is a very good question but I can't answer it.

DR. GOODMAN: Any other questions? If not, we are going to take a very brief break but I am asking people not to leave the room. You can just stretch as we prepare for the open public hearing. I am going to hand the microphone over to Anuja Patel.

MS. PATEL: I would like at this time for all registered open public hearing speakers to make sure they are sitting in the reserved open public hearing section on the left-hand side of the audience, which is the committee's left-hand side, just to help us be more efficient in recognizing the registered speakers. Thank you.

[Brief recess]

Open Public Hearing

DR. GOODMAN: We are about to begin. I would like everybody to find their seats. For the

next four hours we will be holding the open public presentation portion of the meeting. Let me begin by making a statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, 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 connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have 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.

We have approximately 70 speakers in the next four hours who will each be allocated, for the most part, three minutes a piece. To describe the process more clearly to you, let me turn the microphone to Igor Cerney, who is the Director of the Center for Drug Evaluation and Research Advisors and Consultant Staff.

DR. CERNEY: As Dr. Goodman has said, everyone will have three minutes, except for one group that has a consolidated presentation which will be allowed five minutes. When you have 30 seconds left the green light which has been on your timer will turn yellow and that is your wrap-up time of 30 seconds. Then, when you are out of time the light will turn red. It will flash, it will beep, and will cut the sound off automatically at that point. So, that is just letting you know what the ground rules are for the open public hearing. Thank you.

DR. GOODMAN: At first blush, it may seem insensitive to cut off the sound but we have to achieve the right balance between giving an individual an opportunity to express his or her opinion but also ensure that there is sufficient time for everyone here who wants to speak. We are not going to be making exceptions in the timing. It is going to be a relatively automatic process so please gauge your presentation to ensure that you have reached the high points before the mike is turned off.

I also apologize in advance for addressing each of you by a number. The data I have here, at least the most valid data, just gives me a number of each speaker presentation and then I ask you, when you get to the podium, to introduce yourself. No surprises here, we are going to be starting with speaker number one. I would appreciate it if you would stand up to the microphone.

DR. DUCKWORTH: Good afternoon. My name is Ken Duckworth and I am a Board certified child and adolescent psychiatrist. I work part-time as

the medical advisor to the National Alliance for the Mentally Ill, also known as NAMI. NAMI has 220,000 people who have serious mental illness or have people in their families who have serious mental illness. Because I work for NAMI, they have paid for my trip here but I do no work for the industry of any kind and I get my income from clinical practice and taking care of patients.

NAMI would like to start by saying we believe there is sufficient reason to demand better research, which I think is evident from your conversations today. It is very clear that the studies don't answer all the questions that parents, doctors and teenagers need. We feel that longitudinal research is one of the things that is missing from this conversation. We know that it is hard to do and expensive but we feel that it is an incredibly aspect of this work.

The TADS study is a very important and good start, but it is only a start. We still don't know so many aspects of the risk/benefit assessment that parents and doctors need to make when they

make decisions about whether to start a compound, a medication or psychotherapy on an adolescent who walks into the office with suicidality. In that TADS study 20 percent of the patients were presenting with suicidality before they entered the study. To me, this is emblematic of the problem of suicidality that is endemic to the condition of adolescent depression.

I just want to also say that the President's Freedom Commission has told us that the mental health system is a shambles. That is important because if you think cognitive behavior therapy and thoughtfully applied medications, with good monitoring, is going to happen on a routine basis, there is not much evidence to suggest that the system is set up for that, and that is something that NAMI wants to acknowledge, that you know that the work force issues around getting good care for people is a major problem that relates to this.

Monitoring--monitoring is a very important piece of this whole conversation and I would like

you to reflect on your success with monitoring clozapine for people with treatment-resistant psychoses. People with treatment-resistant psychoses have a 10 percent chance of killing themselves. This is people with schizophrenia. Your system for monitoring clozapine enables me to give people a medicine which is risky, may save their life and may cause the rare chance of a catastrophe. Your system for monitoring for this rare thing enables me to prescribe this, give good informed consent, and the patients and the families make good decisions.

We also need to remember that as you are constructing whatever risk/benefit information you are giving to people everybody should know what akathisia is. Every person should know if their kid has a family history of bipolar illness and, finally, every person should know, and you should communicate to them, that untreated depression also kills people. Thank you.

DR. GOODMAN: Thank you very much, and I welcome our next speaker, number two.

MS. TOTTEN: Hello. My name is Julie Totten, and I am the president and founder of Families for Depression Awareness. Regarding financial disclosure, there is no industry money; we just took it out of our operating dollars for coming here today.

Families for Depression Awareness--I would like to speak on behalf of our members who are families coping with depressive disorders, our board of directors and our advisory board. Many of us have lost a family member to suicide and I lost my brother to suicide 14 years ago. He was undiagnosed but afterwards, when I learned about depression, it was very apparent that he suffered from this condition.

I would like to make three points. One is that family care-givers are the ones who need to be active in monitoring treatment. Number two, monitoring is the key issue and, number three, more monitoring advice is needed, first, regarding family care-givers. Families for Depression Awareness is very pleased and enthusiastic that you

have put out a warning that families, patients and clinicians all need to monitor depression treatment and we are so glad that you have included family care-givers, people like me who are in a position to help when patients are not capable and doctors are too busy, which is most of the time. Please make sure to include family care-givers. They are the ones who can make a difference.

Six months after my brother took his life I helped my father get diagnosed and treated for major depression. I am a family care-giver and I am proof that family care-givers can make a difference if we are given a chance.

The second issue is that monitoring needs to be the main issue here. People with depression need medical treatment and every person's reaction to medication is different and has to be handled on a case-by-case basis, as we all know. So, monitoring is what we need to focus on to prevent suicides right now. But the problem is that families and patients do not know how to monitor treatment. So, families need more explicit

monitoring advice. They don't even know how often to make a doctor's appointment.

Families for Depression Awareness is developing a depression treatment monitoring tool for medication, psychotherapy or both to help families and patients track their symptoms, side effects and treatment, and we would welcome collaboration. We can only do so much and we need your help. Please focus on family care-givers make monitoring an issue right now, immediately, and help us develop more specific monitoring advice. Thank you.

DR. GOODMAN: Thank you very much. I would like to invite our next speaker, number three.

MR. WILKINS: Hello. I am Ronnie Wilkins, with the ACNP. Depression in youth, as you have talked about today, is a serious disorder. It affects every aspect of a child's life and increases the risk of more drug, alcohol use, adult depression and suicide. Allowing to go untreated delays improvement and it increases the likelihood

of long-term negative outcomes.

Controlled trials have shown that fluoxetine is effective in the treatment of depression, and the recent data from the NIMH-funded TADS trial provides further support and justification for the use of this medication. In addition, the TADS trial compared fluoxetine to cognitive behavior therapy and found some evidence that both CBT and placebo were inferior to treatment with fluoxetine alone.

The ACNP strongly supports more research comparing psychological and medication treatment for depression in children and adolescents, more methodologically sound research with other SSRIs, more studies of non-SSRI agents such as tricyclic antidepressants, and studies testing strategies to treat depressed children and adolescents who have failed treatment on an SSRI.

Depression as a significant risk factor for suicide is something to be concerned about as well. Treatment of depression is likely to decrease overall suicide rates. Epidemiological

data tends to support this view.

In over 4000 children and adolescents treated in controlled trials with antidepressants there have been no suicides, however, there are indications that there may be an increase in suicidal ideation and suicidal behavior. Recent data from the U.K. in adults are consistent with an increase in suicidal ideation during the initial phases of antidepressant treatment with all medication treatments. These uncontrolled observations need additional rigorous study in depressed children and adolescents before we will have a final understanding of these issues.

The ACNP supports the FDA recommendation that clinicians carefully monitor all patients treated with antidepressants for worsening of symptoms and emergence of suicidality, as well as for agitation and mania. This has always been good clinical practice and adding that information to antidepressant labeling is highly justified.

The TADS study also shows that overall the impact of treatment on depression significantly

decreased suicidal ideation. It is important to put into perspective that while some adolescents may demonstrate a worsening of suicidal ideation, up to 40-60 percent will demonstrate an improvement in suicidal ideation, and similar proportions will demonstrate a meaningful reduction in other symptoms of depression.

It is only through further methodologically sound research that we will increase our understanding of age-specific issues of safety and effectiveness of both medications and psychotherapy in the pediatric population. Limiting clinician choices because of lack of available information would not be in the best interest of patients and it would be unfortunate if these controversies resulted in stifling of research just when more research is needed.

DR. GOODMAN: Thank you very much.
Speaker number five, you have five minutes.

MS. TRACY: I am Ann Blake Tracy, head of the International Coalition for Drug Awareness. I am the author of "Prozac: Panacea or Pandora." My

house is mortgaged to the hilt to pay for the last 15 years that I have devoted to nothing but research on SSRI antidepressants and to fund my trip here.

I testified for twelve and a half years in court cases involving these drugs. Research on serotonin has been clear from the very beginning, that the most damaging thing that could be done to the serotonergic system would be to impair one's ability to metabolize serotonin, yet that is exactly how SSRI antidepressants exert their effects. For decades research has shown that impairing serotonin metabolism will produce nightmares, hot flushes, migraines, pains around the heart, difficulty breathing, worsening of bronchial complaints, tension and anxiety which appear from out of nowhere, depression, suicide, especially very violent suicide and repeated attempts, hostility, violent crime, arson, substance abuse including cravings for alcohol and other drugs, psychosis, mania, organic brain disease, autism, anorexia, reckless driving,

Alzheimer's, impulsive behavior with no concern for punishment, and argumentative behavior.

How anyone ever thought it would be therapeutic to chemically induce these reactions is beyond me, yet these reactions are exactly what we witnessed in our society over the past decade and a half as a result of the widespread use of these drugs.

Can you remember two decades ago when depressed people used to slip away quietly to kill themselves rather than killing everyone around them and then themselves, as they do while taking an SSRI antidepressant?

A study out of the University of Southern California, in 1996, looked at a group of mutant mice that had been genetically engineered. In an experiment that had gone terribly wrong, they were the most violent creatures they had ever witnessed. They were born lacking the MAOA enzyme which metabolizes serotonin. The end result is the same as if they were taking an SSRI antidepressant which does inhibit the metabolism of serotonin.

This has been a national holocaust. It must end. These are extremely dangerous drugs that should have been banned as similar drugs were in the past. As a society, we once thought LSD and PCP to be miracle medications. We have never seen drugs so similar to LSD and PCP as these SSRI antidepressants are. All of these drugs produce dreaming during periods of wakefulness. The higher serotonin levels overstimulate the brain stem leading to a lack of muscle paralysis. That was seen clearly in the case of comedian Phil Hartman and his wife in the terrible murder-suicide. Thank you.

MS. GOLF: Thank you for allowing me to speak here today. My name is Marion Golf. I am here today with my other daughter. It was her twin sister who was put on SSRIs.

I would like to ask all of you a few questions. Why is it easier to have antidepressants prescribed to our children than to have antibiotics prescribed for them? Why are antidepressants handed out so easily to our

children?

During the fall of 2002 my nine year-old twin daughter was diagnosed with an eating disorder by a doctor who never did a sufficient medical or psychological workup. Up to that point she had been a happy and beautiful child, a sweet child. We told him that this was unlike her, that it had come on suddenly and severely. Instead, within a week of seeing this eating disorder specialist, she was given Zoloft up to 75 mg, which was then switched to Paxil. At one point she was given 30 mg of Paxil and up to 10 mg of Zyprexa at the same time. These drugs did not help her. They made her suicidal and abusive to herself and to our family. We almost lost our child twice.

My daughter was finally diagnosed with chronic Lyme's disease, in January of this year. Because of the delay in treatment she has been on intravenous antibiotics and continues in this way, but she has made incredible progress while on these antibiotics.

The antidepressants that were given to my

daughter are dangerous. Would any of you prescribe these medications for you own children? Why are we turning to drugs before we truly understand the problem? My daughter could still be on these mind-altering drugs if my husband and I were not so persistent in getting to the truth.

When a child presents with a multi-systemic problem why isn't Lyme's disease ruled out first? Lyme's disease is the fastest growing infectious disease in this country...

DR. GOODMAN: Thank you for your testimony.

[Applause]

Speaker number five?

MR. CHONILEWSKY: My name is Andrew Chonilewsky. I am not affiliated with--

DR. GOODMAN: Could you bring the microphone closer to you?

MR. CHONILEWSKY: Surely. My name is Andrew Chonilewsky. I am not affiliated with any organization at all, just totally on my own. If you notice from slide one, this is the name of my

ex-wife. She is a VA psychiatrist currently practicing. She is homicidal, suicidal. She is a psychiatric drug user, mother, child abuser and dog killer. This is what she is. I can document everything. It is certainly in the court records. Nevertheless, she is still practicing. That is her workplace, where she is. I am not afraid of exposure.

I would request slide two. I received this, an affidavit in support of preliminary child protection order from the State of Maine regarding my son. This is an affidavit made before Gail D'Agostino, State of Maine, Department of Human Services, being duly sworn.

Next slide, please. This is rather interesting. It comes down to, for all the talk and all the minutia given psychiatric drug trials, regression analysis--I am rather reminded in a far-off time, in a far-off land of the dialectics of Marxism and class struggle. It is meaningless. However, you have one of your colleagues here, a trained, Board certified psychiatrist with added

qualifications in geriatric psychiatry, and I am inclined to believe this time what Dr. Runden wrote about herself in revealing her set of depressions, suicidal feelings regarding my child and herself for she planned to kill my child first, then herself, but there was a snowstorm that she did not expect so she did not. That is her reasoning.

Her comments are very interesting. She has forged my signature, forged documents, perjured herself, stolen, lied. She is a whore. Nevertheless, I am inclined to believe what she writes in terms of her status, mental status. I am inclined to give her credibility for the so-called mentally ill, besides being self-indulgent and being control freaks...

DR. GOODMAN: Thank you. Number six, please.

MS. FURLOUGH: Hello. My name is Susan Furlough. I am not affiliated with anyone. This is my son's letter to you. Good afternoon--

DR. GOODMAN: You need to bring the microphone closer.

MS. FURLOUGH: Is that better? This is a letter from my son. He says, good afternoon to everyone. My name is Ryan Furlough. Please excuse me for not being there in person for, at present, I am currently incarcerated. I was only 16 when I started taking the antidepressant Effexor XR. I started out with a small dose of 75 mg and over a short period of time was up to 300 while I was only 17. While I was on the drug my depression got worse, completely affecting all aspects of my life. Negative thoughts filled my mind night and day. I wasn't living at all; I was just existing. I felt like I was on the outside looking in on life. I believe that everyone hated me and nothing seemed to be right for me. I gave up on life and it seemed like everyone else had no purpose.

Unfortunately, solving this problem meant the death of the best friend I ever had. I felt uncontrolled hate towards him because, beyond my comprehension to where I acted like I was an emotionless puppet, having someone else pulling my strings to what my fate would be. Now the worst

thing has happened and I can't fix it now. I am off Effexor XR and I can't understand what I was then. This medication changed me, who I was then and who I am now. There is no other Ryan there. There is a new Ryan, the Ryan that used to be there before medicines. I know who I am now, just like I did before.

As I said to you, it is too late now. His family and friends are forever traumatized and my own family feels the same way, except they are relieved that I am emerging from a dark cloud of Effexor. I ask you to please take action and stop these drugs now. Too many times have I read about people like me having problems with Effexor and other antidepressants. Too many times have I put the shoes on of the other cases similar to mine, knowing how much pain and suffering they are going through. Too many times have I had to see people die because nobody will take action.

It is sickening to know that cases such as mine will continue to show up, and unless you do something now more men, women and children will

die. Please don't let this continue to happen.
Other countries have started to pay attention and
step up, shouldn't we do the same for our children?
Thank you, Ryan Furlough.

As you have heard from my son, many people
are suffering from these drug adverse reactions.
These drugs change kind, gentle children into
monsters. Please listen now before it happens to
your family. You have the proof in front of you
from all the families that are in this room today.
Even if the drugs can help some people, it is not
acceptable to lose one more life. Doctors are
busy. I am a registered nurse, I know that. They
don't read everything they get. These drugs need
to be taken off the market to protect our precious
children, and also to protect the young adults that
are also having reactions, but nobody is listening.

My son says to you stop the drugs now as
every day is a potential for another death. My
life is forever changed...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number seven, please step forward.

MS. VAN SYCKEL: Good afternoon. My name is Lisa Van Syckel. The FDA and the pharmaceutical industries have repeatedly stated that it is the disease, not the drug, that causes our children to become violent and suicidal. It wasn't the disease that caused my daughter to viciously mutilate herself; it was the drug. It wasn't the disease that caused my daughter to become violent and suicidal and out of control. It wasn't the disease that caused her to scream the words "I want to die."

And, it sure as hell was not the disease that caused Christopher Pittman to kill the two people he loved the most, his grandparents. He had been on Zoloft just three weeks and he was 12 years old. Christopher is now facing life in prison as an adult.

I am asking everyone in this room to help me to help Joe Pittman to save Christopher Pittman's life. It is a life worth saving. Christopher is an honor roll student, doing well in

psychotherapy since he has been off the medication. Does he deserve life in prison because you, as adults, cannot accept responsibility to tell the truth, to come forward? I think it is time, ladies and gentlemen, that you become adults and you come forward and you help this young boy.

Pfizer refers to me and others as a detractor of SSRIs and that I am misinforming legislators with oversight responsibilities. As an adult, I am considered fair game for verbal attacks but, ladies and gentlemen, Pfizer crossed the line the day they attacked a dead child. They viciously attacked a dead child and you all know it. And you, ladies and gentlemen, as adults, need to tell Pfizer that they need to stop.

I would like to end by saying thank you to Congressman Mike Ferguson of New Jersey who has oversight responsibilities, who has spent countless hours with me and other family members in showing compassion. I thank him for his assistance in allowing me, and supporting me in my pursuit for congressional hearings because we need criminal

charges to be filed against many.

I would like to end the rest of my time in a moment of silence for all of those children and adults who have lost their lives to antidepressant-induced violence, homicide and suicide. Thank you.

[Applause]

DR. GOODMAN: Thank you. Speaker number eight, please.

MR. LAGURRE: Good afternoon, ladies and gentlemen. My name is Raul Lagurre. I am here on behalf of my son, whose name I cannot mention, and all the other victims that shall remain nameless. The American government was formed to protect and serve and help the people, yet it has failed us. The FDA was formed to protect consumers in showing that the drugs we consume are, indeed, safe but they still allow companies to distribute dangerous antidepressant drugs on the market even though there are severe side effects to children and adolescents.

My son was under the influence of an

antidepressant drug and now he faces a long prison term and an innocent person was hurt. Before he took these drugs he was a gentle, lovable kid who never hurt himself or any other person. Because of this failure of a major drug company in releasing information on suicide effects of antidepressant drugs, I may lose my son to the system. He is one of a thousand of victims who suffered severe side effects, and continues to do so, yet this company continues to supply the market with them.

The FDA needs to step up, protect the consumer and crack down on these drug companies before more lives are lost. Thank you very much.

[Applause]

DR. GOODMAN: Speaker number nine?

MS. PULP: Distinguished committee members, my name is Gloria Pulp and I am here on behalf of DBSA, the Depression of Bipolar Support Alliance. We are a national patient-driven advocacy organization, with more than 1000 support groups throughout the country that assist the more than 25 million Americans living with a mood

disorder.

Untreated depression is the number one risk for suicide among youth. With suicide as a third leading cause of death among 15-24 year-olds and the fourth leading cause in 10-14 year-olds, medication treatment options for youth are absolutely critical. As an organization, DBSA has been actively involved with the youth population.

On the screen before you is the cover of the "Storm in my Brain," a publication compiled by DBSA and the Child and Adolescent Bipolar Foundation. As you can see, this art work, created by young people with mood disorders, graphically displays the feelings they associate with their illness. These illnesses, if left untreated, can lead to tragic consequences.

DBSA does not believe there should be limits to therapeutic options open to doctors and families. But we do believe that whatever treatment is selected, whether it is medication, psychotherapy or support groups, parents and physicians need to be diligent in monitoring

symptoms to avoid self-harm of all types.

Therefore, we support strict monitoring of existing and emerging treatment options.

DBSA appreciates and supports the very hard work of these two advisory committees in examining whether certain medications increase the risk of suicidality in adolescents. Like NAMI, DBSA believes even further research is needed and that the results of clinical trials should be made available to the public.

We urge the National Institute of Mental Health to increase research on the proper treatments for children. Depression and bipolar disorder are real treatable medical illnesses that affect both children and adolescents. While we recognize that there may be consequences or occurrences where, without adequate monitoring, certain patients have responded negatively to certain medications, in many others they have.

Take, for example, a woman named Tara who contacted the DBSA to say that after trying a number of medications her 12 year-old son had found

a treatment that appeared to be working. My child never actually laughed until he was 12 years old, she said. Imagine what a joy when he finally did.

As FDA looks to potentially regulate certain medications, DBSA urges these advisory committees to look closely at the successes as well as the shortcomings in existing treatment options and act accordingly. We can help children quell the storms in their brains.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number ten?

MR. VICKERY: Good afternoon. My name is Andy Vickery. I am a trial lawyer from Houston, Texas, and for the bulk of the last nine years I have represented the families of victims of SSRI-induced violence.

I have three separate and different things to share with you if my time permits. First, when I was here in February the written materials and the presentation I made expressed a concern that when you search the databases you are looking for

the needle in a haystack--Eli Lilly's words, not mine--needle in a haystack because the clinical trials were not designed to capture suicidality. They use rating scales that have only one item on the rating scale even though there are others that are more refined and difficult to find because we know that there is a redistribution of risk.

Tischer and Cole wrote about this in '93. Dr. Gordon Parker, from Down Under, wrote to Lilly about it in 1990. It may help some over here and harm some over here. So, if you are looking for a signal, you are looking for a needle in a haystack. Miraculously, in spite of that, you have found the needle but I still am concerned that you are looking the wrong way.

Lilly knew in 1990, when they met with the FDA, the best way to answer this question in a scientifically proper way was through a rechallenge protocol, not through RCTs and not through epi. studies. They pledged to the FDA that they would conduct such a study. They never did it. You never made them.

The second item I would like to bring to your attention is that in the interim, since this committee met last, the FDA has blessed a new drug on the market, duloxetine released just a couple of months ago. It is an SNRI. There are completed suicides in the clinical trials, including one of a healthy volunteers, on February 7th of this year. It was, nonetheless, approved. If you are going to differentiate in the warnings, ladies and gentlemen, that one needs a black box on it.

Finally, I wish you could hear from some of the victims themselves. I only have 55 seconds. I would tell you if I could--my name is Christopher Joseph Gangwich. Two weeks from today would be the fourth anniversary of my death. I got the Paxil because my girlfriend wasn't being nice to me. I went to my mom. They put me in the hospital. The doctors increased the Paxil. A week later I was in the hospital again--more Paxil. Four days later I hanged myself in the closet. Before I did, I carved a message, a message for you, the words--"dying; help," in my own groin--in my own

groin. Ladies and gentlemen, kids are still dying.

Will you help them?

[Applause]

DR. GOODMAN: Thank you very much. Is speaker number 11 here?

MS. SHARAV: My name is Vera Sharav, and I am the president of the Alliance for Human Research Protection. In contrast to today's presentations, every independent analysis of the data, including FDA's own, has corroborated King's 1991 report describing the development of intense self-injurious ideation and behavior in six children who received fluoxetine.

The Mosholder report, which was embargoed for six months and didn't see the light of day until we put it up on our website, confirmed that children exposed to an antidepressant are twice as likely to suffer suicidal-related adverse events compared to those given a placebo. Dr. Mosholder identified 78 cases and recommended discouraging off-label pediatric use of SSRIs. Columbia's reclassification identified 17 additional cases.

The FDA and drug companies have known the risks and concealed them for over a decade, and the blinders are still on. Physicians and parents continue to be deceived with false assurances that the drugs are safe and effective. FDA's excuses for its inaction insult our intelligence. Dr. Temple maintains that both the data and Mosholder's interpretation were imperfect, and behaviors labeled suicidal could have been accidents.

When a fire erupts, the fire department doesn't wait until it has absolute proof of causality before it acts. The committee's charge is not to answer why or how the drugs increase suicide risk. Given that the drugs' failure in controlled clinical trials to show an effectiveness for children, and given the link between drug exposure and increased risk of suicidal behavior has been scientifically established, the committee's charge ought to be how to best protect children.

In addition to suicide risk, SSRIs are linked in children to stunted growth, cardiac

abnormalities, mania and a tremendous rise in manic depression. How many children need to be harmed before action is taken? Children's safety in these trials is a concern as well. FDA's review identified Prozac study HCJE as, quote, one of four trials with the largest number of definitive...

[Applause]

DR. GOODMAN: Thank you very much. We are skipping number 13 because the FDA is superstitious--no, actually number 13 has not shown, and we are turning to number 14.

MS. TIERNEY: Hello. My name is Jennifer Tierney, and I have no financial ties to anyone but my husband--

[Laughter]

My daughter, Jamie, and I attended the last advisory meeting during which she described her experience on Effexor. Jamie was prescribed Effexor for migraine headaches, not--and I want to emphasize--not for depression. She became suicidal on Effexor for the first time in her life and, to make matters worse, when she tried stopping Effexor

she suffered tremendous withdrawal reactions.

Following the February PDAC, I met with members of HHS and Dr. Temple. I followed up with a letter to the FDA which I cc'd to the entire advisory panel, detailing the history of FDA's failure to protect the public health related to antidepressants and suicidality.

I have returned today to make a couple of points. First, I want to thank the panel from the February meeting for actually listening to us and for taking us seriously about our concerns.

Second, I would like to say that I am appalled that the FDA would not allow the maker of Effexor to place stronger warnings in its label, stating that, quote, in pediatric clinical trials there were increased reports of hostility, and especially in major depressive disorder suicide-related adverse events such as suicidal ideation and self-harm, unquote. This is what the data shows, yet the FDA will not allow it.

One has to ask whose interest is the FDA protecting here? I honestly do not know how the

individuals responsible for this can even sleep at night. Now the U.K. has all but banned these drugs in children and adolescents. Dr. Mosholder found an increased risk of suicidal behavior in children and adolescents taking the drugs, which certain people within the FDA tried to suppress. Now the review by the Columbia group, despite its flaws, seems to confirm that risk.

Well, it doesn't take a rocket scientist to figure out that if a drug lacks efficacy, which has been a problem for the drug companies in both child and adult clinical trials, and it has serious risks such as suicidality, you probably should not be prescribing it to as vulnerable population as children and adolescents. The argument that one doesn't want to deter people from taking them doesn't hold water when you consider the lack of efficacy. But for those families who still argue that drugs have been helpful to their child, that does not justify withholding warnings that would have helped my child and save lives.

One last comment I would like to make is

that Pfizer's very personal attack on Dr. David Healy and the father who lost his 13 year-old son--he hung himself while on Zoloft--is nothing short of reprehensible. It appears that Pfizer is getting down and dirty. Dr. Healy is a pioneer whose bravery and strength of character has saved lives. As for the boy, even if Pfizer's facts were accurate, the drug is...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 15, please come forward to the microphone.

DR. SALERIAN: Good afternoon. I am Dr. Salerian. I am a psychiatrist and medical director of a private psychiatric clinic, and I primarily practice psychopharm.

As a society, we are wonderful at developing villains and heroes, and it is impossible for me to sit in this room and not to realize that it is as if we had two groups of people, good people and bad people, and depending on what side you are taking, the other side is the

enemy and we are questioning their values and integrity. The truth is, as a psychiatrist, I am very ashamed of how poorly we have served the nation in terms of educating about the dangers of side effects of antidepressants, and this is the truth. So, in that way, I personally apologize to anybody--to mothers and fathers, whose children have been affected adversely by antidepressants.

It is also true that depression is a real illness. It exists. It existed before antidepressants. I grew up in Turkey and I can tell you that even today not many people take antidepressants, but a good number of people manage to commit suicide or have miserable lives. The significant thing to know for all of us is that depression is a dangerous disease, so are antidepressants.

Now, in terms of our approach and the numbers--recently I published an article and reviewed an article in Lancet about antidepressants and safety. My analysis is that we are making a big mistake by not realizing that depression is a

heterogeneous group of depressed kids and adolescents; it is not just one group. When a child is depressed he may grow up and develop nothing; may grow up with a bipolar illness; may grow up and become an adult with schizophrenia or any other serious psychiatric illness. Our current technology and science is not enough to differentiate one diagnosis, particularly children who present with depression and who are dormant candidates to become severely ill as adults. This itself causes tremendous vulnerabilities and, therefore, monitoring is essential to prevent side effects and dangerous consequences such as suicide. So, better monitoring would be my advice. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 16, please come forward.

MS. BOSTOK: Over ten years ago, in the article, "Antidepressant Drugs and the Emergence of Suicidal Tendencies," Harvard doctors described nine

mechanisms by which antidepressants can induce suicidality. My daughter, Cecily, who stabbed herself to death after three weeks on Paxil, exhibited behavior on antidepressants that closely fit these mechanisms. We need warnings for all of them.

One, energizing--antidepressants may provide the energy to enable depressed patients to act on preexisting suicidal plans. The authors affirm the relevance of this mechanism to other classes of antidepressants besides SSRIs but state that in no case was there evidence that strong preexisting self-destructive urges were energized by Prozac. Cecily had no history of suicidality. She was not given Paxil for depression but for racing thoughts and her energy did not improve.

Two, paradoxical worsening--Cecily's mood did worsen on Paxil.

Three, akathisia--in the last days of her life Cecily was jittery.

Four, panic anxiety--after Cecily started treatment she became very fearful upon waking. The

last day of her life she came shrieking from her bedroom, terrified by the noise of a plane--completely uncharacteristic.

Five, manic or mixed states--although Cecily had no confirmed diagnosis for mood disorder, she was being treated for manic-like symptoms. Paxil was exactly the wrong medication for her. Patients should be closely monitored for the emergence of mania which can enhance violent and aggressive behavior or a mixed state can augment suicide risk.

Six, sleep disturbances--on the first night she took an antidepressant she walked in her sleep. She had never done this before. There is evidence she was sleepwalking when she died. She did not turn on any lights or make any noise when she stabbed herself at 2:00 a.m. Quote, Prozac produced a dramatic increase in rapid eye movement even during non-REM sleep stages. It reduced delta sleep, causing emergence of day terrors similar to unmedicated patients with a history of suicidal attempts.

Seven, suicidal preoccupation--on the last day Cecily confessed uncharacteristic fears, and after dinner stared strangely at her knife. This frightened me but I never dreamed she was contemplating self-harm; she had never done so before. Quote, strong obsessive, remarkably violent suicidal thoughts emerged after Prozac treatment.

Eight, borderline state--symptoms of borderline disorder suggest a state of serotonin dysregulation. Cecily's autopsy revealed a very high blood level of Taxol and, thus, acute dysregulation. Quote, patients who do not suffer from borderline disorder may have drug-induced borderline reactions that include emergence of uncharacteristic aggression, self-mutilation and suicide.

Nine, EEG activity--Cecily said when she took a pill she felt like it was frying her brain. One study reported a...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 17, please come forward to the microphone.

DR. FASSLER: Thank you. My name is David Fassler. I am a child and adolescent psychiatrist, from Burlington, Vermont. I am speaking on behalf of the American Psychiatric Association. No pharmaceutical or other industry support was used in conjunction with my appearance here today.

I would like to emphasize a few key points. First, childhood and adolescent depression are very real illnesses which affect between 3-5 percent of all young people.

Second, these are extremely serious conditions with very significant consequences. Research tells us that over half of all kids who suffer from depression will eventually attempt suicide at least once, and over 7 percent will actually die as a result. Fortunately, effective treatment is available. Medication, including the SSRI antidepressants, can be extremely helpful and even life-saving for some children and adolescents, but medication alone is rarely an adequate or

sufficient intervention for complex child psychiatric disorders such as depression.

With respect to the SSRIs, I would offer the following comments and observations. The studies currently available do suggest that the use of these medications may be associated with an increased risk of certain suicide-related thoughts and/or behaviors in some children and adolescents. However, the data is far from clear.

For example, as we heard this morning, the same data indicates that there is no significant increase in the worsening or emergence of suicidal symptoms. As you have also heard, concerns about suicidal thoughts and behaviors early in the course of treatment are not new. They are also not limited to the SSRIs, nor are they limited to the treatment of children and adolescents. Thoughts about suicide are also not uncommon, especially during the teenage years. According to the CDC, one adolescent in six thinks about suicide each year. Fortunately, the overwhelming majority of young people who have suicidal thoughts do not

actually commit suicide. But every suicide is a tragedy and any increased risk of suicidal thoughts or behavior, no matter how small, must be taken very seriously.

However, based on the data currently available, most clinicians believe, and I would concur, that for children and adolescents who suffer from depression the potential benefit of these medications far outweighs the risk.

There is also general clinical consensus that all of the antidepressants are effective for some but not all children and adolescents. Research indicates that between 30-40 percent will not respond to an initial medication, however, many of these young people will ultimately respond to a different medication.

Let me close with the following specific recommendations. First, we strongly support the development of a national registry of all clinical trials.

Second, we support the continuation of the current FDA warnings with respect to SSRI

antidepressants. We believe the language is appropriate and consistent with our current knowledge, understanding and scientific data.

Finally, we fully support the call for additional large-scale research studies. Thank you.

[Applause]

DR. GOODMAN: Thank you very much for your presentation. Speaker number 18, please come forward.

MR. WOODWARD: My name is Tom Woodward. My wife, Kathy, and I have four children. Julie, the oldest of our four children, took her life on July 22, 2003. Julie was a gentle and beautiful young girl. She was only 17. She was deeply loved and is truly missed by all who knew her. Julie was a normal teenager, dealing with normal teenage issues. She had no history of self-harm or suicide.

She was prescribed Zoloft and we were told that it was safe, very mild, extremely effective and essential to her getting better. Seven days

after taking her first Zoloft tablet Julie hung herself in the garage of our home. We have since learned that Julie began experiencing akathisia almost immediately after taking the first pill.

Julie never harmed herself in her 17 years. The only variable was seven days of Zoloft. We are certain that Zoloft killed our daughter. The recent JAMA article stated that the risk of suicide is 40 times greater during the first nine days of treatment with an SSRI. I believe this is a national crisis.

The drug industry has oversold the purported benefits of SSRI drugs and aggressively promoted their use. As the Spitzer lawsuit confirmed, drug companies have purposely misled the public about the safety and efficacy of their drugs.

The problems associated with these drugs are particularly frightening in light of the Bush administration's new Freedom Initiative, a program designed to subject every school age child in this country to psychological testing. The way these

tests are designed, many children will fail and inevitably be prescribed an SSRI. Tragically, some of these children will then go on to mutilate themselves, commit acts of violence, or kill themselves as a direct result of these drugs. We are too quick to medicate our children.

Our system of medical treatment is based on a sacred circle of trust. This trust has been broken. Children look to their parents to protect and guide them. Parents seek out the advice and counsel of physicians and mental health professionals who, in turn, largely rely on the drug industry opinion leaders and the FDA to allow them to fulfill their role as informed intermediaries. The drug industry has employed tactics of deception, distortion, misdirection and manipulation.

Big PhARMA's money has corrupted the process and destroyed the sacred trust. They buy political influence that secures the placement of individuals within the FDA to do their bidding, such as Dan Troy whose mission is clear--damn the

public and protect his former drug industry clients at all cost. Troy is more concerned with tort reform than with children's lives.

Senior leadership at the FDA drag their feet and make Orwellian statements such as, just because these drugs have not been proven to be effective does not necessarily mean they are ineffective. This gibberish is an insult to the American public and would be laughable if the consequences weren't so terribly tragic.

Drug industry CEOs at Pfizer and those at Glaxo and Lilly, senior leadership under FDA--Troy, Crawford, Temple, Katz and Laughren know the truth and therefore have blood on their hands.

I deeply appreciate the work of this committee. I know there are good people at the FDA trying to do the right thing in spite of the FDA's current leadership. Implement class-wide, strongly worded black box warnings immediately, inclusive of Prozac, not some carefully worded drug industry version designed to protect their interests instead of the public's. The FDA needs to be restored to

its vitally important mission of protecting the welfare of the American public.

[Applause]

DR. GOODMAN: Thank you. Speaker number 19.

MS. MCDONALD: Good afternoon. My name is Sheila McDonald. I am the vice president of the Board of the Child and Adolescent Bipolar Foundation.

The public is alarmed that SSRIs may cause children to become suicidal. What alarms us is that untreated children, prepubertal children and teens with affective mood disorders are already suicidal at high rates. This is the crux of the problem.

Just two days ago there was a posting on our website, and I quote a woman about her 10 year-old son where she says, "I thank God for each and every pill, each and every day that I don't have to listen to my son, my little boy say that he wishes he was dead." She was talking about mood stabilizers, not SSRIs but we come back to the crux

of the problem, which is that untreated children are already suicidal.

I have prepared remarks. I think they have been handed out to you, and this may be a little disjointed. I wanted to talk actually about some testimony that we have heard this morning. I have two points on that. One is that the research is not where it should be. It is not advanced enough for us to be able to distinguish between children with major depressive disorder and children with bipolar disorder.

Secondly, as a lay person, which I admit that I am, many of these events I think can be explained perhaps by SSRI's triggering disinhibition for children who perhaps have presented with a major childhood depression disorder but, in actuality it is bipolar disorder.

This morning Dr. Laughren asked the committee what research is needed. In my prepared remarks we urge that significant resources be devoted to both the suicidality component inherent in certain pediatric brain disorders and on the

efficacy and safety of medications used to treat these disorders in the pediatric population. We must realize that children are not short adults.

What I think this morning's testimony has made clear is that research must be devoted to diagnosing appropriately the pediatric psychiatric disorders. All the presenters have made the assumption--as I like to say, they have put the bunny in the hat. It is easy to pull the bunny out once you put the bunny in--bunny in the hat. Dr. March says that his studies have excluded bipolar disorder. Dr. Dubitsky speaks of the, quote, potential influence of study design on suicidal risk. Our children are ill. Our children need medical help and they are excluded from these studies, our children who have bipolar disorder.

At this time we don't have a magic dip-stick to tell whether you have MDD or BP. Clinicians must be cognizant that an episode of childhood depression can signal bipolar disorder and that in certain cases antidepressant use may trigger or provoke mania. We do want amplified

warnings and monitoring, but we do oppose any attempt to ban the use of antidepressants as they can be an important and potential life-saving tool in the treatment box when carefully monitored.

Thank you.

DR. GOODMAN: Thank you. Speaker number 20?

DR. WALKUP: I am John Walkup. I am a child and adolescent psychiatrist, on the faculty at Johns Hopkins. I currently have grant support from Eli Lilly, Pfizer and Abbott, and within the past year I have received honoraria from Lilly, Pfizer and Janson. No one is paying for me to be here and I don't represent anyone today other than myself.

I am a clinician and also a clinical investigator. I have conducted federally-funded trials like TADS. I was a participant in TADS and I have also participated in industry-sponsored trials. As a clinician, there is much at stake today. There are many, many children who have benefited from appropriate assessment and

treatment, and I am afraid their stories may get lost if someone doesn't speak for them.

Prior to this controversy we knew a lot about depression, and one of the things that we knew about was the early risk for suicidal ideation early in the course of treatment. In addition, we were also trained that medications, not just SSRIs but other medications, can cause behavioral side effects. So, other antidepressants, the tricyclics, antihistamines like Benadryl, and anti-malarials were recently reported in the newspaper. Anti-psychotic medications and stimulants can all cause changes in behavior. What is unusual is the link between changes in behavior and suicidal acts that we do not understand even though changes in behavior are a part of the spectrum of drug effects.

With that said about suicidal behavior, I would like to talk a little bit about the efficacy trials. It is very surprising to me as a clinician that the clinical trials do not document efficacy of antidepressants in depression. When I look at

the clinical trials, there are two types of clinical trials. There are the federally-funded trials and then there are the industry-sponsored trials. If you look closely at the methodologies for both, there are significant differences in the methodologies for the federally-funded trials and the industry-sponsored trials, with the federally-funded trials having a much higher standard for ongoing quality assurance and training of investigators and participation.

My recommendations to the FDA, as humble as I can be, please don't make policy based on complex and rare events. It is a dangerous precedent and it can do more harm than good. If you do go to a stronger warning, please provide a warning that clarifies but doesn't magnify. Magnification of the warning may actually do more harm than good to the kids who actually need to come to care.

Lastly, I would encourage the FDA, as it reviews future clinical trials in children, to think about those kinds of standards that are set

through the peer review process for clinical trials in kids, and to incorporate some of those quality measures in those clinical trials. Thank you.

[Applause]

DR. GOODMAN: Thank you. Speaker 21, please come forward.

MR. TAYLOR: My name is Mark Taylor and I am one of the victims, one of the many victims of the SSRI antidepressant era. I took 6-13 bullets in the heart area at my high school when Eric Harris who was, in fact, on Luvox fired at me. They almost had to amputate my leg and my arm. My heart was missed by only one millimeter. I had three surgeries. Five years later I am still recuperating.

I had to go through all this to realize that antidepressants are dangerous for those who take them and for all of those who associate with those who take them. I hope that my testimony today shows you that you need to take action immediately before more innocent people like me and you get hurt or die horrible deaths as a result.

As Americans, we should have the right to feel safe, and if you were doing your jobs we would be safe. Why are we worrying about terrorists in other countries when pharmaceutical companies have proven to be our biggest terrorists by releasing these drugs on an unsuspecting public? How are we supposed to feel safe at school, at home, on the street, at church or elsewhere if we cannot trust the FDA to do what we are paying you to do? Where were you when I got shot?

You say that these antidepressants are effective. So, why did they not help Eric Harris? According to Eric, they helped him feel suicidal. He reported to his psychiatrist he was having psychotic reactions to the drug. They took him off it. He said he was doing great. They put him back on it. He was having suicidal thoughts again. These drugs help increase the rage in people and cause them to do things they would not do anyways. So, why do these so-called antidepressants not make him better?

I will tell you why. It is because they

don't work. We should consider antidepressants to be accomplices to the murder.

MS. TAYLOR: Hello. My name is Donna Taylor and Mark did go through these injuries. Mark and I both know that had Eric Harris not been given the antidepressants both Zoloft and Luvox the nightmare at Columbine would never have happened to our family and our lives. But Columbine was only the beginning of the antidepressant-introduced nightmare. I was also given antidepressants and suffered side effects, including suicidal thoughts and horrible Paxil withdrawal.

To this day, four years later, I am still suffering adverse events. Many other members of my family have been on antidepressants with disastrous results. Where there was never a...

[Applause]

DR. GOODMAN: Thank you. Speaker number 22, please come forward to the microphone.

MS. WOODSACK: Hi, my name is Kin Woodsack and my husband of almost ten years, Woody, died of Zoloft-induced suicide after being on the drug for

five weeks, with the dosage increased just prior to his death.

He was prescribed Zoloft by his general physician for the diagnosis of insomnia. He had just started his dream job as vice president of sales for a start-up company two months prior. He was having trouble sleeping due to the new stresses of the job. Woody wasn't depressed, nor did he have a history of depression or any other mental illness. He was told the drug was safe and was sent home and a three-week Pfizer-supplied sample packet automatically doubled the dosage from 25-50 mg. No cautionary warning was given to him nor me. In fact, I was out of the country and there was nobody monitoring him the first two and a half weeks.

Shortly before he died, I found him curled up in a fetal position with his hands like a vice going, "help me; help me. I don't know what's happening to me. It's like my head is outside my body looking in. I'm losing my mind." This is not just a children's issue. Adults are also dying

from SSRI-induced suicides.

As I was preparing for today one thing kept coming to mind, and that is the outrageous marketing of these drugs. These drugs were originally designed for major depressive disorder. Now they are being prescribed for everything from mild depression, anxiety, shyness, insomnia, migraines. Just last week people were on the "Today Show." Doctors were telling people they could take two weeks on, two weeks off because having depression is so serious with PMS. One drug fits all? Are these marketing based or are they science based?

You know, my entire career has been in advertising and I just want to say thanks to the drug companies that are here because the Harvard Business School is actually doing a study, one of the case studies, which is all about the marketing of antidepressants. I have to say that children who have died on these drugs matter. The adult victims of this tragedy matter. Woody, my best friend, matters. The time has come to do the right

thing. We should never have been here today if the right thing had been done 13 years ago and the follow-up safety studies had been done, and if FDA followed up with the drug companies.

Let's continue not to waste hours of precious time and lives. We have to fix the problem. The system is broken. We have to do it; people's lives are at stake. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 23, please come forward to the microphone.

MS. BARTH MENZIES: Thank you. My name is Karen Barth Menzies, and I am an attorney with Baum Headland. We represent over 100 families whose loved ones have committed suicide or they, themselves, have attempted suicide. You heard from a few of them today.

Approximately half of those cases involve children. We have been doing this for over 14 years. Through the litigation process, our experts see more evidence concerning the true risks versus

the true efficacy of these drugs than anyone anywhere. That includes FDA. Court-imposed protective orders don't permit us to show this evidence to FDA or even the congressional investigators or you.

This evidence shows, I can tell you, that the companies have known about the serious risk and the lack of efficacy since the mid 1980s. But today I am not going to talk about suicide risk. Plenty of people are going to be addressing that today. What I want to talk about is efficacy.

For purposes of illustration and because of what I have just heard earlier today, I am going to focus on Zoloft. Dr. Paul Lieber, former FDA veteran of 20 years, who was principally involved in the investigation, analysis and approval of the SSRIs, wrote in a memo, from August of 1991, and I quote, in recommending the approval of Zoloft for adults, I have considered the fact that the evidence marshalled to support Zoloft's efficacy is not as consistent or robust as one might prefer it to be. Back in 1991, Dr. Lieber noted that

numerous countries around Europe have already rejected or were about to reject approval of Zoloft because Pfizer could not demonstrate efficacy. It was only until FDA approved Zoloft that the rest of the countries followed.

In 1991, Dr. Lieber stated, and I quote, approval of Zoloft may come under attack by constituencies that do not believe FDA is as demanding as it ought to have been in regard to its standards for establishing the efficacy of the antidepressant drugs.

Just yesterday Dr. Lieber was quoted again in the "Denver Post" article, stating, second generation antidepressants were approved by a regulatory process that requires only limited proof of efficacy and safety. Dr. Lieber also quoted, you are working in a sea of ignorance. He concluded, I do have some doubts about these drugs' values in the big picture.

The drug companies have been so successful in misleading the medical profession that their drugs are remarkably effective that it is hard...

[Applause]

DR. GOODMAN: Thank you. Speaker number 24, please come forward to the microphone.

DR. GREENHILL: Thank you. My name is Larry Greenhill. I am a child and adolescent psychiatrist, from New York. I am speaking today on behalf of the American Academy of Child and Adolescent Psychiatry and the American youth that they represent. This organization represents over 7000 child psychiatrists across the country and has supported my trip here today. I have also received support for research from the pharmaceutical industry in the past but not for this meeting.

In the brief time I have been given I want to focus on four points. Both I and the Academy support education about depression, which is a serious illness which needs very good treatment immediately.

Second, the Academy supports better adverse event elicitation and safety monitoring procedures.

Third, the Academy supports the formation

of a national registry of clinical trials and, finally, they support more prospective research.

To get to the first point, the Academy finds untreated depression to be a serious illness which interrupts youth's normal emotional development, undermines self-esteem, interferes with learning in school, and undermines friendship with peers. It afflicts many of the 500,000 adolescents who attempt suicide annually in this country.

Second, the Academy supports the FDA's more detailed evaluation of safety data found in the clinical trials of SSRIs we are discussing today; supports its Columbia reclassification project; and supports the public airing of the resulting data analysis.

We also agree with the FDA's decision to insert warning language into the package instructions that accompany all antidepressant medications, alerting physicians and families about the need to monitor for signs of new suicidal thinking or activity during the early days of

treatment.

Many child psychiatrists, including me, have found these antidepressants to be helpful for treating carefully diagnosed depressed adolescent patients when these drugs are used in a well-monitored treatment program. It is reassuring that the analyses that we have heard today fail to find a single completed suicide among the 4400 youth who participated in clinical trials.

Third, the AACP is pleased to join the APA in support of a national registry of clinical trials. We believe that physicians and parents must have all available knowledge about a medication's safety and effective to make informed decisions about treatment choices.

Fourth, the Academy calls for more research on SSRIs to obtain more precise estimates of the risk of suicidal behaviors and suicidal ideation during treatment. The Academy supports the funded research efforts now under way, and we encourage the FDA to support new data in the future using an incentive program. Thank you.

DR. GOODMAN: Thank you. Is speaker number 25 here? Okay, we will turn to speaker number 26, please.

DR. DILLER: I have prescribed psychiatric drugs to children for 26 years. I have written two books on children and psychiatric drugs. I have appeared before Congress and the President's Council on Bioethics. But today I come before you as a physician in private practice with a report from the front lines, news from the primary care pediatricians and family doctors, the private practice child psychiatrists and the families of the patients themselves.

I am here, representing the views and the reactions of a silent majority of physicians who aren't intimately connected financially with the drug industry. Here is what they are saying and thinking: The battle over the SSRIs in kids' depression is over. The ongoing publicity and negative reactions have already changed the average doctor's opinions and practices. No longer are pediatricians, willy-nilly, prescribing SSRIs for

minor mood swings and phobias. Even child psychiatrists have become more careful to whom they prescribe. All the doctors have become aware of the problems that may be developed in the early stages of SSRI treatment. They are warning the families and following the children far more closely.

I think this is a very good development. However, many of the leaders in organized psychiatry and academia are publicly wringing their hands--pediatric depression is untreated they say. Now even more families will refuse medication. I find this cavilling worry the height of psychiatric sanctimony. For years we were told to practice evidence-based medicine and now, when there is no evidence for SSRI effectiveness and yet higher risk of suicidality, the leaders say, "wait, not so fast." I say, "where's the beef?"

That brings me to my major point. There is a growing credibility gap between the front-line doctors with the leadership and researchers in psychiatry. We simply do not know what to believe.

We are increasingly bewildered, skeptical and cynical. The final blow was learning about the eight negative SSRI studies in children that were never released to either the doctors or the public.

This loss of credibility within the medical profession extends beyond psychiatry into all of medicine and the general public. The blame is clear. The money, power and influence of the pharmaceutical industry corrupts all. The pervasive control that the drug companies over medical research, publications, professional organizations, doctors' practice, Congress and, yes, even agencies like the FDA is the American equivalent of a drug cartel. It is long overdue to make changes in the way we approve and market pharmaceutical drugs in this country.

Suppression of negative studies in the name of protecting stockholder interests at the cost of children's health highlights the immorality of an unfettered, unregulated marketplace. Specifically, we need true transparency in research. We also need a more organized system of

follow-up by neutral third parties once a drug is released. Let us not lose the momentum to reform this moment gives us lest the tragedies of the families who appeared before us today go in vain. Thank you.

[Applause]

DR. GOODMAN: Thank you. Speaker number 27?

MR. BUTLER: My name is Reese Butler, and I am a survivor. I lost my wife, my best friend, my life partner to a suicide on April 7th, 1998. Her name was Kristin Brooks Roussel. It is my belief, and the belief of many experts I have met since her death that her suicide was preventable.

What began the chain of events that led to her suicide was a severe bout of postpartum depression treated with SSRIs, which triggered what is known as an SSRI syndrome. Kristin became pregnant in July of 1997 and was taking SSRIs on a daily basis. She had been taking SSRIs for close to five years. They worked. They gave her peace and very little depression.

The pregnancy was unplanned so during the first trimester she was still on the SSRIs. As soon as she found she was pregnant she stopped taking the drug. On December 7th we learned that our baby daughter had many significant birth defects, one of them life-threatening to our baby. She immediately decided to terminate the pregnancy. After losing our baby she started down a path that led to her death.

A bipolar mom is 31 times more likely to suffer postpartum depression. The standard of care is prescribing SSRIs. This can trigger an SSRI syndrome when a bipolar patient is prescribed SSRIs without a mood stabilizer. The opinion of many experts is that bipolar patients should not even be prescribed SSRIs at all due to the risk of violent behavior, both inward and outward, that can be caused by the SSRIs in a bipolar patient without a mood stabilizer.

The way the syndrome can manifest is by causing a mania that does not end on its own. The depressive side is abated but the drug does not

stop the mania, which is a form of euphoria that can cause the patient to have an extended high like a runner's high. As a result, the patient may not be able to sleep or sleep well. In the case of my wife, she had sleep disturbances that lasted approximately two weeks. Her doctor switched the SSRI she was on to another, hoping for a better effect.

In the end she became suicidal and homicidal. We were left with no choice but to admit her to a psychiatric facility. There, they administered trazodone to help her sleep. Thirty-six hours into the stay she managed to hang herself on an electrical cord. Her last words from her diary are chilling: "I am experiencing major drug doubt feeling from the meds. This is ridiculous. My body chemistry has changed so dramatically from the SSRI and the additional crap on top of it. This sucks. Reese, darling, I will always love, Buddy too and Hank and Rich, mom and dad, etc. This is no way for me to live. It doesn't serve the world. I am becoming a chronic

insomniac due to the meds. I am being tortured. I must leave now. Bye-bye, my love. I will always love you, Kristin."

To say the SSRI caused her death would be unfair and inaccurate. The SSRI without a mood stabilizer prescribed by a psychiatrist who had poor training in risk assessment and not enough concern about SSRIs in a bipolar patient led to the sleep deprivation which I believe led to her suicide.

As a survivor and a founder of the Kristin Brooks Hope Center, I ask that the FDA require educational materials about the risk factors in all prescriptions of SSRIs...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 28?

DR. VOGEL-SCIGILIA: Thank you very much for allowing myself, Dr. Suzanne Vogel-Scigilia, and my son, Anthony, to speak to you today. It may seem paradoxical that you see many more families who have concerns about these medications than

children who have done well since thousands of children have had their lives saved by these medications and the suicide rate in our youth has dropped.

The view that this community receives is skewed towards the minority who claim tragic adverse events because families who are doing well don't have much motivation to be here. Some can't believe that antidepressant medication access can be restricted directly or indirectly by your committee's decision. Others are hesitant to parade their children whose lives have been saved in front of this media circus.

Please do not make a decision without clear, reliable scientific evidence. The only issue at hand here, in my opinion, is whether there is credible evidence to show a danger. This you will have to decide, and I ask you not to make a hasty decision. In all my years as a physician, I have never seen a warning removed on a medication, even later if evidence proves it should be. If you inappropriately release a strong warning, either

due to true concerns or because of intense pressure from the other viewpoint, managed care companies or nervous physicians willingness to pay for or prescribe these medications may decrease. This will gravely harm far more children than any number who have appeared before the committee thus far.

My father and husband are pediatricians who have prescribed psychotropic medications for two generations of children in Beaver County without adverse events. I am a practicing clinical psychiatrist in the same area where there are woefully few pediatric psychiatrists and most care is done by other physicians. Some family practitioners, pediatricians and psychiatrists in western Pennsylvania have told me they may have to stop prescribing if an inappropriate warning, not backed by reliable research, occurs due to the threat of malpractice in this litigation-based society. Managed care companies also do not want a suit when their attempts to protect themselves may lead to prior authorization processes or other barriers to access that may frustrate families of

physicians.

The most chilling thing I have heard to day is that since the initial hearing on your committee occurred antidepressant prescriptions for children and adolescents have declined ten percent. One consequence of the prior warning is that more children are not receiving treatment that they need. I hope that you think about these absent children and their families when you look at Tony and I.

MR. SCIGILIA: Hello. Ladies and gentlemen of the FDA, my name is Tony Scigilia and I am diagnosed with bipolar disorder. I currently take Wellbutrin. My mother told me what was going on today and I want to tell you that I have been taking several--I took several antidepressant medications. And, they consist of Zoloft, Prozac and Effexor, and they have caused me no side effects, none however.

Please, help me preserve my future. Don't take away my medication. Thank you.

DR. GOODMAN: Thank you very much.

Speaker number 29?

MS. WINTER: Hello. My name is Mary Ellen Winter. This is my husband Jeffrey. Exactly 342 days ago we lost our daughter, Beth. Beth was only 22 years old and had recently graduated from the University of Rhode Island, in May, 2003. Beth was looking forward to a career in communication and was experiencing some anxiety and having trouble sleeping when she consulted our family physician.

He prescribed Paxil and said she would start feeling better in two weeks. Seven days later Beth took her own life. Since October 7th, 2003 our family's life has been indelibly altered. We, like most of you in this room, grew up with confidence in the strides made in medicine and accepted with faith antibiotics and vaccinations prescribed. We believed the FDA would always act to protect our family's well being.

When my daughter went to our family GP last year, we trusted that our doctor was well educated and informed. We were wrong. We now know that pharmaceutical sales is a high stake business,

driven to increase shareholder wealth. The consolidation of pharmaceutical companies like GlaxoSmithKline has resulted in increased sophistication in the quest to market and distribute pharmaceutical products. Priority has moved from health to profit. Not all doctors are equipped to understand the marketing targets they have become. The FDA has allowed our daughter to be the victim of a highly commercial enterprise that selectively releases clinical data to maximize sales efforts and seek only to gain corporate profits.

We quickly learned, after Beth's death, that Paxil and SSRIs in general are highly controversial and cases of suicidal behavior are well documented, yet the prescription Beth received contained no such warning. Beth was not told about the hidden data or the clinical studies or the untold lawsuits that GlaxoSmithKline had been quietly settling. The bottle of Paxil that Beth received only contained pills and had no warning as to the risk of suicide.

As residents of the State of New York, we thank our Attorney General, Elliot Spitzer, for addressing issues that the FDA has been unwilling to address.

[Applause]

In a few summer months, Mr. Spitzer has forced GlaxoSmithKline to release secret clinical data, and in the future GlaxoSmithKline will be required to perform under the terms of the consent agreement. We believe every state's attorney general in this country should seek similar action against GlaxoSmithKline.

The FDA needs to regain their leadership position and restore lost respect and integrity. This will clearly require complete and full disclosure of the risk associated with prescription drugs regardless of the impact on potential sales and profit margins of the major pharmaceutical companies. This will also mean full and complete disclosure of what the FDA knows to Congress and the American people about SSRIs.

If we, or Beth, knew the information we

now know, Beth would have recognized the side effects when they were taking effect. We know for certain that Beth would have never hung herself in the home of her family whom she so loved...

[Applause]

DR. GOODMAN: Speaker number 30, please.

MS. HATCHER: My name is Beverly Hatcher and I want to tell you how Paxil destroyed my mother's life. She was a normal, healthy person who loved life to the utmost. She loved to eat, cook, travel and talk on the phone. She had a smile for everyone that she met. She had no history of mental illness.

In 1997, after my dad died, she moved from North Carolina to live with me, in Virginia. She soon found work but later chose to retire. She soon ran across another one of her childhood sweethearts. They began to travel everywhere. This was life before Paxil. On August 18, 2003, she was prescribed Paxil because of a small bout of depression that was due because of a heart attack of her closest cousin. She quickly transformed

into someone that began to complain of having constant bad dreams, having no appetite, being nervous, hearing voices. She stopped taking baths at night and bit her nails down to nubs. She said she thought things were crawling all over her and that she was losing her mind. Nothing mattered anymore. These were not normal signs of normal grief.

On September 2nd, 2003, the day before her daughter's birthday, she hung herself in that daughter's basement. This was 16 days after starting Paxil. She was only 60. How did Paxil get the FDA stamp of approval and make it to market? How or why would any healthcare provider prescribe such a medicine capable of causing this? As a nurse and healthcare provider myself, we take an oath to save life, not destroy it.

Are drug companies providing the FDA and healthcare providers all the facts about Paxil? No. Drug companies are not telling the truth to the FDA, healthcare providers and certainly not to consumers because they have figured our a way

around all the loopholes. In this case, the FDA's guidelines are meaningless and they contain even bigger loopholes.

To the FDA, we will never understand why this had to happen to us. There is no excuse. It was your job to protect my mother and not the drug company's profits. Because of this, we will be motherless for the rest of our lives. Nothing can change that. When will enough be enough? Stop taking innocent lives.

To the drug companies, and especially to the FDA, this T-shirt sums up how we, the family of Barbara Jean Darton, feel about Paxil. The back reads "cocaine is an illegal drug that kills." On the front it reads, "Paxil is a legal drug that kills." Don't put another family through this. Remove Paxil from society. Until then, remember the faith and the message of this T-shirt and do the right thing. Sincerely, in memory of my mother, Ms. Barbara Jean Darton. Thank you.

[Applause]

DR. GOODMAN: Thank you. We are now going

to take a brief break. We will reconvene in ten minutes.

[Brief recess]

DR. GOODMAN: Please start gravitating towards your seats. As soon as we receive a few more committee members back from their break, we will recommence.

First let me reiterate my apology that I issued before. That is, we have a system that basically, once we start up, is automated and sometimes the microphone is turned off on people at a very key moment in their presentation. We have to balance that with the desire to make sure that we are treating everybody uniformly. I think that or the most part I am very pleased with the way this has been going, the respect that everyone has shown each other in the process. I need to remind you that everyone has a chance to speak who had signed up. Really we should not have any outbursts from the audience. If there is somebody who has something to say, they should have had an opportunity to be up at the podium. With that,

speaker number 31.

DR. SCHAEFER: My name is David Schafer. I am a child psychiatrist and pediatric at Columbia University, and I have engaged in research on adolescent suicide since 1970. I have never received any financial support from the pharmaceutical industry, and my travel expenses are going to be reimbursed by an endowment from the University.

I am please to be able to make this brief statement because my main interest professionally has been in suicide prevention, and I believe that the decisions that will be arrived at by your committee will probably have an important effect on suicide prevention.

I would like to make three points, starting with the point that was referred to this morning, by Dr. Wysowski about the coincidence perhaps, or perhaps not, of the very striking decline in the youth suicide rate that coincides with the very striking increase in the rate of prescription of SSRI antidepressants to

adolescents.

Starting in 1964, the youth suicide rate started to increase, and increased in an unstoppable fashion until about 1990. At that point it stabilized and started to decline in 1994. This pattern was not confined to the United States. It was also found in most other developed countries where SSRIs are also available. The general consensus is that SSRIs must be considered as one of the possible causes of this abrupt change in a pattern of mortality.

I think Dr. Wysowski said quite clearly that this is an ecological situation. The fallacy is there. But I think it also was somewhat unfair in not giving cognizance to the large number of analyses that have been done to try and look at alternative explanations for the decline. Most importantly, there has really been no decline in exposure to substance and alcohol abuse, which is recognized as one of the major risk factors. There has been a decline in other forms of psychotherapy during this period, rather than an increase. And,

the rates have declined in many, many countries. Firearm suicide is almost unknown. And, the CDC have recently produced data showing that there has been a significant switch from firearms to hanging in the United States during this period. So, I think that we do have to give serious consideration to the possibility that there is a causal relationship.

The second point is that there is another whole area of research which has not been discussed, which is toxicology analyses in suicide victims which have failed to show high rates of...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 32, please.

MR. MILLER: My name is Mark Miller. The first thing I would just like to say in a response to a comment made earlier here this morning is that I would rather be scared to death by a label on a medication than be changed forever by the death in our family seven years ago.

Seven months ago my wife Cheryl and I

stood here and shared our story. Our 13 year-old son, Matthew, had committed suicide after taking Zoloft. We shared how he had become akathistic on the drug and, despite what Pfizer would like to have you believe about our son as they attempt to portray him in a letter posted on your website, the one indisputable fact that matters most is that Matt, our son, never attempted suicide or self-harm prior to taking Zoloft. In fact, in testimony that Pfizer did not share with you, Matt revealed to his doctor before he ever took a pill that suicide was something that he could never bring himself to do. His doctor did not see suicide as a threat. His mother did not see suicide as a threat, nor did I. Yet, within a week, one week on the pill, Matt violently and with great difficulty took his own life.

Pfizer's strongly worded 50-page document continues to show a pattern of how drug companies disparage victims and anyone else who dares speak out against them. Pfizer was so afraid of our case going to trial where the facts could best be

weighed by a jury that they tried to discredit the science of an internationally respected expert. If that is the case, the conclusions from this science are now being validated by regulatory bodies around the world. Months ago, in fact, they were validated by your agency's own internal review.

Health Canada, in the meantime, has demanded that Pfizer level with its citizens. In a warning on their own letterhead, Pfizer Canada admitted last May that Zoloft, quote, may be associated with increased risk of suicidal ideation in children under 18, unquote. Where is your demand for a similar clear and unambiguous warning in the U.S.?

You have to go to page 13 of Pfizer's new 38-page prescribing information for Zoloft until you read anything about the possibility of suicide, and even then there is no mention that the drug may be associated with it, as they admit to in Canada. That is a warning?

Are we to believe that children in the U.S. react differently to Zoloft than Canadian

children? Last year in Great Britain, as you know, these drugs were banned for children under 18. It is very possible they could ban their use for anyone under age 30. Why, I ask, has the FDA, contrary to your own mandate, allowed negative trial data to be so easily kept from doctors and the American public? Why haven't parents, like Cheryl and myself and countless others, been told the truth about these medications? That is your job, to make sure that we get the information we need to make careful, wise and informed decisions. We learned the hard way that these drugs can kill. Many of the people are testimony to that.

Ban these drugs...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 33, please come forward.

MR. FARBER: I am Donald Farber. I am an attorney from Wren County, California. I represent antidepressant victims and there are a lot of them, believe me.

Dr. Hammad said this morning that there

are no consistent patterns of trial design. He cited 12 variables. He is wrong. There is a consistent pattern of trial design, and that is to conduct them so that they don't detect suicide at the crucial times.

The Columbia project, though interesting and I am sure professionally stimulating, does not advance the knowledge necessary to know whether antidepressants are safe. The only real question the world wants to know is do antidepressants cause suicide? Congress asked Dr. Woodcock the question last Thursday, and she said the jury is still out. Well, the jury has been out on that question for 15 years.

We have heard the same rhetoric the last six months as we heard in 1991 with the original Prozac hearing. If you go back and read the transcripts, it is the same thing. Everybody knows why no progress has been made to answer that question. The drug companies will not do the clinical trials to specifically test the suicide hypothesis under any condition. If ethical

barriers are involved, as Dr. Temple claimed in "The Wall Street Journal" and PBS, the FDA should give as much attention to ensuring clinical trials are properly designed to test that hypothesis as it has to this Columbia project to bail out the industry.

While I have my opinion, the public cannot tolerate another 15 years of professional ignorance on whether antidepressants cause suicide or not. Test them right and find out the answers. Thank you.

[Applause]

DR. GOODMAN: Thank you. Speaker number 34.

MR. ROUTHIER: I testified once already in February and I am not happy about having to do it again. My beloved wife of 18 years went to her doctor sick with abdominal pains and was coerced into trying an unmarked sample of Wellbutrin. After a week of serious adverse reactions and insomnia, she shot herself. She was never depressed, was a perfect wife and mother, and

worked 25 years in the Department of Public Welfare.

The product information guide, which she was not given, states patients treated with bupropion have experienced psychosis, but it is impossible to determine the extent of the risk. How can any benefit be worth the risk if risk is impossible to determine? The list of side effects--psychosis, mania, hallucinations, insomnia, agitation, suicidal ideation, etc., etc.

GlaxoSmithKline's answer is we told you so, and everyone knows the inherent dangers. Hundreds of cases were settled on Prozac alone a decade ago. Two main ingredients are fluoride and hydrochloric acid, the most caustic, corrosive substances known. These neurotoxins poison the brain, triggering adrenaline, masking symptoms. Nobody can know what it is to lose the most beautiful, intelligent, strong, loving, caring wife of 18 years, incredible mother of two boys that she adored, my soul-mate. There was nothing ever wrong with her until these damned pills. Which they want

to question and deny?

She left a legacy of love that was witnessed by hundreds as the most unselfish wife and mother, sister, daughter, friend, co-worker. She left me and two sons with a need for justice. We all know this stuff is dangerous. Anyone denying this, especially anyone in a position to make a difference, in the face of such horrific testimonies is an enemy of humanity.

After 18 amazing, wonderful years, at 40 years old she became deathly ill for a week and then ended her pain. One week after the first pill. Then the autopsy found the gallstones. Guess what, don't take poison, toxic chemicals while having a gallbladder attack. I absolutely worshiped her and everyone told us we had a rare love. Even our middles names are Mary and Joseph. We were a match made in heaven. We were ripped apart by a nightmare conspiracy no one could imagine. My wife was murdered.

How many settlements have silenced victims? I don't care about any perceived benefit

when this stuff kills people. My wife was worth the risk? Other victims here were? Which ones? The FDA has to get off their ass and move on this, and make it clear it is children and adults. Don't try to minimize the numbers by dividing groups. There is plenty of proof. I call on everyone to carefully investigate every episode where a person on these drugs had uncharacteristic, uncontrolled violence or suicide. I am aware of many. Don't let them blame psychotic episodes on depression. Many are given these drugs for reasons other than depression, including my wife.

Look at the studies, the NDAs, the MedWatch reports, the settlements, witnesses, read the side effects. The body count is climbing and we are sick of the coverups. The risks are too great to be...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker number 35?

MS. MCBRIDE: My name is Sharon McBride and I am a dental hygienist. I am here as a mother

and a friend--

DR. GOODMAN: Could you bring the microphone closer to you?

MS. MCBRIDE: Sorry. I am here at my own expense as a mother and a friend. I am here today to remind the committee of the serious suicide attempt of my then teenage daughter shortly after being prescribed the SSRI medication Zoloft. After seven years on Paxil, she is still attempting to recover from the problems incurred from abruptly stopping that medication.

I have only in the last three weeks learned of the higher suicide ideations of the other SSRI type medications that she has been prescribed. Two days after beginning Seroquel, my daughter overdosed on that medication. She denied suicide attempt but had no explanation for her action. She continues to have difficulties more, in part, to the side effects of the medications and the devastation they have caused in her life.

Liz Torklingson was a beautiful high-spirited young lady who was a purist and very

Careful about what she put into her body, only eating organic foods and no red meat. She did suffer from a nagging depression and became, over time, convinced to try medication. She took Serzone for a year but discontinued after hearing on the radio that it can cause long-term health problems. Celexa was recommended as a healthier replacement. Because of a bad cold, the dosages of Celexa were forgotten and Sudafed was taken. Upon resuming the Celexa, she quietly walked into the subway, entered into the dark tunnel, sat down on the track and let the train run over her. One week later came the FDA warnings about antidepressant medications but too late for Liz.

This morning I received an email from my neighbor in Arizona about her 13 year-old daughter. Erica was never suicidal while on Paxil, although we had some of the worst incidents with her rages and meltdowns during the time that she was on Paxil. She was literally uncontrolled about home school and church. Teachers in school and church were not able to handle her. At one point in

school she had such a serious meltdown that the entire classroom had to be removed and the school officer was brought in to control the situation. Another time her behavior reached a point of kicking the teacher and aids resulting in her getting arrested. These incidents led to her admittance into a behavior health center. She was admitted twice within two months.

This report is also similar to the report you heard from Todd Shivick about his 11 year-old son Michael. Michael not only had these same type of rage behaviors but made four suicide attempts while on Paxil. Now, one and a half years after discontinuing Paxil, Michael, now 14, has returned to a normal teenage life, participating in high school activities.

I respectfully request that not only suicide ideation be investigated but also these personality and behavior changes in our children prescribed these SSRI medications. This affects our homes, our society, our nation and our future. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 36, please.

DR. BREGGIN: I am Peter Breggin. I am a psychiatrist without financial ties to the drug industry or anyone else.

It is gratifying to see the FDA finally considering, after ten years, data that I produced in talking back to Prozac and since then in numerous books, medical articles, peer reviewed articles, including the one I have given the committee. Some of my data comes from suits against the manufacturer in which I have been an expert. I have been involved now in dozens of cases against the manufacturers and they have, for good reason, settled every single one. In addition, a number of criminal cases have come out well for the defendants.

Dr. Laughren knows that he is wrong about the absence of any suicide signal in adult cases. By a 6:1 ratio there were more suicide attempts on Prozac compared to imipramine and compared to

placebo in all of the clinical trials used for the approval of Prozac. Beasley, at Lilly, kept this data initially from the FDA but I disclosed it ten years ago, in 1994, in the Westecker case and it has since then been published numerous times.

The Prozac data would have been much worse, as Dr. Laughren knows, if Lilly had not been illegally medicating its patients by actual memo from Ray Fuller to all of his principal investigators, empowering them to give tranquilizers against the protocol for these patients, also, if Lilly had not been hiding its adult suicide events in the coding items, innocuous items such as "no drug effect" in a suicide case. This kind of thing makes the collection of data, as done in the present cases today, just fraught with risks of fraud about coding because Lilly, we know for sure, has coded with absolute ability to hide their data and I found it by going through the files, which the FDA doesn't do.

Again, in adults I have reanalyzed suicide data from other high profile SSRIs and found adult

signals, but the data is sealed because the cases have been settled but the FDA hasn't empowered me to release that data or, in fact, ask for it.

SSRIs cause suicide and violence in the early stages of treatment or during drug changes because of stimulation, euphemistically called activation. It is an amphetamine- or cocaine-like effect, which the FDA has now recognized by putting out a list of agitation, hostility, anxiety, irritability, and so on, on its own website, symptoms wholly indistinguishable from methamphetamine or cocaine...

[Applause]

DR. GOODMAN: Thank you. Speaker 37, kindly come forward.

MR. ORR: I cannot see my notes with the lights off.

DR. GOODMAN: Somebody may be leaning against the dimmer somewhere. That was probably inadvertent. We won't start you until we get the lights right.

MR. ORR: Thank you. My name is Bruce

Orr. I have no financial ties to anyone. I am from Charleston, South Carolina. I am a former law enforcement officer, with approximately 20 years experience. I am also a former director of a children's ministry. I currently have a child in my life whose meds. were switched three times, in four months, with three suicide attempts.

As a law enforcement officer, I spent a career combating illegal drugs and the influence that they had on our children. As supervisor of the violent crimes and homicide division of my agency, I dealt with the aftermath of the unnecessary violence associated with these drugs. Times have changed. There are still, and always will be, crimes related to street drugs, but more and more I am seeing a pattern of violence associated with the excessive use, sudden withdrawal from, or switching of antidepressants and, frankly, it is quite disturbing.

While we sit in this air conditioned room, looking at pretty charts, cops like I was are dealing with the blood and gore accompanying these

suicides. Have you seen the aftermath of a suicide? I have and I still do every night when I go to sleep.

Our children are our hope and our investment in the future, and we sit here today hearing the cries of parents whose hope and future were destroyed by the very drugs they thought would help preserve it.

As I stated earlier, I was a law enforcement officer and a children's church director. I was a pretty easy-going person but in 2002 I was placed on the antidepressant Paxil for post-traumatic stress disorder and major recurring depression. Prior to that time I was awarded "Supervisor of the Month," in line for promotion, and had just received a medal for saving a life. After four months of horrible side effects, my doctor attempted to switch me from Paxil to Remeron and stopped abruptly in four days. During severe withdrawal, I attempted suicide by overdosing and driving my truck into a parked car and shoving it through my home. I was subsequently charged and

eventually pled guilty to lesser charges, and now I am a convicted felon. I guess you could say Paxil brought my career full circle, from cop to criminal.

Two years ago, as a 38 year-old man, I wanted to die in withdrawal. I recall laying on a friend's bathroom floor and begging him to kill me. When he didn't do it I tried to do it myself. I cannot fathom what that must be like at 18, 15, 12 or even 10 years of age. The pain and mental anguish is unbearable.

Something must be done about these drugs and the effects that they have on both children and adults. If the drug companies withhold potentially life-threatening information just to turn a profit something must be done. My family and my career were forever destroyed but at least I still have my life. I never would have thought that a little pill, that ironically comes in little-girl pink for lower doses and baby-boy blue for larger doses, could alter my personality so drastically, but it did. It is not worth another parent losing a child

over or, in my case, children losing a parent over. This medication cost me a year of my children's lives but I have them back now. I just wish that some of these parents could say the same thing. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 38, come forward, please.

MR. REED: Good afternoon. My name is Jerry Reed and I am the executive director of the Suicide Prevention Action Network, SPAN, U.S.A. Suicide claims the lives of over 4000 young people each year, making it the third leading cause of death for those between the ages of 10-24. In 2003 16.9 percent of high school students seriously considered attempting suicide, while 8.5 percent made an actual suicide attempt.

Research shows that over 90 percent of children and adolescents who die by suicide have a mental disorder. Among adults, psychotherapy and antidepressants are regarded as the most effective treatments for depression, but only limited

research has been conducted on the efficacy of antidepressants in children and adolescents and the studies that have been conducted thus far have three major problems: One, they have been too short in duration. Two, they have excluded those at highest risk for suicide and, three, not all of them have been published.

The limited evidence available and the shortcomings of the research conducted thus far underscore the need for continued and improved research. Most suicide prevention is based on the principle that suicide is generally preceded by the signs and symptoms of a mental illness or other behavioral or emotional problem which can be treated. If we are to continue screening young people, it is imperative that we have safe and effective treatments to provide to those identified at risk.

Since most young people with a mental disorder do not receive mental health services, prematurely prohibiting the use of antidepressants for young people with depression, one of the most

widespread treatment methods, may discourage a significant number of people from seeking out help and ultimately do more harm than good.

As an organization comprised mostly of suicide survivors, we have heard the stories of mothers and fathers who sought out treatment for their children but were never educated about the risks associated with their loved one's condition or treatment. In survivor suicide support groups nearly all parents who lost a child report if they had only known 30 days before the suicide what they knew 30 days after, their child's life might have been saved.

The fact is that most young people receiving treatment for depression or other mental illnesses do not get services from the specialty mental health sector but, rather, from schools, primary care providers, child welfare services or juvenile justice facilities. It is, therefore, essential that everyone prescribing antidepressants to youth know about the need for increased monitoring and vigilance, particularly during the

first weeks of treatment. All those involved with the treatment of children and adolescents with depression should be forewarned about the potential risks and may be informed as to what signs and symptoms are indicative of potentially serious problems. Patient education is a proactive action that should be taken now. It is the least we can do while the requisite research is pursued.

Suicide has been a leading cause of death among young people for far too long. Any concerns about the efficacy of antidepressants for treating young people with depression must be addressed immediately. SPAN, U.S.A. represents people who know all too well the terrible tragedy of suicide. We must act now. There are too many lives at risk...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 39, please come forward.

MR. COFFIN: Good afternoon. My name is Chris Coffin. I am with Pinley law firm in Plackman, Louisiana. I am standing before you

today in two separate roles, number one, I am an attorney who represents thousands of individuals whose lives have been negatively affected by the use of SSRIs. Some of them are parents who have been misled about the safety and efficacy of these drugs. Some of them are adults who have ingested the drugs and experienced suicidality or experienced severe debilitating withdrawal symptoms when they tried to reduce their dose or terminate the use of the drugs.

The second role I am in here today as a healthcare professional. I am also a practicing registered nurse. I understand the risk/benefit analysis that goes along with treatment decisions. I understand what it means to be a provider who is passionate about the care, in this case, of his patients.

For the sake of my clients, my patients and for the sake of our colleagues as healthcare providers, I come to you with three requests today.

Number one, take further action.
Contraindicate the use of SSRI drugs in children.

I understand that you want to be thoughtful and careful in your analyses. I understand that you want to consider all angles. At this point, however, we now have the benefit of the analysis done by British regulators, by Dr. Mosholder and by the Columbia University group. Although the data is not absolutely perfect because it was not always looking at suicidality, we do know that the risk outweighs the benefit. That seems very clear.

The second request I have to you is to dig deeper. By dig deeper, I mean to look deeper into the data. Look further, beyond just the pediatric issues. Realize that there is far more data in the halls of the pharmaceutical companies than has been presented to you. Because of litigation, my legal colleagues and I have been able to look at that information and I think if you look you will find an abundance of information that will further educate you about the debilitating risks of these drugs. Do not trust and do not be misled by the pharmaceutical companies. Whether you take my position or anybody's position in this room, you

owe it to the American people to look further into the information that the drug companies have within their houses.

The third request I have of you today has been made by many others, and that is to educate. From a healthcare provider's standpoint, I ask that you go beyond the regular minimal requirements that FDA imposes on drug companies. Force the drug companies to provide better education on SSRI drugs for children and adults. You will prevent serious injury in the future if you do so. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 40, please come forward.

MS. ERBER: Hi. I am Alice Erber and this is my family, Robert, Talia and Rachel Steinberg. We live in Palo Alto, California. My son, Jacob Steinberg, died last year, on Wednesday, July 23, after being on Paxil for about a month. He was 20 years old. Jake was going to be a senior at college. He played the piano, sang in the glee club, was the entertainment editor of the school

newspaper. He was involved with student government. He was a great kid, so full of life. He loved music, films and had many friends.

In mid-June, Jake went to see an internist, whom he had never seen before, to get a referral for a hand specialist because his hands were sore from playing the piano. The internist who saw him for 30 minutes prescribed Paxil because he bit his fingernails and the doctor thought it might help with that. Jake had been taking Wellbutrin for anxiety and mild depression for about six months. He was doing fine on Wellbutrin. The internist told him that it was okay to take the Paxil with the Wellbutrin.

Jake had begun a six-week internship in New York City in June and he was not going to be supervised by a doctor. He went on a trip with my husband to Israel for two weeks in July, and felt sick and had diarrhea. My husband was concerned. I talked to Jake on Saturday before he died. He told me he was staying up late; he wasn't sleeping. He left me a great phone message on the day that he

died. In the morning he sounded fine. He talked to his sister at lunchtime and they had a good talk, but before he hung up he complained to her that his stomach hurt. Then, on that afternoon, on Wednesday, July 23, we found out that he killed himself.

They said at work he started acting bizarre. He started having erratic behavior and he ran through the building, throwing his clothes off and fighting the office security guard, and ending up throwing a chair through a window and jumping to his death from the 24th floor of a Manhattan office building. What a horrible way to die.

We went to get his body the next day and the detective said he found two empty bottles of Paxil and Wellbutrin. When the autopsy report came back it showed that there was Paxil and Wellbutrin in Jake's body but not in overdose, just a regular amount. We are sure that the Paxil caused his death. He had the symptoms of akathisia. We also think Paxil and Wellbutrin may have created a manic psychotic episode.

We want to tell our story to make sure that if he had not taken Paxil he would be alive today. The public and the doctors need to know these suicides in young people. Tomorrow is Jake's birthday. He would be 22 years old. We are here in his memory, making sure this does not happen again. He was impulsive and out of character. We know he did not want...

[Applause]

DR. GOODMAN: Thank you. Sorry for your loss. Speaker 41, please.

MS. WEBB: I am here because three years ago my daughter was suffering some symptoms that the doctor felt represented depression and started her on samples of Paxil. I trusted this decision as a mother and based on my medical background as a registered nurse.

Unfortunately, she did have an obvious worsening of symptoms. Were we aware that the antidepressant could be the cause of this? No, we were not. I am here because I agree that the FDA needs to require further studies to be done to see

if it is true that certain antidepressants increase the risk of suicidality.

When I learned that I would have the opportunity to speak before this committee I wasn't sure what I would say. So, I replayed an audiotape of a confrontation with my then 17 year-old daughter during the time she was taking these antidepressants. We could not believe the changes we saw in our daughter in the very short time she had started on the antidepressants. It was unbelievable--the rage, anger, the hostility she exhibited that night. She ended the night by cutting her wrist. Now I am learning that the changes we saw in our daughter, more likely than not, were the side effects of the antidepressant she was taking at the time.

Yes, we did report a worsening of symptoms shortly after she started the Paxil. The doctors only changed her to another antidepressant, Zoloft. She then continued to worsen and they continued to increase the dosage until she began to further harm herself with self-mutilation, cutting, overdose,

numerous things. We were fortunate to get her help in the right environment with counselors who spent many hours with the children. She was taken off of the strong antidepressants and, within a short time none of the staff could believe she had done while she had been on Paxil and Zoloft. She continued there, getting counseling, and returned as the child we knew before she took these antidepressants.

Why did we not know about these adverse side effects that are now being reported in children? Was it possible the drug companies may have been aware of these adverse side effect? If we had known, I believe it is possible that maybe my daughter and our family would not have had to go through the agony and heartache we went through.

My daughter is hearing impaired and has a cochlear implant, and has worked hard all her life to overcome the stigma of being hearing impaired and deaf. It has been hard but she has always had a positive attitude. Now we are sad but also find relief in telling her that what she went through

could have been prevented if the drug companies had made public these adverse side effects. Yes, relief but, unfortunately, too late. She now has to endure the stigma that mental illness brings to those who suffer it. Luckily, she has shown her determination to overcome this, as she did her hearing loss. She is now a junior in college and doing great. Her determination has brought her through many obstacles but this was one she should not have had to battle.

Guidelines for the use of antidepressants in children should be reevaluated and studies done to determine which, if any, are safe for use in children. Thank God, we were able to get my daughter help before it was too late. I am sure there are many more children who did not get that help and may have succeeded in their suicide attempts. Thank you.

[Applause]

DR. GOODMAN: Thank you. Speaker 42, please.

MR. WITZCAK: My name is Chester Witzcak.

I am a resident of York, Pennsylvania, and I have no financial relationship with the FDA, drug companies or any advocacy group. I am attending this hearing at my own expense.

On August 6th, 3002 my oldest son, Timothy, died of a Zoloft-induced suicide at age 37. He died after taking the drug a total of five weeks. It was prescribed for insomnia.

How did this happen? Zoloft was prescribed off-label and there was no information regarding Zoloft's serious side effects with the Zoloft samples given to him by his physician. Why did this happen? Soon after SSRIs were introduced the drug companies began a campaign to establish that they were effective treatment for other diseases although there was no clinical basis for this, and none of the serious side effects were discussed or highlighted in the literature or on the labels.

Today these drugs are prescribed for a long list of ills. Physicians and patients are using it for just about anything except hangnails

despite the fact that SSRIs are only approved to treat a few conditions. In 1997 FDA added a major weapon to the drug company arsenal, direct-to-consumer advertising. FDA issued guidelines that allowed drug companies to air broadcasts and print advertisements that contained minimal information about a drug's possible side effects. The United States is the only industrialized nation that allows direct-to-consumer advertising to the public. Other countries consider the practice to be unethical.

How effective are these SSRI drugs really? At present, drug companies not only plan and pay for the trials of their own drugs, but also analyze and publish the results. This conflict of interest has introduced a bias into the testing since drug companies suppress test results they don't like when drug companies show that the drug isn't more effective than a placebo, a sugar pill or, said another way, better than nothing. That is a very low hurdle.

What is needed? We need warnings for all patients, not just juveniles being prescribed SSRI drugs, informing them of the serious side effects. Families and spouses must be warned as well to allow them to be aware and to watch for the signs for these serious adverse reactions. We need this now, not more studies or hearings. We need to eliminate the direct-to-consumer advertising. You authorized it. Stop it now. Eliminate the off-label use of drugs.

If a drug is to be used for a particular treatment, require that it is more effective than existing treatments, with real clinical tests not based on a journal article hyped by the drug companies. Establish a truly independent drug testing agency. We can't go on with the fox in the henhouse situation we currently employ. Without the positive actions I have indicated the FDA will continue to be a co-conspirator in the assault of the public, with the SSRI drug-induced violence and suicide. Thank you.

[Applause]

DR. GOODMAN: Thank you. Is speaker 43 present? If speaker 43 is not present, then speaker 44.

MS. PARKER: My name is Nancy Parker, and I am a mother of a 12 year-old African-American girl, Rebecca, whom I adopted at the age of three weeks. I am also a member of NAMI, NYC Metro.

First of all, I want to say my heart goes out to everyone here who has lost a loved one, but I am here to tell a very different story. My daughter has suffered from severe mental illness for the past seven years. Her present diagnosis is depression with psychosis NOS. She is presently on a regimen of 800 mg of Seroquel, a milligram of Haldol and 225 mg of Wellbutrin.

At the age of five and a half, Rebecca had her first episode. I was cleaning up a glass that had suddenly broken when she ran in, appearing to be in something of a trance, picked up what I assumed was a small piece of glass and swallowed it--her first attempt at trying to hurt herself. She was then in therapy and had her first

hospitalization where she was given a diagnosis of bipolar disorder.

So, a little girl comes home on depakote and after a week she has another episode, and when I think she may be gaining control she comes up behind me and clocks me over the head with a big toy hair dryer. We both wound up in the ER and when the doctor asked her, "why did you hit your mom over the head?" she replied flatly, "because I had to." At this point her doctors concurred it is very likely that Rebecca is not bipolar. Now there is no diagnosis so the doctors tell me if she acts up just give her Benadryl.

She left the hospital and was seeing a therapist regularly, and in September of 1999 she began hearing voices. At this point, her therapist and psychiatrist put her on the first of many antipsychotics, Risperdal. While this was going on her behavior became very self-injurious. One impulse was she would walk out in front of cars. When I told her she could get killed, she answered, "maybe I wanted to." She would bang her head on

the wall and tell me how she wanted to die and be with her grandma in heaven.

For Rebecca, the time between ages 5-12 meant five hospitalizations and one year in residence. She has been on everything from Risperdal, olanzapine and BuSpar. While in the hospital, they put her on lithium and then took her off for three days because she became violently ill. When she was in residence they started Rebecca on a low dose of Risperdal and Wellbutrin. While that helped somewhat, it was not the perfect mix. Finally they tried Serecol [?] with Wellbutrin. There were some difficult times there but they had upped the Serecol and Wellbutrin to her present dose.

Presently, she has been on Wellbutrin and does not hear any voices. She has not had any hospitalization and is relatively happier now and there is no impulse to hurt herself.

I just want to say that we have to have clinical trials for these children. They must be started at a low dose and if there is any problem

the doctors have to be told that these kids, if they are not working out on these particular drugs, have to be taken off the drugs. Or, if it is a cocktail, as in my daughter's case, maybe the cocktail has to be stopped. Finally...

DR. GOODMAN: Thank you. Speaker 45, please.

MR. SCHNEEBERG: Yes, my name is Richard Schneeberg and I have a masters in counseling. Between 1997 and 2000 a person is given 14 different types of antidepressants on eight hospital stays. During one of the stays he tries to jump out of a hospital window. After another hospital stay he is found walking on the railroad tracks, and when he is brought to the hospital he is a catatonic zombie. He can't speak and he is in a fetal position, rubbing his knees together. After another hospital stay the person has a delusion of murder. After yet another hospital stay this very same person makes a threat to burn down a hotel. He is brought to a hospital and starts having hallucinations after being medicated

again.

The common thread in all of these bizarre actions, including suicide, is that none of them ever occurred before this person was given antidepressants. The focus of this conference is on children, however, the person who I refer to is not a child. It was me, a man, then in his late 40s.

England has banned all antidepressants for kids except Prozac. Let's have an American revolution and ban antidepressants for everyone and prevent many suicides.

All of the above is documented in my autobiography, "Legally Drugged," being produced and published soon, and will be produced as a motion picture. Excerpts from the hospital reports will be in the book, where the psychiatrists themselves state they were worsening my condition. Counseling only, no drugs. Antidepressants, weapons of mass destruction.

[Applause]

DR. GOODMAN: Thank you. Speaker 46,
please.

DR. RISINGER: I am David Risinger and
this is my wife, Sarah. I have no financial ties.

Next slide. This is my 15 year-old son,
Josh.

Next five slides. All these pictures were
taken about a year ago before Josh started
antidepressants.

Next slide. See that smile? Suicidal?
No way!

Next slide. Not that he didn't have
problems. He had been seeing a psychologist who
thought an antidepressant might help.

Next slide. This is Josh before Zoloft.
He was popular, athletic, had a girl friend, was
making plans. He had hope and enjoyed life.

Next slide. Twelve tablets later he was
gone.

Next slide. Three times in those 12 days
I talked to his doctors to tell them that he wasn't
doing well; to tell them that he couldn't sleep at

all; that he seemed agitated. He cried out to us that this medicine was making him worse. I was told, "give it time; these take a couple of weeks to work." Twelve days. None of us recognized the danger he was in because none of us had adequately been warned.

Next slide. The first I ever heard of this controversy was this article that ran shortly after Josh's funeral.

Next slide. There is certainly no mention of it in any of the product literature.

Next slide. The reason I come to you today is to caution don't rely only on the clinical trials data to base your recommendations.

Next slide. I would like to give an example from my practice, and that is x-ray contrast media.

Next slide. Doctors and patients are warned of the risks of these drugs.

Next slide. Specialized training and preparation are required to use these drugs.

Next slide. And many lives have been

saved to reactions that never happened in any of the clinical trials, reactions that most of my younger colleagues have never seen and would never believe until they saw their first case, and by then it would be too late.

Next slide. But I know this happens. I have seen it.

Next slide. I know this happens too. I have seen it, and I am here to tell you.

Next slide. Don't rely only on the clinical trial data. I think what you are looking for maybe too rare to find there.

Next slide. But just because it is rare doesn't mean it isn't important. There are millions of people on these drugs. Thousands of lives literally are at risk. What do we do? I would like to give an example from my practice. To interpret mammograms, every three years I have to get 15 hours of CME. Why can't we do something like this with these drugs? Every prescriber should be required to periodically pass a mandatory certification in psychopharmacology. Surely this

committee would find this tool useful for keeping clinicians up to date, and the time is long overdue for effective warnings on the drug label, in the package insert, and in all advertisements. This can't wait any longer or it will be too late.

Next three slides. For Josh and many others it is already too late. Thank you.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 47, please.

DR. HEALY: Ladies and gentlemen, I am here and have paid all my own costs to be here. This meeting you are having is more than about a crisis about one drug-induced side effect; this is a crisis for evidence-based medicine that has enabled the FDA and the companies to state openly and repeatedly that there is no credible evidence that there is a link between SSRIs and suicide when this is scientifically quite wrong.

There have been 677 trials involving SSRIs, and having helped review all of these, I can let you know that roughly only 1/4 suicidal acts

that have happened in these trials have been reported in the scientific articles that have come out of those trials. Nevertheless, when you combine all of the trials year on year, as of 1988, the odds ratio that SSRIs are associated with suicide over placebo over double the rate is there from '88 onwards, and for each year onwards. The odds ratio without risk of getting well in these drugs is actually much less. It is only half of the odds ratio of picking up a suicide.

The original Paxil suicide figures that SmithKline submitted to the FDA, in '89, showed an eight times greater risk of suicide on Paxil for adults than for the same suicidal acts on placebo. Telling SmithKline that FDA believed concerns about suicidality were a public relations first, Martin Brecker, of FDA, invited them to resubmit their figures. SmithKline did so and in the process re-coded as placebo suicides and suicidal acts acts that had not happened on placebo. They were only doing what Lilly and Pfizer had also done.

In contrast, FDA, when faced with

debatable evidence that the SSRIs worked, had a completely different approach. Such as the volume of negative studies that people within the FDA suggested to Bob Temple that the label for these drugs should include some indication of how many negative studies there were. Martin Brecker, in the case of Zoloft, where two of the three trials back then when the drug came to FDA first were actually negative, and still are negative, said he would be embarrassed to be associated with this portfolio. FDA, Dr. Temple, chose not to write into the labeling the number of negative studies there had been. In the light of what has happened with Elliott Spitzer, who characterized such behavior as close to fraud, it may be time to revisit this choice.

Having said this, I think FDA made the right choice to approve Zoloft and other SSRIs. But there is a sauce for the goose and a sauce for the gander issue here. The best estimate we have of suicide on these drugs is 2.4 times greater. In the Paxil OCD trials the best estimate we have...

[Applause]

DR. GOODMAN: Thank you very much. Is speaker 48 here? You are speaker 49?

MS. WAINSCOTT: Yes. I am chair of the National Mental Health Association. I am an unpaid volunteer and I am family member.

Depression itself creates a significant risk for suicide and we have known for a long time that as a person emerges from the black hole that is severe depression, there is a risk that they will marshal the strength to act on the suicidal thoughts that often accompany this illness. I saw this happen two times to my mother as she bravely struggled with depression for almost half a century without the benefit of today's treatment advances.

Today, because the topic of suicide is uncomfortable for many, because insurance plans limit visits and often flatly deny psychotherapy, because practitioners are very time pressed and sometimes they are wrong, kids are often not adequately monitored after they receive medication, and parents often are not told what to look for to

protect their children. There are heart-breaking stories of the consequences.

But I came to tell you a success story. As a young child Jessica was sunny and cheerful, loving, affectionate. Then, as she turned 11 it was clear that something was very wrong. She was suddenly crabby, difficult to get along with. She became moody and withdrawn. Jessica's father approached her directly, "you have to tell us what's the matter." She replied, "I have been telling you." "No," he said, "you have just been going away." After a long silence Jessica said, "I don't know, Dad. It just seems like I'm mad all the time." As the words tumbled out and she described her pain he realized she needed professional help.

She was diagnosed with depression and together she, her family, their pediatrician and a consulting psychiatrist developed a comprehensive treatment plan that included SSRI medication with close monitoring.

I am happy to tell you, and I want to show

you a picture, that my granddaughter is doing extremely well. She is the tall one. She is an outgoing, happy 15 year-old, engaged in her family, successful at school. She has a lively group of friends and is displaying a real talent for art. She sticks to her treatment regime and she still takes medication.

As I prepared this testimony I talked with Jessie about it. She told me, "Babi, tell them not to do anything that will make people afraid to go for help. Life is so much better with treatment." I asked her how it is better and she said, "I'm just able to be myself. There are no invisible strings pulling me down."

So, I ask you for Jessica and for the millions of kids like her who do and will struggle with depression balance the risk of medication with the risks of untreated depression. Help tear down the barriers to treatment. Don't erect new ones. Address the issues in the broadest possible context. Be mindful of the many children like Jessie who benefit from these medications and the

hundreds of thousands who need treatment and get nothing.

The written testimony of the National Mental Health Association, which you have, makes specific recommendations. We support the call for closer monitoring of...

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 51, please come to the podium.

MS. GRUDER: My name is Deborah Gruder.

My husband, Scott, was never diagnosed, ever, with depression but on March 30th, the morning of March 30th, after being on Paxil for 13 days--13 days only--he went to Walmart at 7:16 a.m. and bought a shotgun and returned to his office and locked the door and shot himself.

Neither he nor I had any idea that there was any need to beware. We were never told we should beware. We knew people who had been on Paxil or other SSRIs and we had seen many of them benefit, and we had seen the numerous television commercials that showed people that were in very

desperate psychological trouble, after taking SSRIs, all of a sudden they were dancing through fields of flowers; they were laughing; they were happy. This is what we knew. We didn't know there was anything to be concerned about. Not once--not once did we ever see in any of these commercials--we never-ever saw a follow-up of anyone stepping off of a bridge into the icy waters of a river to their death. We never saw a woman lock herself behind her bathroom doors and slice herself up with scissors. We never saw anyone take a gun and go behind closed doors and shoot themselves.

My husband and I did not once hear about the subpopulation of people, which evidently he belonged to, that had a very adverse reaction to Paxil and other SSRIs. Early this year I understand, and for the past 10-15 years you have been aware that there is a problem with SSRIs. Shame on you! Shame on you for being aware when you should be protecting us, the people, all these people sitting behind me! My story is not unlike

theirs. You should be protecting us. Where were you? Where have you been? Why haven't you done anything about this? This is just a small percentage of people that have had a loved one die violently because you have not done your job...

[Applause]

DR. GOODMAN: Thank you. Speaker 52, please.

MS. GUARDINO: My name is Mary Guardino and I am the founder and executive director of Freedom from Fear, a national mental illness advocacy organization, and someone who suffers from anxiety and depression.

I want to thank the committee and all those who have participated in the process of gathering and sharing information related to this very important issue. As a mother and mental health advocate for the past 20 years, nothing has been more important to me than the health and safety of our children.

My own depression and anxiety began when I was very young. Most tragically, it was not until

I was 40 years old that I received a proper diagnosis and successful treatment. I was one of the lucky folks back in 1982 because my treatment combined medication and cognitive behavior therapy. That treatment brought me from the darkness of despair into the sunshine of hope. I have never forgotten those dark, long, painful days. They continue to motivate me in my work as an advocate for those struggling with mental illnesses and the family and friends who love and care for them.

When my own children showed signs of anxiety and depression, fortunately, I was better prepared to find the treatment they needed. I truly believe that my daughter would not have been able to complete law school nor my son complete a masters in psychological counseling if it were not for the early intervention and successful treatments of their illnesses.

What also is important is that their positive experience with treatment has taught them to trust the mental health network and to utilize it with confidence when it is needed. Their proper

treatment has increased their resilience and empowered them to help others.

In closing, I want to remind the committee to never lose sight of the goal all of us here so passionately strive for, that is, to improve the mental health status of all our citizens. To achieve that, we must encourage people in need of help to seek treatment and provide consumers and providers with access to the latest scientifically valid data and information on the best treatment options. If we fail in either of these endeavors, we will not be achieving the goal we all aspire to. Thank you.

DR. GOODMAN: Thank you. Speaker 53, please.

MS. WILLIAMS: I am here representing Jacob Williams who died of Prozac-induced suicide, December 5th of 2000. I was here last February. Therefore, I will give a brief synopsis of my previous statement and add a few additional comments that I feel are pertinent.

My son, Jacob Williams, was born on

October 15th, 1986. On October 11th of 2000, Jacob's pediatrician prescribed him Prozac. It was to be increased to 20 mg if there were no side effects. The doctor did not describe to us what side effects we were to look for. I assumed the prescription insert would indicate all side effects related to this drug. I was wrong. My husband asked the doctor if Jacob's problem could be hormonal, and did Jacob have to be put on medication. The doctor replied that this medication would help him because it is the most commonly prescribed drug for teenagers to help them with their needs.

On November 6th, 2000 Jacob was back in the doctor's office for a follow-up visit. At this time his dose was increased to 20 mg. This was Jacob's last visit to the doctor. Shortly after this visit I began to notice an aggressive behavior in Jacob which had not been there before. He also showed a verbal aggression and short temper that had not been present before. When questioned about this behavior he stated, "I don't know what's

making me do this." On December 5th of 2000 I found Jacob hanging from the rafter in our attic.

During the time Jacob was on Prozac, he went to a psychologist on several occasions. The psychologist asked Jacob on these occasions whether he thought about suicide. He responded that he would never do such a thing because it was against his religion. My sole purpose in being here today is to, hopefully, prevent other parents from having to go through the pain and anguish our family has gone through. Had I known suicide was a possible side effect to this medication I never would have allowed my son to take it.

I appreciate the action that has been taken since the last hearing. However, I am concerned that many are still saying Prozac is a safe SSRI. It is not safe. Since my last appearance before you I have heard statements from others who survived their encounters with SSRIs, specifically Prozac. My son cannot speak for himself since he did not survive, and it is my responsibility as his mother to speak for him. It

is my firm belief that his death was a Prozac-induced suicide.

In conclusion, Jacob trusted me. I trusted the doctor and the doctor trusted the FDA to make sure the drugs that are approved are safe and have proper warning labels. I plead with you to live up to the trust our society has placed in you. Thank you.

[Applause]

DR. GOODMAN: Thank you very much. Is speaker 54 here? If not, speaker 55, please come forward.

MS. YORKE: Good afternoon. My name is Laurie Yorke and I am here on my own accord.

Seven months ago I stood in my living room and watched my 16 year-old son slash his wrists in a full-blown Paxil-induced rage, screaming, "I was born to die." I am one of the lucky ones. My son is alive.

The process of weaning and withdrawal began without the help of my son's prescribing psychiatrist. He had refused to take my son back

as a patient after the suicide attempt. It was an Internet message for the Paxil survivors that walked me through the withdrawal process. With each lowered dose, my son experienced the anger, aggression, brain zaps, visual disturbances and insomnia. His withdrawal symptoms followed stunningly similar patterns that others have experienced. He took his last dose of Paxil at the end of April.

Prior to my son being prescribed Paxil for a single panic attack I did the research on this drug. As a nurse of 20 years, I am probably in the minority because I do read drug inserts. I do read the PDR. I do ask questions. When I questioned his psychiatrist about the use of an SSRI in a child his age, I was reassured by this adolescent psychiatrist that he has never had a problem with it before.

Paxil turned my child, in a period of 13 months, from an A/B student, social, outgoing personality like you would not believe into an angry, death-obsessed, anti-social recluse. My

son, now off Paxil, is once again happy, outgoing, socially active. What he must now deal with is the lack of concentration still existing after the Paxil withdrawal. I shudder to think of what the long-term ramifications of Paxil use will be in his case.

The FDA's lack of action on the evidence presented years ago caused my son to become a victim of Paxil. The FDA chose not to act on information you received that documented these reactions in clinical trials. GlaxoSmithKline chose to hide clinical trial data to protect profits instead of protecting our children. GlaxoSmithKline said on "World News Tonight" that they gave the information to those who needed to know. I am responsible for my child. I spend 24 hours a day with him. I needed to know. I was not told.

Delaying banning of SSRIs for children means more children will die and the violent behavior will continue. You have failed to protect our children from a bad drug. I was under the

impression that FDA approval meant that drugs actually went through a rigorous investigation prior to their being approved for safety. I know that the FDA approval now means nothing. Drug companies are allowed to pick and choose the clinical trials that they like. You rubber-stamp the approval and allow the children of the United States to become the guinea pigs. I believe the FDA has forgotten the Hippocratic oath, the basic that we all must adhere to, first do no harm.

[Applause]

DR. GOODMAN: Thank you very much.

Speaker 56, please.

MR. FRITZ: I told the story of my 15 year-old daughter, Stephanie, last February 2nd. She was on Zoloft and hung herself on November 11th.

DR. GOODMAN: Can you start over and bring the microphone closer?

MR. FRITZ: Sure. I told the story of my 15 year-old daughter, Stephanie, on February 2nd here. She was on Zoloft and hung herself on

November 11th. I attended the congressional hearing last Thursday at which Dr. Woodcock testified that the FDA had clinical information that showed that these antidepressants were not effective in treating children; that they caused an increase in suicidal thoughts. Some of these trials are years old so the FDA has had knowledge and decided not to share this information with parents so that they could make informed decisions on how to care for their children.

Dr. Woodcock said there is something in the law that kept the FDA from putting the information out. She couldn't cite the law. I guess it never occurred to her to ask Congress to change the law so that this information could get out. Maybe the FDA was too stupid to ask them to change the law but I don't think so. The FDA made a conscious decision to hide this information from the public because they say there is no other treatment available, even though they knew the drugs weren't effective and kids would be put at higher risk for suicide.

Doctors are charged with first doing no harm, just like Laurie said. But you, Drs. Temple, Laughren, Katz and Woodcock, have abused the public trust. You have greatly misused the power of your positions by keeping the information from the public while protecting the drug companies' profits.

I am asking that four of you resign as soon as the congressional investigation is over so that we can get people to work at the FDA that will work to protect our children and not the drug companies and their profits. You say that depression is the cause of suicides that occur with children on these drugs. Well, you have known all along, because of off-labeling, that kids have been prescribed these drugs for illnesses other than depression and still have completed suicide or they have attempted suicide, and you can't explain away these events on depression.

Those that have survived these drugs talk of violent thoughts and actions that went away and haven't come back since being off the drugs. You

say the jury is still out on these drugs. But it isn't out on you people. You need to go. We need to get people who will fulfill their duty and protect the people, not the drug companies. And, these drugs need to go. Until the drug companies can show that they work they shouldn't be prescribed to children.

The FDA should demand that the drug companies open up their files, not just the clinical data, on these drugs so we can see what they thought and what they are saying about these drugs--if they haven't shredded them, that is. If they have nothing to hide, they should do it right away but I don't think they will. They have known all along that these drugs don't work and were potentially dangerous to children who took them.

Dr. Cleary, from Pfizer, testified at the congressional hearing on Thursday as well. She testified in front of Congress that she wanted to be open and let people know what was going on. Well, I call on them to open up their files now so we know what is going on.

[Applause]

DR. GOODMAN: Thank you. Speaker 57,
please.

DR. VARON: I am a full-time child and
adolescent psychiatrist. I would like to thank the
North Baltimore Center, which is a community-based
health center treating the children of Baltimore
City. I would like to thank them for allowing me
to come down today. Although they didn't provide
financial support, they forfeited a day of billable
services to allow me to speak to you today.

Each day I realize that some of my
patients may one day die from the depression I seek
to treat. Antidepressants in children and
adolescents do work. In many cases I have seen
depression improved with the use of antidepressant
medication. In cases where medication has been
helpful, the child has been involved in a
multi-disciplinary approach where individual
therapy, family therapy, including parent
management training, has been utilized; the patient
had access to partial and/or inpatient

hospitalization when needed; and educational intervention was available when appropriate. As well, medications were helpful only if the right diagnosis was made. For instance, if we were really treating bipolar disorder as opposed to a depression the antidepressants, in fact, were not helpful. Also, they were helpful if comorbidities were also treated.

Second, discrimination in obtaining mental health care can compromise the patient's ability to be monitored appropriately for the dangerous side effects that we are talking about. And, shortages of child and adolescent psychiatrists can also exacerbate this issue as these are the physicians most fully trained in prescribing these medications.

Would a potential life-saving cancer drug with the risk of, say, aplastic anemia be taken off the market because of poor access to proper physician monitoring, or due to denial of an important hospital admission due to insurance purposes?

Third, I believe that there is a subpopulation of children that require lower starting doses, almost homeopathic doses as it were, and a longer titration periods of SSRI dosages. As such, these individuals may actually be more sensitive to the activation or disinhibition that we are talking about on the SSRIs. Thus, if they are started on the higher doses, they may be more subject to the events that we are talking about today. Thus, I would like to suggest that any future research take this subpopulation in mind.

Fourth, in my practice over the last ten years I have seen one case of an antidepressant causing suicidal ideation, as reported by the mom, prior to the child actually coming to me. In that case, no act, fortunately, was involved but the child still needed to be put on an antidepressant medication and subsequently did well.

I would like to talk about a female who was successfully treated. She had recurrent depression for many years on many medications. She

subsequently, over the last six months, has resolved on a combination of high-dose Zoloft, Risperdal and Wellbutrin and she is currently living without depression...

DR. GOODMAN: Thank you. Speaker 58, please.

MS. ZITO: My name is Julie Zito. I am Associate Professor of Pharmacy and Psychiatry at the University of Maryland, in Baltimore. I am a pharmacoepidemiologist and I have been studying the use of psychotropics in children for the past 12 years.

I am here, despite the late hour and our exhaustion, to really ask the panel to consider seriously a specific scientific model in addressing the need for additional research on the benefits and risks of SSRIs in treating youth. Namely, I ask you to recommend conducting a very large cohort study on a systematic sample of youths in treatment, and to follow them for a period of at least a year. This non-clinical trial longitudinal approach can address many of the currently

unanswered questions that you are here to consider.

The sample should include youths from both primary care and psychiatry. Data suggest there are about two million children a year getting an SSRI prescription so there shouldn't be too much trouble in identifying 100,000 7-17 year-olds who can be systematically assessed on outcomes at periodic times across a year.

A cohort study would allow us to document outcomes in four treatment groups, those who get better and stop meds., those who get better and continue meds., those that stop treatment because of a lack of improvement, and those that stop because of adverse events. Of course, in the case of the last example, those rare serious events can be fully described.

The rationale is simple. A signal of 1.78 from retrospective trial data is really too weak to be definitive. Randomized trials are typically too small to address rare events. And, finally, depression is, indeed, too serious a condition to unwittingly deprive those use who would benefit

from treatment simply because of lack of data that can distinguish between the SSRI at risk youth from the SSRI improvers.

Federal sponsorship is necessary to assure that the design and assessment of such a study would be adequate to address the clinical public health questions that we are really after at this point. We do need collaboration among the numerous disciplines that are involved around this question. We need the participation and support of youths and their families, and we need support from the treatment settings in which they receive care, particularly large HMOs and large mental health clinic settings.

There is no existing data source now that is adequate to address the SSRI safety and even the community effectiveness questions that you are here to discuss. Sadly, it is the suffering of young people...

[Applause]

DR. GOODMAN: Thank you very much. Is speaker 59 here? If not, will speaker 60 step

forward?

DR. ROBB: I am Dr. Adelaide Robb and, while I am the psychiatric liaison to the American Academy of Pediatrics Committee on Drugs, I am here speaking today as a child psychiatrist, practicing at Children's National Medical Center in Washington, D.C.

I wanted to give you a bit of a different perspective, that of somebody who takes care of kids who are sick every day with depression and their suffering. I first became aware of adolescent depression and suicide when I was 16 and a classmate called me at two o'clock in the morning, saying he wanted to kill himself. I spent the next two hours talking on the phone, trying to think of good reasons to stay alive, and the next two weeks combing the obituaries in the "Buffalo Evening News" seeing if anybody under the age of 20 had died. I never found out who that classmate was but it made me think a lot more about what I was going to do when I went to medical school, and I went off and did training in psychiatry.

I then went on to a fellowship at the National Institute of Mental Health where I took care of a lot of families with bipolar and major depression. Many of them were bringing in their kids who were five and six years old and suffering from depression, and none of the doctors in Washington, D.C. wanted to treat depression in a five year-old because it was dangerous, and scary, and what kind of five year-old gets depressed?

So, I ended up going back to do additional training in child psychiatry and for the last ten years as a Board certified child psychiatrist I have admitted 3000 patients to our inpatient unit at Children's, and 2000 of those kids were suffering from a mood disorder, and from those 2000, about 70 percent had major depression and went on antidepressants. While we have lost several patients from our unit to things like cancer and AIDS and other illnesses that can cause death in the under 18 year-olds, we have not had a single suicide out of those 3000 kids admitted. I want you to remember that.

I have also treated outpatients with major depression and have had about 500 kids that I have taken care of in the last ten years who have gone on antidepressants. Again, none of them has died. A hundred have gone to college; two have gone to law school and two to medical school. I don't think any of that would have been possible for them if they hadn't gotten treatment which consisted of careful monitoring, medicine when necessary, and therapy and education about side effects. I tell parents I want them to call me if they have any questions. I tell them these medicines, especially in the beginning, may lead to suicide and if they have any questions--none is too silly--I will answer email; I will answer a phone call. I am there to help the kids.

But I am a child psychiatrist and we spend more time with our patients and we want to help them. In addition, I have actually been a PI in ten of the trials that you guys are talking about. We have had 63 patients randomized in those trials. We have not had a single suicide in those trials

either, nor have we had increase in suicidal ideation...

DR. GOODMAN: Thank you very much.

Speaker 61, please.

DR. REBARBER: Hello. My name is Dr. Steve Rebarber and I am an outpatient child and adolescent psychiatrist. I have been working in Bethesda, Maryland since I completed my child psychiatry training in D.C. Children's Hospital in 1991.

I appreciate the opportunity to come before the committee to briefly share my experience concerning the safety and efficacy of SSRI usage in children with depression, and urge the committee to allow sufficient time for reliable research to be done on this crucial matter before taking any dramatic steps, such as prohibiting their usage.

In my practice I have had broad experience in working with families whose children have tried SSRIs. SSRIs are neither the panacea, as some proponents suggest, nor are they the scourge that some opponents claim. I have seen some children

who have become agitated with SSRIs, some rare instances where perhaps they have become suicidal, but I have also seen many children with beneficial and sometimes life-saving reactions in responses to SSRIs.

I have no doubt that if SSRI usage is prohibited before reliable scientific evidence demonstrates that they are dangerous that many, many children will suffer devastating untreated depression, and many of them are likely to go on to substance abuse or suicide.

I realize that the committee has heard dramatic examples by caring and sometimes devastated families; that SSRIs have had terrible effects on their children. In some cases the families may be correct in blaming the medication. In some cases, it seems to me, given the complexity of children's lives, the families may be wrong. You may be hearing from far fewer of the far greater number of families for whom SSRI treatment has been beneficial. I can imagine the pressure that the committee may be feeling hearing these

stories because at times I also find myself hearing the plea of parents, urging me to do something, anything, and sometimes the most difficult part of my work is to tell parents that I don't yet have enough information on which to act and that the best thing to do is to gather more information before acting.

I urge the committee to act, not in the heat of the moment, but only after you have the sound scientific information necessary for making good decisions. Thank you.

DR. GOODMAN: Thank you very much.

Speaker 62, please.

DR. KRATOCHVIL: Good afternoon. My name is Chris Kratochvil and I am a child and adolescent psychiatrist, from the University of Nebraska Medical Center, in Omaha, Nebraska. I receive support from pharmaceutical companies but no support for this testimony.

Thank you for providing me with this opportunity to talk to the committee today. I come to you today as a clinician that treats children

and adolescents with major depression and a clinical researcher who studies the treatment of pediatric depression. I am the principal investigator of the Nebraska side of the TADS study, which you heard Dr. March talk about earlier today.

In my role as a clinician I work closely with the children and adolescents suffering from depression, as well as their families. These youngsters experience significant distress and impairment as a result of the depression that impacts their daily life at home, school and with their friends. Sadly, as you have also heard, depression can all too often lead to suicide.

In the context of a careful clinical evaluation and close monitoring, I have seen many youths make significant gains in their battle with depression when antidepressants are included as a part of a comprehensive treatment plan. As a clinician, I see antidepressants playing a critical role in helping many of these young people.

That being said, I do agree with the

current warnings in place on the use of antidepressants. Close monitoring is good medicine and includes educating and including the families in the monitoring. In my role as a clinical researcher in the TADS study, I have had the opportunity to systematically study the safety and effectiveness of two specific treatments for adolescent depression. The results of the study, as you heard, have shown a significant importance in depression in adolescents treated with fluoxetine combined with cognitive behavioral therapy. But these findings are just the beginning.

What about other pharmacotherapies, other psychotherapies and other age groups? How do we select the best treatment for a specific child who comes to us with a unique story and a unique set of problems? Significant research remains to be done to help guide us in our efforts to help these young persons and their families.

My recommendations to the committee at this time: Warnings for careful and systematic

follow-up when antidepressants are used, particularly during the initiation, titration and discontinuation. Additionally, further studies on the safety, effectiveness and role of all antidepressants that are used in the pediatric population need to occur. Thank you for your time.

DR. GOODMAN: Thank you. Is speaker 63 here? Speaker 64?

MR. SWAN: My name is Eric Swan and I lost my brother-in-law, Tim Witsack, to SSRI suicide. His story is told on the website we have created for him at woodymatters.com. I urge each and every one of you to go there and study his story.

Albert Einstein said it best when he defined insanity, it is doing the same thing over and over and expecting a different result. I am here to simply ask that you include adults in safety action you recommend or take. I believe that if the patterns taken in the past are repeated we will be having a similar hearing sooner than later on adults on these same issues. I believe that no one here truly knows that the side effects

of SSRIs are any less dangerous to a 19 year-old than an adolescent. Adults matter too.

Every person sitting in this room can do something to help fix this tragedy. Members of the develop committee, please hear the stories of adult victims of SSRI-induced suicide and include adults in your recommendations to FDA. Please also focus on patients given antidepressants off-label who are not depressed who went on to commit suicide out of character.

Employees of the FDA--Dr. Temple, Katz, Laughren, I assume that since FDA included adults in the March warnings that you are also looking at the original safety and efficacy studies for adults from the late '80s and early '90s. If you truly are part of the jury that is still out, please decide sooner than later. Lives are in the balance. And, please investigate from other angles as well. We have some ideas on this and will follow-up with you.

To the pharmaceutical industry here, your industry is important. With that, however, comes

an awesome responsibility to your fellow Americans who take these drugs. The very minute a safety issue is discovered it should be disclosed and openly worked out. There is no excuse to ever put one penny of profit over the life of a child, husband, wife, mother, father, brother, sister or friend. Please disclose all you know on this matter so a solution can be found.

To the media here, thank you for bringing the stories into the spotlight. Please continue to write and tell the stories that need to be told.

On August 6th, 2003 I walked into a nightmare when we found my brother-in-law hanging, at age 37. Tim Witsack lived his life by the gauge of doing the right thing. If we all apply that same standard to the work before us today we have a chance to end the patterns of the past and save lives.

As an aside, Dr. Laughren, I heard you mention earlier that you have not seen the same indications in adults. Please use Woody's story and the adult stories behind me as your indication.

Thank you all for your time.

[Applause]

DR. GOODMAN: Thank you. Speaker 65,
please.

MS. WEATHERS: My name is Patricia
Weathers. I am a New York mother and president and
co-founder of ablechild.org, a national grassroots
parent organization representing over 900 members,
such as Mrs. Vicky Dunkle whose 10 year-old
daughter died in her mother's arms as a direct
result of the antidepressant prescribed her.

I am one of the lucky ones. My child is
still alive. My own story has been featured on
"Good Morning, America," "The Today Show," A&E
investigative reports and "The New York Times,"
just to name a few. I have testified before state
legislatures and twice before Congress. My
activism began after my son's school coerced me to
place him on Ritalin, a drug that caused him to
become extremely withdrawn. The school
psychologist and psychiatrist then diagnosed him
with social anxiety disorder and recommended Paxil

as a, quote, wonder drug for kids.

On Paxil, he began hearing voices in his head, drew violent pictures and even attacked me. I could no longer recognize my own son. He pleaded with me at one point, "Mom, make it stop." I finally realized that it was the Paxil that put him in a drug-induced psychosis so, naturally, I removed him from the drug. I was then charged with medical neglect when there was no proof that anything was medically wrong with him. I soon discovered social anxiety disorder, like bipolar disorder and attention deficit disorder, are not medical conditions. Parents are told that their child has a chemical imbalance or a neurobiological illness. We risked our child's life based on this fundamental lie.

I now know this is not true but, more importantly, so do you. The FDA is well aware that there are no x-rays, biopsies, blood tests or brain scans that verify these mental disorders as a disease or illness. My point is simple. The FDA should not be condoning or approving these drugs

without evidence of disease, illness or physical abnormality that would justify risking our children's lives with a harmful and potentially lethal drug.

We are gathered here today, discussing warning labels on antidepressant drugs. Why? The FDA had enough evidence 14 years ago to issue these warning labels on these drugs and you know this. Now the FDA must do more. The FDA's own mission statement says that it is responsible for helping the public get accurate science-based information. It is failing. The FDA is risking our children's lives based on nothing more than junk science. The FDA is responsible for protecting the public health, not vested interests. I remind you that children's lives are in your hands and I call...

[Applause]

DR. GOODMAN: Thank you. Speaker 66, please.

MS. STEUBING: We are Celeste and Dan Steubing. This is our daughter, Ann. On June 8th, 2003, our 18 year-old son, Matthew, graduated from

high school with his whole life ahead of him. Six weeks later Matthew jumped to his death from the Cooper River Bridge in Charleston, South Carolina. He had been taking the antidepressant Lexapro for less than ten weeks. Matthew was the youngest of our six children. He was a happy and healthy child with no prior history of depression. Matt was a normal teenage boy. He loved sports, loud music, pretty girls, cool cars and Seinfeld. He loved his family.

Matthew had plans for college. He had plans to join the Air Force ROTC program. He did not plan to die. Matthew was experiencing some difficult life lessons. He began to withdraw from his friends and his normal activities. He lost interest in school, work, his plans for college, even basketball, the thing he loved most. We sought the help of a counselor who recommended a combination of therapy and medication as the best way to help Matthew's chemical imbalance. A family practice doctor prescribed Lexapro. Prior to taking the medication, Matthew was depressed; he

was not suicidal. After beginning the Lexapro things changed. In Matt's words, "it just got worse."

He became more withdrawn. He had trouble sleeping. He was anxious and restless as though he couldn't stand to be in his own skin. He had tremors in his hands and complained several times that he felt like his heart was beating too fast. He said things like, "I feel like I'm here but I'm not here," and "it feels like my head is disconnected from my body." As for side effects, we were told there could be things like dizziness, nausea and insomnia. Never did the doctor discuss the possibility that this drug could worsen my son's depression or cause a condition called akathisia, a condition we now recognize as being present in Matthew.

As parents, we have a right to make an informed decision regarding our child's care. That right was taken from us when you elected to turn a blind eye to the evidence that had been mounting against these drugs for years. Had we known the

truth about the potential dangers of this medication we would have been better armed to protect our son. Matthew would be alive today.

I said before that we lost our son. What I truly believe is that our son was murdered by Forest Laboratories and the FDA has his blood on its hands. How many more children have to die? How many more families have to be torn apart before you do the job you were charged to do? When you err on the side of caution, it must be in favor of the innocent victims who put their faith, their trust and their lives in your hands. We demand full disclosure. You owe us...

[Applause]

DR. GOODMAN: Thank you very much. Is speaker 67 here? If not, speaker 68, Dr. Mann?

DR. MANN: My name is John Mann. I am president of the American Foundation of Suicide Prevention, which represents families who are survivors of suicide, and supports research into the prevention and causes of suicide. I am also a psychiatrist at Columbia University.

First slide, please. I would like to make several points. I know that some people have blamed the treatment and other people have blamed the condition for a series of tragic suicides that we have heard about today. The point I would like to make is that depression is a real lethal condition. You may not be able to take an x-ray but it is definitely killing a lot of people. Principally, it is untreated depression that is the major cause of suicide in the United States in both adults and children.

Next slide. When you do psychological autopsies and talk to the families who have lost their loved ones, it is clear that the principal problem in these suicides is not that they have been taking antidepressants that have killed them. The principal problem is that they have been taking nothing. Most of them have taken no antidepressants and a small minority have taken low doses of antidepressants, and very few have had adequate treatment.

Next slide, please. Do antidepressants

work in children? What is of interest is that fluoxetine, where three studies have shown efficacy, those three studies were not conducted by the pharmaceutical industry; they were conducted by academics. That probably suggests something about design and who should be doing the studies.

Next slide, please. Non-SSRIs, however, pretty unanimously do not seem to be effective.

Next slide. Now, what is remarkable is that those individuals in the United States that live in particular areas where the highest prescription rates exist for SSRIs, in those demographic groups that have received the highest prescription rates of antidepressants, in particular SSRIs, have had the biggest fall in suicide in the United States. This applies to both adults and children and it is true around the world.

Next slide. The suicide rate rose 31 percent in the United States up to 1986 or prior to SSRIs. Since 1987 there has been a steady fall in the suicide rate. Why?

Next slide. The women, for example, who have received roughly twice the prescription rate of men, have had about double the drop in suicide rates.

Next slide. Those areas of the United States that have the highest prescription rates of SSRIs, both in adults and children, have had the biggest falls in suicide rates.

Next slide. In fact, if you calculate, for every 10 percent increase in prescription rates, there are approximately almost a 1000 decreases in suicide...

DR. GOODMAN: Thank you. Speaker 69, please.

DR. BRAIN: I am Lawrence Brain, child psychiatrist practicing in Bethesda, Maryland and president of the Child and Adolescent Psychiatric Society of Greater Washington.

Until two years ago and for over 20 years I treated seriously ill children in psychiatric hospitals, and for most of that time was medical director of these large programs. Therefore, I

have been involved in the treatment of thousands of significantly ill child patients and have had an opportunity to observe the effectiveness of the SSRI antidepressant group.

I wish the committee to focus on another clinical element. Until approximately ten years ago seriously depressed children were admitted to psychiatric hospitals for assessment and treatment. Initially this required a comprehensive evaluation and the development of an extensive treatment plan. I believe it is essential that in evaluating the effectiveness and safety of the SSRI group it is imperative that this be placed within the context of an adequate and comprehensive treatment plan.

In the past, after evaluation, depressed children were prescribed antidepressant medications, frequently of the SSRI group. However, they remained hospitalized in a safe therapeutic environment where, in addition to medication, they received numerous psychotherapeutic services during which we had an opportunity to observe the impact of the medication

so that if activation and escalation of suicidal ideation or impulsive and potentially dangerous behavior occurred, this was able to be contained.

As it is known that this activation typically occurs within the first three weeks of treatment, the patients remained in the facility until we observed a therapeutic response and a pattern of safe behavior. Patients were then discharged to day treatment where intensive daily treatment was provided until safe discharge to outpatient care was achieved.

This process changed with the intrusion of managed care, such that now significantly depressed children are not hospitalized unless there is an absolute assessment of being a danger to themselves or others. Currently, it is typical for hospitalization to be brief; assessment to be superficial and if medication prescribed, the patient is discharged within 3-5 days. Managed care reviewers have focused on the utterance of suicidal thoughts as the only determinant of potential dangerousness.

As a clinician, I have argued vociferously on many occasions that, if not present, this does not represent real change and that potential danger exists. Given the known duration before clinical effectiveness can occur, it is evident the current policies are exposing children unnecessarily to the vicissitudes of their illness. It is my experience that these medications are safe and effective provided they are used within the context of a comprehensive treatment plan, and I urge this committee to look beyond the limitations of brief studies, to provide guidance and direction as to the totality of care as outlined in the practice parameters developed by the American Academy of Child and Adolescent Psychiatry.

While it is the responsibility of the treating psychiatrist to ensure as much as possible...

DR. GOODMAN: Thank you. Speaker 70, please.

MR. SHAPIRO: My name is Mark Shapiro. I am here from Duke University. I have no financial

association with any drug makers.

First of all, I know you are tired so I would like to thank you for listening to me and thank you for your thoughtful deliberations on this difficult topic. I am speaking here as a member of the public. However, I am the manager of child and adolescent psychopharmacology trials. I am also a past sufferer from major depression.

In my early 20s I sought treatment for depression and, like many sufferers, it was not until I was suicidal that I even recognized the need for treatment. In my case, paroxetine and frequent session with a psychiatrist saved my life. Although I was skeptical of psychiatry before that experience, therapy helped me to understand and overcome my illness. However, without antidepressant medication I could not have made it to this session and might not be standing before you today.

I would like to comment on the DNDP and ODS analyses and to commend those involved for their efforts to address the current issue in a

fair and scientific manner. However, it should be noted that the potential pitfalls of meta-analysis are well documented and grow as the heterogeneity of the included studies grows. As Dr. Dubitsky noted, these analyses include nine drugs plus an extended release formulation, five distinct psychiatric disorders, varied treatment durations and both in- and outpatient settings. In other words, meta-analysis in this case may be better for generating a hypothesis for a randomized, controlled trial than actually making a policy decision. Although there may be a weak signal, the results are not conclusive either for the individual drugs or in aggregate.

Why might this be? I believe that the regulatory climate in which they were conducted creates a situation that may have affected the trial teams and sites. This stems from the fact that many of the trials were aimed at gaining six-month exclusivity. From a financial perspective, the six-month marketing exclusivity is frequently worth a great deal more than a pediatric

label change, particularly in cases where a drug is already being used off-label. When planning a trial companies may, therefore, view labeling changes of secondary importance.

In my own experience, study sponsors have often set unrealistically aggressive time lines for these projects. Such pressures can lead to questionable or at least expeditious choices regarding trial design and implementation and subject recruitment. This may result in an elevated placebo response, reduced trial power and distorted safety profile.

In contrast, the publicly funded TADS study offers meaningful and clinically useful information about how best to treat adolescent depression. However, to address the risk/benefit ratio of antidepressants and detect rare but, nonetheless, significant adverse effects such as increased suicidality, a large randomized and well designed study is required. Faced with similar challenges, other areas of medicine have successfully adopted practical clinical trials.

The Child and Adolescent Psychiatry Trials Network is an NIMH-funded initiative that has recruited more than 200 child psychiatrists who are willing to conduct this research in a real-world setting in an attempt...

DR. GOODMAN: Thank you. Speaker 71, and then our last speaker will be number 73, so three more speakers.

MS. MILLING-DOWNING: On January 10th, 2004 our beautiful little girl, Candice, died by hanging four days after ingesting 100 mg of Zoloft. She was 12 years old. The autopsy report indicated that Zoloft was present in her system. We had no warning that this would happen. This was not a child who had ever been depressed or had suicidal ideation. She was a happy little girl and a friend to everyone.

She had been prescribed Zoloft for generalized anxiety disorder, by a qualified child psychiatrist, which manifested in school anxiety. We were monitoring her diet, encouraging her physical activities and had testing accommodations

put in place at school. She had the full support of a loving, caring, functional family and a nurturing school environment. Her death not only affected us but rocked our community.

How could this have happened to such a happy and loving child? When Candice died her school was closed for the day of her memorial service, a service that had to be held in the school gym in order to seat the thousand or so people who attended. How ironic, Dr. Laughren, that your family attended Candice's memorial service. Our daughters had been in class together since kindergarten. How devastating to us that your daughter will graduate from the school that they both attended for the past eight years and that Candice will never have the opportunity to do so.

Bishop Chain wrote to me following Candice's service which he helped officiate. He referred to Candice as a spiritually gifted child. How fitting that he officiated at President Reagan's memorial service on June 11th, what would

have been Candice's 13th birthday.

Candice's death was entirely avoidable, had we been given appropriate warnings and implications of the possible effects of Zoloft. It should have been our choice to make and not yours. We are not comforted by the insensitive comments of a corrupt and uncaring FDA or pharmaceutical benefactors such as Pfizer who sit in their ivory towers, passing judgments on the lives and deaths of so many innocent children. The blood of these children is on your hands. To continue to blame the victim rather than the drug is wrong. To make such blatant statements that depressed children run the risk of becoming suicidal does not fit the profile of our little girl.

We attended the public hearings held in February three weeks after Candice died. We had a very hard time learning about the specifics of this meeting as none of our calls to the FDA were ever returned. Imagine our shock as we sat and listened to person after person describing their personal pain and suffering at losing a child like us. How

could we not have known? These warnings were not an isolated case. We were never told of any danger associated. I voiced concern and was told that there was no problem.

After the hearings I again tried to contact the FDA and again no one returned my phone calls. I wrote a formal letter complaining about Pfizer and was told it would be forwarded for a reply. It is six months later and I am still waiting for my reply.

I want to know why. Why you have done these things to us, and why...

[Applause]

DR. GOODMAN: Thank you. Speaker 72.

DR. KAHN: My name is Dr. Peter Kahn. I am a Board certified child and adolescent psychiatrist, in practice for 25 years. I am one of the medical directors of the Shepherd Pratt Health System.

DR. GOODMAN: Please bring the microphone closer.

DR. KAHN: Okay. Do you want me to start

again? I am one of the medical directors of the Shepherd Pratt Health System. I am also on the clinical staff at the University of Maryland School of Medicine. Our experience at Shepherd Pratt in prescribing antidepressants to treat children and adolescents with major depressive disorders has been overall positive, particularly when combined with psychotherapy. Too often our young patients keep suicidal ideation and harmful behavior secret from their parents and, thus, parents may be unaware of how negatively severe depression influences their child's thinking and behavior.

When prescribing medication, it is good practice to carefully evaluate patients for comorbid conditions that might negatively influence their response to antidepressants, and to probe for history of suicidal and homicidal ideation and history of harm.

Informed consent includes both risk/benefits of antidepressant use and the risk/benefits of not prescribing antidepressants. As one college age patient said to me last week in

thinking back about her adolescence, "without my antidepressants I would have been dead."

Psychiatrists have known for years that during the initial phase of treatment the risk of suicide may increase. Thus, it is good practice to carefully educate patients and their parents, provide 24/7 emergency phone coverage and assess outpatients at least weekly during the first weeks of antidepressant treatment, following dose changes and during discontinuation.

As all patients do not respond to a single antidepressant, it may be necessary to switch an antidepressant ineffective in one individual to another, hopefully, more effectiveness medication. To make these decisions we need unbiased data.

I am aware that my experiences in prescribing these medications, while positive, are retrospective and anecdotal. Clearly, we need more unbiased clinical research not just on antidepressants but on all medications for children. Towards that end, I support the establishment of a mandatory clinical registry for

all clinical trials. In the meantime, this process has finally gotten the appropriate attention of physicians patients and their families.

The FDA's warning must be clear. Judicious monitoring is necessary. I believe that it is imperative that physicians be properly educated and then have the option to prescribe antidepressants for the child and adolescent patients. Thank you.

DR. GOODMAN: Our final speaker for this evening?

MS. MCGINN: Good afternoon. My name is Eileen McGinn. I have a master of public health degree and I have several members of my family who have schizophrenia, bipolar disorder, alcoholism.

The current process for the approval of drugs for the American market is scientifically flawed. Science requires reliability and validity. The trials for many psychotropic drugs are not reliable nor are they valid. Reliability in science requires that research be independently replicated in different labs by different

researchers. In the case of drug trials, the same firm producing the drugs conducts all the trials. This is an inevitable source of bias and a breach of the scientific method.

In terms of validity, there are several problems. First and most important, the samples are not representative. People in a research study are supposed to represent the general population with the illness. Most trials systematically exclude many people, especially those with severe illness. The group study does not represent the population with the illness so we cannot generalize the results.

Second, often the outcome measures are not clinical measures. There is no blood test or brain scan to mark the presence of psychiatric illness so researchers use rating scales, similar to questionnaires, to measure the severity of symptoms. On a scale of 1-20 clinicians may agree that a score under 7 demonstrates wellness, while a score over 7 shows that the person is ill. It would seem logical to use the cut score of 7 to

sort out the responders from the non-responders. This simple, direct method is not used. Instead, researchers use a mathematical formula based on a percent decrease in scores. A person may decrease from 20 to 10 but at 10 he is still quite ill. In children the percent decrease is often 20-30 percent, not 50 percent.

The dropout rates for some trials approach 50 percent, a dropout rate that biases the results and calls into question any conclusions of the trial. The information from the dropouts, like adverse events or non-response, is rarely analyzed or reported. Scientific methods exist to deal with the dropout data but they are rarely reported in the trial results.

Trials are short and small. Small size means that less common adverse events are not captured. Short duration means that delayed harmful events are not known by the end of the trial.

Fifth, trials are not valid because the double-blind...

Summary by the Committee Chair

DR. GOODMAN: Thanks to you and to everybody else who has taken out the time and poured out their hearts today. It has been a long day. I appreciate your attentiveness and your patience. I, for one, feel exhausted not only because of the late hour but because of some of the heart-rending stories that I have heard today.

On your agenda, the next item is for me to take a stab at a summary of what we heard today. We could take a break before that. I will leave it up to the committee. My preference would be just to go into it so that we can leave, hopefully, by 6:15 as originally planned.

What I would like to do then, as I see no objection, is to summarize some of what we heard today, touching on some of the salient points. I don't mean this to be a comprehensive summary by any means.

First let me begin with where we stood going into this meeting. We learned at our last meeting that there was a suicidality signal in

several of the studies that were submitted in pediatric depression, meaning that there was more suicidal behavior or ideation reported in the drug versus the placebo group--not the expected finding. It is opposite, in fact, to what you would expect since suicidality is one of the symptoms of the underlying condition. In fact, the only drug for which there was no suicidality signal at all were the trials submitted for fluoxetine.

Coupled with this, we learned that three out of the 15 studies in pediatric major depression were positive so that the majority of the studies were either failed or negative. So, in addition to adverse effects that were of concern, we had question about the overall benefit of this class of agents, raising then naturally questions about benefit/risk ratio.

Finally, we heard public testimonies last time as well, and many of those, like the ones we heard today, were passionate and plausible. When I listened to them last time, as I did today, I was looking for a pattern. Certainly they don't

necessarily fit into a pattern but several of the cases--I didn't exactly count but quite a few of the cases seemed to suggest that suicides or the suicidal behavior that was reported by the public testimony occurred relatively early after the initiation of medication.

That observation I think resonated, at least with my own clinical experience and that of many other clinicians, as something that we have known for a long time, both in children and adults, that there are some patients who are susceptible to a behavioral toxicity. We know for sure that patients with bipolar diathesis seem to be particularly prone to developing a syndrome that may represent induction of mania after the exposure to antidepressants. We also know from child psychiatrists that they are particularly alert, even before the warnings were issued--they have been alert all along as part of their training that there are some patients, some kids who are exquisitely sensitive to these medications and then they adjust the dose, the titration and the

observation accordingly.

There is also an impression, despite the lack of efficacy in most of these trials that were submitted--a strong conventional wisdom among clinicians that there are many children out there who have benefited from the use of antidepressant medications. However, the data supporting that observation is rather elusive.

We also heard from John Mann today during the public testimony that untreated depression is the major cause of suicide in youth.

Now, based upon what we heard last time, we did not conclude that there was sufficient evidence to articulate a direct link between administration of the antidepressants and the suicidal behavior. However, I think we heard enough to suggest that there was a potential risk; that we needed to do something quickly to mitigate that risk. I think what we gravitated to was a hypothesis that many of these cases, from what we heard both in the public testimony as well as what we saw in the clinical trials, can be attributed to

behavioral toxicity, particularly something that occurs early in treatment and perhaps--and this is only perhaps, it is a hypothesis--if one is more vigilant, if the prescriber, and the family members and the patients are more vigilant about monitoring for side effects such as activation, things that have been referred to as akathisia and insomnia, that those symptoms or signs may represent a precursor to the symptom we most fear, that of suicide intent.

We reconvened this time with the intention of going back to the data after a reclassification of the events and also the opportunity to look at any additional data that emerged in the interim. So, reviewing what we heard today, first we heard from Dr. Laughren who brought us up to speed and reviewed some of the history of the clinical trials, the FDA steps that have been taken, and he also reminded us of something that I wish to revisit tomorrow.

So, in part I am giving the summary as kind of a demarcation between today and tomorrow,

and also to try to set the stage for some of our discussions. I reminded us that a number of these studies were conducted under the conditions in which the sponsor could be granted six months exclusivity if they submitted a trial in pediatric depression. I think this was certainly well-meaning.

There had been an outcry previously that these drugs were being looked at off-label but there weren't sufficient studies. But the question that I think is on all our minds is whether this well-meaning action could have led to some unintended consequences. Although we haven't exactly articulated what those might be, that is certainly what comes to my mind--could the sponsors have used marginal estimates of power? If their goal was to have a positive study, not just a trial submitted but a positive outcome, would they have set the sample size higher? Would we have had a different outcome? I will turn to the statisticians tomorrow perhaps to say whether there is any evidence of that. There is though, from

what I can tell, a powerful effect size so I am not sure that that is the case. Nevertheless, I think we should talk about that more tomorrow.

One of the other speakers also mentioned the possibility that there might have been some incentives or encouragement towards rapid enrollment, and could some of that process to speed it up since the companies were going to receive six-month exclusivity--could that have led to some contamination in the data set? That is all speculation but I think we should turn to a discussion of those possibilities tomorrow.

Dr. Wysowski then turned to other sources of data that might have bearing on our discussions, including ecological studies, and mentioned work, published by Dr. Schaefer at Columbia, showing an inverse relationship between the use of antidepressants and the decrease of suicide in our youth, and pointed out that correlation does not equal causality and that there were other factors, intervening variables that could explain that pattern over time. Dr. Schaefer did have an

opportunity to rebut during the open presentations later.

What was also presented were some patient-level controlled observational studies, including a study by Jick that was published in JAMA. This was a study that compared several different antidepressants to each other with respect to suicide risk. It was pointed out that our ability to infer the suicide risk contributed by the drugs is limited since there was no unexposed group as one of the controls.

Interestingly, however, what was found significant was a relationship between time of onset of medication and reports of suicidal behavior, such that the patients who had started antidepressant medication in the past nine days showed a significantly higher rate of suicidal behavior than those who had been on antidepressants for six months or more. That finding certainly did fit with one of the hypotheses that I think has been on our minds and that led to some of the warnings in the interim, that the adverse effects

could be something that will occur early in the course of treatment.

Dr. March then presented results from the TADS study. This is in contrast to the other studies we have looked at, sponsored by NIMH. It was a trial that had four arms that included cognitive behavioral therapy. Our focus on this study though was not on the cognitive behavioral therapy so the most germane component of that study is the comparison between fluoxetine and placebo. Furthermore, those are the two studies that were conducted in a double-blind fashion.

What we learned is that on several but not all measures fluoxetine was superior to placebo. As I understand it from the presentation and reading the article, talking about benefit, fluoxetine was not significantly superior to placebo on changes in mean scores on the Children's Depression Rating Scale, although it nearly met statistical significance. With regard to suicidality, reported rates of suicidal ideation decreased in all the treatment groups.

Dr. Dubitsky gave us a summary of the data and a handout that I think will be extremely useful tomorrow as a reference, and reminded us that only three of the 15 studies in major depression were positive.

Dr. Posner, from Columbia, then reviewed the methodology and how it was implemented to reclassify the data from the clinical trials. The presentation struck me as being very rigorous and comprehensive, and it was validated by Dr. Iyasu, from the FDA who looked at a sample using the same strategy that was used by Columbia and came out with very good agreement between their results and the reclassification as ascertained by the Columbia group.

Then we moved into what I would see as the cornerstone of the data that was presented today, the new data that we had been anticipating and that I think we will continue to examine tomorrow. Dr. Hammad presented the reanalysis that was conducted by the FDA based upon the reclassification of suicidality. I will not, in the interest of time,

attempt to review all the findings, but suffice it to say it is my impression at this juncture that that reanalysis reinforced the existence of association between drug and suicidality.

He also introduced another metric to us, that of risk difference, something that I think helps translate the risk into something we can understand more at the patient level, and said that overall the risk difference was computed to be 2.3 percent, meaning that two to three out of 100 patients might incur an increase in suicidality during exposure to one of these antidepressants.

There was also a time-to-event analysis that I would like to revisit tomorrow. My understanding was that Dr. Hammad did not find any evidence for relationship between time of exposure to drug and suicidality. This is certainly disappointing to me. It certainly deviates from my working hypothesis but I think I would like to understand it a little better. I know there was a statistical discussion around the table but I had a little trouble following it so I hope that tomorrow

maybe we can revisit it so I can at least convince myself that there was no evidence base for earlier, rather than later, suicidality.

The reason that is important, of course, in my mind, in addition to a failing hypothesis that matches your own clinical experience, is that it does give you hope that by merely--not merely but by introducing increased vigilance about the early phases of treatment one can abort or prevent suicidality if, in fact, the risk is evenly spread over the course of treatment, or the strategy that we have adopted is going to be less effective.

Dr. Mosholder then compared the analysis he conducted with the subsequent analysis based on the reclassification of the data. Although there were some individual differences, for the most part the findings were in the same range.

Also, a metric that he came up with that I thought was helpful is in giving some sense of the magnitude of the suicidality signal. As he said, there would be one suicide event every 12 patient-years of drug exposure.

During the presentations by industry, one of the presenters argued not to consider the medications as a class. That is one of the questions before us tomorrow. He pointed out that we need to attend to the differences in their pharmacodynamic as well as their pharmacokinetic properties.

Another presenter pointed out the limitations of the data based upon the clinical trials with regard to understanding the risk of suicidality, indicating that these studies were not designed to test the suicidality. So, this is a post hoc analysis, and I think we did our best with the existing data set but there are certainly limitations based upon how those studies were designed and the instruments that were used. There is also no direct drug-drug comparison.

In the public hearing we once again heard passionate and moving testimony, and many cases that, again, seem quite plausible to me that in some way implicated a role of antidepressants in suicide. It was pointed out by other speakers, as

well as myself earlier today, that in the process we cannot forget about all the other individuals that we think are out there with depression who have been protected against suicide because of their treatment.

What didn't we learn today? We didn't learn much about the long-term efficacy of the antidepressant medications. I think most of the conventional wisdom and clinical lore about their effectiveness is not so much based upon the results of an acute trial but the impression of what happens over a longer period of time. The available data presented here or that I have looked through do not give us an answer to this very important question. There is an overall dearth of prospective data on the question of efficacy of antidepressants in the pediatric population.

We also don't have enough information to know whether some of the events that we might classify as a result of behavioral toxicity represent an interaction with an underlying vulnerability of that individual. What comes to

mind in particular is an individual that might be bipolar or have a bipolar diathesis. Or, maybe there are other factors that are patient specific, even the way they metabolize the drug, that may make them more vulnerable to that behavioral toxicity.

So, I think the work is cut out for us tomorrow. What I would ask you to do this evening in preparation for tomorrow is review the questions that the FDA has asked us to address. Some of those will come to a vote. I don't think we have decided which ones yet but I think some of them will come to a vote, and certainly most will involve considerable discussion.

One of the decisions I think we are going to make is in answering the over-arching question, have we done enough yet. Has it been enough to issue warnings to make everyone more vigilant about possible adverse effects that could lead to suicide or suicidality?

Is there anything anybody from the committee would like to add at this point?

DR. FOST: Just one comment that I would like to have on the record for today's meeting. Many of the families who spoke in their grief and anger, understandably, felt a need to find blame or cause of the tragedies that have befallen them, and Bob Temple, Tom Laughren and others were sometimes identified by name and, by implication, others in the FDA.

I think it needs to be said that these are all people who work very hard, with great integrity, to try to find out what the right thing to do is. I have no ties, by the way, to any companies involved in any of these issues. Bob Temple, in particular, is I think one of the most important public servants we have had in this country in the last 25 years. I would guess conservatively that he has saved tens of thousands of lives, probably hundreds of thousands, by setting very high standards for the agency to ensure that drugs that are dangerous do not get into the marketplace. So, the notion that he would be soft on dangerous drugs is just not plausible.

So, I understand the grief and the anger and the need to place blame, but I think these are not the people to assign it to.

DR. GOODMAN: Thank you. Anyone else that would like to comment before I give you a few ground rules?

[No response]

So, before adjourning, I will ask the members of the committee to take the materials with them, including the statements received from the public. Wear your name tags tomorrow. I guess that has been added because some of you haven't been doing that. We ask all the FDA presenters to be prepared with their backup slides--I am sure they will be--for tomorrow's discussion. Once again, I wish to remind the committee to refrain from speaking to each other about the meeting. If I see you together, I assume you are talking about sports or the weather.

I wish to inform the public that they can submit their written statements to the FDA through Dockets Management. The fliers on the information

desk outside the ballroom will explain the procedure.

Finally, to remind the committee and the public that the meeting is scheduled to begin promptly at 8:00 a.m. tomorrow. We plan to end at 5:00 p.m. but may or may not end early. Thank you very much for your attention.

[Whereupon, at 6:10 p.m. the proceedings were adjourned, to be resumed at 8:00 a.m., on Tuesday, September 14, 2004.]

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