DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

WITH THE PEDIATRIC SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Monday, February 2, 2004

8:00 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

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Matthew Rudorfer, M.D., Chair
Anuja M. Patel, M.P.H., Executive Secretary

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Irene E. Ortiz, M.D.
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Robert Temple, M.D.
Russell G. Katz, M.D.
Thomas Laughren, M.D.
M. Dianne Murphy, M.D.
Susan Cummins, M.D., MPH
Anne Trontell, M.D., MPH

C O N T E N T S

C O N T E N T S (Continued)

Call to Order and Opening Remarks

DR. RUDORFER: I am Dr. Matthew Rudorfer, a research psychiatrist at the National Institute of Mental Health, 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 ring, beep, or play show tunes.

I have some official language to read. All committee members and consultants have been provided with copies of background materials from the FDA and with copies of letters from the public that were received by the January 26th deadline. The background materials have been posted on the FDA web site. Copies of all these materials are available for viewing at the FDA desk outside this room.

We have a large table and a full house as you can see and a very important and exciting topic to discuss, so we would like to start with a few rules of order. FDA relies on its advisory committees to provide the best possible scientific advice available to assist us in a 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 discussions take place in an open and public forum. To that end, we request that members of the committees 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 is for this 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 and can appreciate that these comments are intended as a gentle reminder. We look forward to a productive and interesting meeting.

Just to reiterate a couple of points. This is an unusual meeting in that we have two advisory committees represented here, Psychopharmacologic Drugs and a subcommittee that is equivalent of a Pediatric Drugs Advisory

Committee chaired by Dr. Joan Chesney here to my left.

Suppose we begin by going around the table for introductions. Can we start at that end, please.

Introductions

DR. TEMPLE: I am Bob Temple. I am the Office Director for Office of Drug Evaluation I.

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

DR. LAUGHREN: Tom Laughren, Psychopharm Team Leader in the Neuropharm Division.

DR. MURPHY: Dianne Murphy, Office Director, Office of Counterterrorism and Pediatric Drug Development.

DR. CUMMINS: Susan Cummins, Medical Team Leader with the Division of Pediatric Drug Development.

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

DR. FUCHS: Susan Fuchs, member of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee.

DR. FINK: Bob Fink, pediatric

pulmonologist, Dayton, Ohio.

DR. ORTIZ: Irene Ortiz, geriatric psychiatrist, Albuquerque VA and the University of New Mexico.

DR. LESLIE: Lauren Leslie, behavioral and developmental pediatrician and health services researcher in San Diego.

DR. LEON: Andrew Leon, Professor of Biostatistics and Psychiatry at Cornell Medical College.

DR. GOODMAN: Wayne Goodman, Professor and Chairman, Department of Psychiatry at the University of Florida.

DR. PFEFFER: Cynthia Pfeffer, Adolescent Psychiatrist and Professor of Psychiatry at Weill Medical College of Cornell University.

DR. GORMAN: Rich Gorman, pediatrician in private practice in Ellicott City and member of the Pediatric Advisory Subcommittee.

DR. GLODE: Mary Glode, Professor of Pediatrics, Pediatric Infectious Disease Specialist at Children's Hospital, University of Colorado at Denver.

DR. HUDAK: Mark Hudak, neonatologist and Professor of Pediatrics, University of Florida at

Jacksonville, and member of the Pediatric Subcommittee.

DR. MALONE: Richard Malone, child psychiatrist, Drexel University, College of Medicine, and I am a member of the Psychopharm Advisory Committee.

DR. SANTANA: Victor Santana, pediatric hematologist/oncologist, St. Jude's Children's Research Hospital and University of Tennessee at Memphis, Tennessee.

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

DR. RUDORFER: Dr. Matthew Rudorfer, Acting Chief, Adult Interventions Branch, National Institute of Mental Health and Chair of the Psychopharmacologic Drugs Advisory Committee.

DR. CHESNEY: Joan Chesney, Professor of Pediatrics at the University of Tennessee in Memphis, and at St. Jude's Children Research Hospital, and the Pediatric Subcommittee.

DR. McGOUGH: Jim McGough, Associate Professor in Child and Adolescent Psychiatry at UCLA and member of the Psychopharm Drugs Advisory Committee. DR. GRADY-WELIKY: Tana Grady-Weliky, Associate

Professor of Psychiatry at the University of Rochester, School of Medicine and Dentistry, and member of the Psychopharm Advisory Committee.

DR. WANG: Philip Wang, psychiatrist and epidemiologist, Harvard Medical School.

DR. O'FALLON: Judith O'Fallon, recently retired from the Cancer Center Statistics Unit of the Mayo Clinic. I am a member of the Pediatric Subcommittee.

DR. NELSON: Robert Nelson, Pediatric Critical Care Medicine at the Children's Hospital, Philadelphia.

DR. ANDREWS: Elizabeth Andrews, pharmaco-epidemiologist at Research Triangle Institute and the University of North Carolina Centers for Educational Research and Therapeutics, and I am a consultant.

MS. GRIFFITH: Gail Griffith. I am a writer. I live in Washington. I am the Patient Representative, a parent of a child suffering from MDD, and a patient who suffers from MDD.

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

MS. BRONSTEIN: Jean Bronstein, nurse with

a background in psychiatry, retired, and I am the Consumer Representative for Psychopharm.

DR. EBERT: Steve Ebert, pharmacist and infectious diseases, Professor of Pharmacy at the University of Wisconsin/Madison, member of the Pediatric Subcommittee.

DR. DANFORD: David Danford, Professor of Pediatrics and cardiologist in the Joint Section of Pediatric Cardiology, University of Nebraska, Creighton University, member of the Pediatric Subcommittee.

DR. PINE: Daniel Pine, child psychiatrist, National Institute of Mental Health, Intramural Research Program.

DR. MALDONADO: Samuel Maldonado, Chair of the Pediatric Working Group at PhRMA and member of the Pediatric Subcommittee.

DR. MEHTA: Dilip Mehta from New York. I am the Industry Representative on the Psychopharmacologic Advisory Committee.

DR. RUDORFER: Thank you. Our session today is actually the first of two planned advisory committee meetings convened to address recent concerns about reports of suicidal ideas and behavior developing in some

children and adolescents during treatment of depression with an SSRI or similar newer 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 this meeting, many of which were quite informative as well as moving.

Much of today's meeting will be devoted to a two-part 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 medications 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 essential to our work that all voices be heard.

Major depression remains an underdiagnosed, understudied, and undertreated serious and even life-threatening mental disorder among thousands of our nation's youth, leading to considerable dysfunction, disability, and heartbreak in many families.

I am hopeful that with a fair and open-minded review of the evidence in hand and that still emerging, this advisory committee can constructively address the challenges we all share to assure that interventions for this deadly disorder are available for those young people who desperately need them and that those treatments meet high standards for both effectiveness and safety.

Now, I will ask Anuja Patel, of the FDA Center for Drug Evaluation and Research, to review some of the ground rules for the open public hearing.

MS. PATEL: Good morning. 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.

Due to the vast majority of requests by registered speakers to speak in the morning

session, we will lengthen the morning session of open public hearing and shorten the afternoon session accordingly.

To make the transitions between speakers more efficient, all speakers will be using the podium in front of the audience. Each speaker has been given their number and the order of presentation, 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 two minutes for their presentations. The three combined groups' presentations have been allotted three minutes. We will be using a timer and speakers who run over their time limit will find that the microphone is no longer working.

We apologize for the need for the strict rules, but we wanted to give as many people as possible an opportunity to participate. Thank you for your cooperation.

I will now state the Conflict of Interest Statement for the record.

Conflict of Interest Statement

The following announcement addresses the issue of conflict of interest with respect to this

meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All Special Government Employees have been screened for their financial interests as they may apply to the general topics at hand. To determine if any conflict of interest existed, the Agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has granted general matter waivers to the Special Government Employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30

of the Parklawn Building.

Because general topics impact so many entities, it is not prudent to recite all potential conflict of interests as they apply to each member and 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.

In addition, FDA would also like to note that one member of the Psychopharmacologic Drugs Advisory Committee, Andrew Leon, and an FDA speaker, David Shaffer, were members of the American College of Neuropsychopharmacology ACMP Task Force that has recently issued a preliminary report on SSRIs and suicidal behavior in youth.

This task force reviewed published and unpublished data from controlled trials in youth,

data from epidemiological studies, and data from autopsy studies.

Based on their preliminary review, they concluded that the available evidence does not suggest that SSRIs increase the risk of suicidal behavior in youth and with depression, however, they acknowledge that their conclusions are preliminary and they recommend that the pertinent data available to pharmaceutical companies and FDA be rapidly made available to ACMP and others, so that they may be independently evaluated.

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

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

Thank you.

DR. RUDORFER: Thank you.

To put the meeting in context, I would now like to turn to Dr. Russell Katz, Director of the

FDA Division of Neuropharmacologic Drug Products, who will provide a brief overview of the background leading to today's deliberations and the likely next steps.

Overview of Issues

DR. KATZ: Thank you, Dr. Rudorfer, and good morning. I would like to also add my welcome to all of you here for this joint meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee.

In particular, I would like to welcome our invited guests who are not members of the committee, but who have graciously agreed to help us grapple with the difficult problem that we bring to you today.

As you know, we are here to discuss with you an issue of enormous importance and interest, namely, the relationship, if any, between treatment of pediatric patients with antidepressant drugs and suicidal behavior.

This has been an issue of extreme complexity and we are here both to inform you of our efforts to date to examine the question and our plans for further examination of the data, as well

as to ask for your comments and advice about these plans.

We come to you at this time for several reasons. Under current law, the Agency is required to present postmarketing adverse event data to the Pediatric Subcommittee for the first year of marketing for those drugs granted market exclusivity under the pediatric exclusivity provisions of the Act.

At this time, therefore, the Agency is meeting its obligation under the law to present this data for Paxil and Celexa. More importantly, however, given the intense interest in the Agency's efforts to examine the question of antidepressant use in pediatric patients and suicidal behavior, we concluded that it would be appropriate to inform you about these latter efforts at this time, as well.

As you know, we most recently became aware of a potential signal of concern during the review of the controlled trial data for Paxil. In the course of that review, we became aware that the sponsor had categorized some events that could have represented suicidal behavior or suicidal thinking using a description that seemed somewhat

inappropriate.

We asked them to clarify their presentation of the data, and their response raised a concern that such a signal existed. Based on these concerns, the Agency issued a public statement in June of last year recommending that this drug not be used to treat pediatric patients with depression, but based on the Paxil data and the problem of idiosyncratic characterization of events of potential concern identified in that application, we asked the sponsors of the other antidepressant drugs to search their controlled trial databases in a more formal way to identify potential cases of suicidal behavior.

Our review of their responses resulted in a second Agency statement that alerted practitioners to a similar potential signal for other drugs in this class, and recommended that these drugs be used with caution in these patients.

Our continued review of these data, however, convinced us that the data submitted from the various companies involved may not have been collected or reported to us in a form that would permit us to adequately evaluate the potential relationship between these drugs and suicidal

behavior.

Indeed, we became convinced that with the data before us at that time, we could not adequately answer the question of whether there was such a relationship for any specific drug or whether there were any differences between drugs.

You will hear in greater detail later the deficiencies with these data as previously submitted and why we have therefore continued to work with the sponsors involved to submit to us data in the form that will permit us to adequately and comprehensively address the critical question before us.

It is because we are not yet able to do this that we could not present definitive analyses at this time. It is absolutely critical, in our view, that we make every effort to provide the best answer possible to this question. The wrong answer in either direction, prematurely arrived at, could have profound negative consequences for the public health.

However, we now believe that we have obtained from the sponsors all of the relevant data collected during the trials, presented in a standardized manner that will permit us to perform

analyses that will give us the best possible chance to address this question.

Before we embark upon these analyses, however, we are taking this opportunity to inform you and the public about the problems we have encountered in trying to answer this question, how we have attempted to address those problems, and to describe our plans for analyzing the data.

We are primarily interested in your views about our proposed approaches to the data and are eager to hear if you believe we should request additional data from the sponsors and whether you believe we should perform additional analyses beyond those we will describe to you later today.

In our efforts to further evaluate the data, we have enlisted the help of outside experts with particular expertise in the issue of pediatric depression and suicide, and in particular, we have enlisted a group from Columbia University, who will objectively reclassify potential cases of suicidality from all the drug development programs, so that we may move forward with our more definitive analyses. You will hear about this from Dr. Kelly Posner in more detail later.

We will also present the postmarketing

adverse event data for the drugs in question, but as you will hear, and for the reasons you will hear, we do not believe that this data can reasonably inform our judgment about any relationship between these drugs and suicidal behavior.

It is the controlled trial data that we believe is best able to help us provide an adequate answer to this question, but as you have heard, and you will hear throughout today's presentations, we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully.

It should be noted that this view of the data has not been a unanimous one among Agency staff. Some within the Agency have examined the data and concluded that the data, as currently submitted, do permit definitive analyses and that these analyses support the conclusion that this class of drugs is associated with a risk of suicidal behavior in pediatric patients.

However, the staff of the Neuropharmacological Drugs Division has examined the individual cases reported by the sponsors that allegedly represent suicidal behavior, and we are

convinced that the categorization of these events, as performed idiosyncratically by the individual sponsors, is not entirely reliable.

Examples of these categorizations will be presented to you later today, and we are confident that this conclusion will become clear to you.

Further, the pattern of these potential signals is also difficult to understand, for example, arising from one single study out of several similarly size studies for a given drug. This unusual pattern gives us further reason to more closely examine the data.

We are, of course, aware that there is great concern among the families of children and adolescents with depression about whether or not these drugs can be used safely. For them, I am sure answering this question has already taken too long.

We, too, are frustrated with the time it has taken to come to a definitive answer to this question. Indeed, we had originally hoped to be able to present to you today more definitive analyses and conclusions, however, as I have described, closer examination of the data at each step of our analyses convinced us that it would be

premature to arrive at a conclusion without additional work, the plans for which we will present to you later today.

We are firmly convinced that we serve no one's goals or needs by rushing to a judgment that has not considered all reasonable sides to the question. We are committed to, and fully expect to, come back to the committee in late summer with the results of the analyses we will discuss today.

At that time, we expect to be able to present the best possible answer that the current data can provide to the question of whether or not any of these drugs, all of these drugs, or none of these drugs increase the risk of suicidality in pediatric patients.

With that as an introduction, I will turn it back to Dr. Rudorfer.

DR. RUDORFER: Thank you, Dr. Katz.

We will now hear from Dr. Dianne Murphy, Director of FDA's Office of Counterterrorism and Drug Development, who will speak about the Pediatric Drug Development Program.

Pediatric Drug Development Program

DR. MURPHY: Welcome. Thank you very much for taking time to make this endeavor an important

part of your scientific and academic life. We hold your advice very important and look very much forward to your discussion.

[Slide.]

I am going to ask you to step back for a moment. My comments are not going to focus directly on the topic of depression or the therapies for that. The goal of my presentation is to provide you some background on pediatric drug development because I think you will see that is the process that has brought us some of this data and we need to make sure everybody understands how this evolved.

It is also an example of watch out what you ask for because we now finally, in the last few years, are beginning to get the kind of information that we wanted for a long time to be able to understand how we could better treat children with the therapies that we have.

Of course, we will be reviewing FDA's specific responsibilities during these activities.

[Slide.]

Acronyms. Throughout the day, you will be hearing these potentially. You have FDAMA. That is the Food and Drug Administration Modernization

Act. This is important because this is the legislative initiative that provided the Agency with the ability to provide an incentive that has been a tremendous -- I call it the engine that has really been driving this process for being able to develop information on how to use these products in children.

Remember, before this, most children, if it was not a pediatric disease like otitis media, these products were not being studied in children, and each child was an n of 1 in which we did not learn anything, and that was not an approach we thought useful. That's FDAMA.

Best Pharmaceuticals for Children, renewal of the legislation basically expanding not only the legislative mandate to look at products that have patents remaining where the incentive will work, but a process which mandates FDA and NIH to work together to develop the same sort of data for products that are older and would not benefit because that was an area that was not being developed.

The way that is done is important to understand because it is done via what is called the written request in which FDA -- and this is

distinctive from most other drug development -- FDA determines what the public health need is and issues a written request defining the studies that they think need to be done, so that we can better understand how to dose children or if it works in children, or what are the distinctive adverse events that occur in children, because as we all know, the variability between a preemie and a fullback is tremendous, and we have that in children, and evolving developmental processes.

PREA was the recently legislation that in essence said yes, FDA, you have the authority to require that if a sponsor submits an application for a disease -- I am going to call it indication throughout the rest of this -- for an indication that exists in children for which this product will likely be used, you are to study it in children also. You are not just to market it for adults.

This proposed pediatric study is a process that applies to the written request, which if industry is interested in studying a product, they can submit it to FDA, and we can look at that.

That is important because what you need to understand is that this whole exclusivity process is voluntary, so it is up to the sponsor whether

they want to participate or not. This process is not.

[Slide.]

The interesting thing about pediatric drug development is that many of the legislation that has developed has developed because of misfortunes and severe tragedies that have happened in children, and yet every time new legislation would be mandated, it would apply to adults, and not to children.

Many of you have heard this talk, so I am just quickly putting these up here to remind everybody.

[Slide.]

We have for decades been trying to have products that are being used in children studied, and this is just to give you really the benchmarks, starting in the '70s, in which the Academy of Pediatrics issued a statement saying we ought to be studying these products we are using in children, why do we think that children are going to be less variable than adults. All reason and information would say they are going to be more variable, and we need to.

The Agency actually issued a statement

saying we think children should be studied, and we would like you to conduct two adequate trials also for children, to evaluate the safety and efficacy in children.

What happened was not much, and as everybody has heard, the majority of products were not studied in children until really here.

In 1994, FDA published a regulation which basically said we understand that there are times in which you can extrapolate efficacy only. If the disease is similar enough, the pathophysiology, and the expected response have been defined well enough, that you might be able to extrapolate efficacy, hoping to incentivize in a way the interest in developing information and conducting trials in children. Safety and dose finding were still trials that you would need to conduct in children.

Again, minimal response. So, bottom line, the first incentive program was the major push. The FDA published a regulation, which was then enjoined by a court saying we didn't have the authority to require it, so Congress came back in 2003 and said, yes, FDA, you do.

So, right now here are the two things that

are driving pediatric drug development, so that we can better understand how to use these products in children.

[Slide.]

It has been a tremendous response. This is just simulated to exclusivity. We have received over 300 proposals. You could have counted the number of products developed on your fingers and toes before this that weren't primarily pediatric diseases.

We have issued over 283 written requests where FDA has determined what needs to be developed in the way of studies, and has issued sponsors' requests. This is updated from your handout, by the way, these numbers are slightly different because we updated it for the slides.

The important thing about exclusivity determinations, it means that over 100 products have been brought in with the studies that have been requested, and you are discussing some of those today, with the type of information that helps us better understand.

We have an entire one-hour talk on some of the very significant findings that have been developed, that we have discovered in this process.

Today is another example of we are finding out what more information we need if we are going to properly use these products.

I only put these numbers up because once exclusivity is granted, you can see some were denied, even though it may have been denied, it still could have been approved. It just meant that they didn't meet the terms completely that we asked for.

There are now 63 new labels, so products that are being used in children, there are now 63 of them that have new labels, new important dosing and safety information in them including information that says they don't work in kids with these studies.

[Slide.]

These are the products that were mandated, not the individual products, but the process that was mandated by the Best Pharmaceuticals, the BPCA. I point this out because one of these, our set of data you are going to hear today is the result of BPCA saying FDA, one year after a product has been granted exclusivity, you will follow all of the adverse events that are reported for that product, and you will present it to the Pediatric Advisory

Subcommittee that will soon be a full committee, and that this is an area which BPCA wanted to make sure that additional attention was paid to the process of reviewing what happens.

The thing to understand about that is that a product could be approved way back 10 years ago, and it could then be studied later in its life for pediatrics, so that the one-year post-safety assessment is at varying stages of these different products, they are not all the same, and the Division has tried to standardize that for you today in looking at the safety assessments at more standardized times because each product is coming in at a different time.

[Slide.]

The only other thing I really wanted to point out to everybody, to bring us back to the topic at hand today, is that this drug development process that has begun to occur really since 1998, five, six years, has brought forth not only new information that challenges some of our preconceived thoughts about safety and how children respond, it has been a tremendous bounty of information because children are finally getting studied.

We are beginning to have to figure out how do you measure that endpoint in children. That type of science was not being developed. We are also dealing with the ethical issues that come up, that are different for kids who cannot consent, so this is a whole different process, and I just want to make sure that you all knew that we have brought various ethical issues to the committees, and we have a wonderful cadre of ethicists who are Special Government Employees, who work with the Pediatric Advisory Subcommittee, who attended these meetings and advised us on such topics as should children be enrolled in trials in which they are not going to receive direct benefit, should children be enrolled in placebo-controlled trials, should children who are especially vulnerable -- most people think of children as a vulnerable population, but in truth, there are subsets, subpopulations that are even more vulnerable, and this was a population of children with CP, how do you develop a product in that population. These are difficult issues.

[Slide.]

This is, quickly, and I am not going to go over every one of these, but to give you an idea of the broad array of products that are being

developed in children and the questions that have come up.

Actually, Neuropharm, the Division of Neuropharmacological Drug Products, has brought a number of these issues to the committee, including how do we develop pediatric products -- NIMH also participated in this meeting -- from such issues as -- also, this was another Neuropharm Advisory Committee meeting with the Pediatric Committee -- chronic hepatitis, reflux in infants, HIV drugs, how do you approach the whole field of developing a product that may be put in almost every newborn who develops hyperbilirubinemia, tremendous issues, long term study issues.

Again, more, what do you do about some of these products. Most of our products' safety databases are collected on weeks, usually, maybe months, but certainly not years, what do you do with products that we know can potentially suppress your adrenal axis or products that we know can be oncogenic, but have to be used.

[Slide.]

Some of the ongoing lessons that we have learned during this process -- which we think is a positive process, it is much better than ignorance

-- it is that children are even more variable than we really thought.

We are finding, for certain classes, you may have to have dosing based on clearance in three different age groups that is very different, and it is not just the preemies, it is not just the neonates. It is actually children of all ages, from adolescence, preschool, et cetera.

Adverse reactions that are pediatric-specific are being defined. Clearly, growth is one everybody would expect would be defined, that we are finding that products, and Prozac was an example of that, are having an effect on growth. But there are many other products that we are beginning to look now, and beginning to look in a more systematic way, that we are finding that they do have an effect on growth.

But there are other issues - school behavior problem, other products where aggression and behavioral changes have been seen. So, this is a very important area that we are trying to look at as we develop these products.

Trial designs are being modified as we learn, and I think that is probably why we are here today. We are learning. We take the best

knowledge we have, we get the best experts, we issue the type of study we think will be the best, and sometimes something happens in the meantime, more data becomes available, we need to update that, or what we thought we were going to be able to evaluate didn't turn out to be as valuable as something else in the study.

We learn from these studies. Remember, there is a huge amount of science that has not been developed, that is now being developed for children, and, as I said, the ethical issues have to be reassessed from the pediatric perspective.

[Slide.]

I just got the signal that my time is up, so I will leave you with the general principles that we have developed from the International Conference on Harmonization on how one should approach the whole process involving children in trials, and this is a group that involves European nations, Japan and the United States, and I think that it is a shared responsibility. That is why we thank you for being here today. Thank you.

[Slide.]

This is where you can go onto the web. There is a tremendous amount of information posted

on pediatric numbers, stats, and studies.

Thank you.

DR. RUDORFER: Thank you, Dr. Murphy.

As Dr. Katz pointed out, an important way to put issues of drug safety in context is to understand more about the disorder being treated, so we are pleased to have a couple of experts in the area of depression in young people to address us on the latest understanding of this complicated disorder.

First, from Weill Medical College of Cornell University, we are pleased to have Dr. Cynthia Pfeffer, who will address Pediatric Depression and its Treatment.

Pediatric Depression and its Treatment

DR. PFEFFER: I want especially to provide an overview of pediatric depression, which in fact is a major mental health problem in the United States and probably worldwide.

[Slide.]

There is a tremendous need to develop treatments for these problems and also prevention efforts primarily because these disorders, particularly major depressive disorder, dysthymic disorder, and for that matter, other mood disorders

are very prevalent and recurrent, they have high rates of morbidity and comorbidity, they are often accompanied by very poor psychosocial outcomes for children and adolescents. They are associated with high risk for suicide and also for substance abuse.

[Slide.]

There are a number of problems which I will touch on in my talk in reducing major depressive disorder in children and adolescents, and these include problems in actually diagnosing children and adolescents. There are developmental variations that need to be considered.

There is a complexity of factors that are associated with the clinical course of children who have such mood disorders and a need for specificity of treatments.

[Slide.]

Epidemiologically, we know that the prevalence of major depressive disorder in children who are prepubertal is approximately 2 percent, and it increases in adolescents to a rate of between 4 and approximately 8 percent.

The male-to-female ratio for younger people, prepubertal children, is about equal, but in adolescents, females outnumber males who have

major depression 2 to 1.

By the time a youngster reaches the age of 18, there is approximately a 20 percent prevalence rate of those who are depressed, who show major depression, and since prior to World War II, each successive generation seems to have a higher risk for major depressive disorder.

If we look at dysthymia, the prevalence rate is somewhat lower although something to be concerned about, with the highest rate of approximately 2 percent in children, and in adolescents, ranging from almost 2 to 8 percent. Dysthymia is a condition that is often under-recognized.

[Slide.]

There are a number of complexities in diagnosing major depression in children and adolescents. These include an overlap of a variety of the mood symptoms, and in addition, the symptoms often overlap with comorbid disorders.

There are developmental variations in the symptoms and how they are manifest. There are etiological variations of mood disorders that do involve gene and environmental interactions, and there is a question of whether some of these issues

are actually spectrum related or categorical disorders.

Finally, the effects of medical conditions on the prevalence and incidence of major depression and other mood disorders needs to be considered.

[Slide.]

The DSM criteria for major depressive disorder involves a pervasive change in mood, which is manifest for at least two weeks by either being depressed or irritable or having a loss of interest in pleasure.

There are other symptoms that are necessary in making the diagnosis, that include changes in appetite, weight, sleep, activity levels, concentration, and sometimes indecisiveness, changes in energy level, self-esteem, including worthlessness and excessive guilt, changes in motivation, and recurrent suicidal ideation and acts.

These symptoms should represent a change from the child or adolescent's previous functioning and produce impairment. These symptoms are not attributable to substance abuse, medications, or other psychiatric illness, bereavement, and medical illness.

[Slide.]

There are developmental variations which have been identified. For example, in children, they tend to have a greater number of symptoms of anxiety, including phobias and separation anxiety, more somatic complaints, and if they do occur, auditory hallucinations.

They express irritability with temper tantrums and behavioral problems, and the children tend to have fewer delusions and fewer serious suicide attempts, however, adolescents tend to show more sleep and appetite disturbances, if they occur, delusional thinking, greater degrees of suicidal ideation and acts, and greater impairment of functioning.

Compared to adults, however, adolescents have more behavioral problems and fewer neurovegetative symptoms.

[Slide.]

The diagnostic criteria for dysthymia involves a persistent long-term change in mood which is less intense, but more chronic than major depressive disorder. These children in adolescence have extensive psychosocial impairment.

The depressed mood or irritability occurs

most of the time during the day for at least one year, and there are at least two other symptoms that are associated in making the diagnosis. These include again changes in appetite, sleep, lowered self-esteem, problems with concentration, problems with decisionmaking, changes in energy level, and a sense of hopelessness.

People who have no symptoms for more than two months at a time, and do not have a major depressive disorder in the first year of disturbance, may be considered to have dysthymic disorder, and these are also youngsters who never had manic or hypomanic episodes.

[Slide.]

Other symptoms tend to go along with dysthymic disorder. These include feelings of being unloved, angry outbursts, self-depreciation, somatic complaints, anxiety, and often disobedience.

[Slide.]

There are a variety of variations that the symptoms of major depressive disorder involve. For example, psychotic depression, bipolar depressive states, atypical depression, seasonal affective disorder, subclinical or subsyndromal depression,

and treatment-resistant depression.

[Slide.]

I will touch on some of these variants now more specifically. Psychotic depression includes major depressive disorder symptoms that are associated with mood-congruent or incongruent hallucinations and/or delusions, and unlike adolescents, children tend to manifest more hallucinations.

Psychotic depression occurs in up to about 30 percent of those youngsters with major depressive disorder. It is associated with more severe depression, greater long-term morbidity, resistance to antidepressant monotherapy, a low placebo response, increased risk for bipolar disorder, and a family history of bipolar and psychotic depression.

[Slide.]

Bipolar depression presents similarly to unipolar depressive disorder. The risks for bipolar disorder is indicated by psychosis, psychomotor retardation, psychopharmacologically induced hypomania, and a family history of bipolar disorder.

Adolescents are likely to have rapid

cycling or mixed episodes, and an increased suicide risk and difficulty in treatment compliance. There is a need to rule out bipolar II disorder, which is more prevalent in adolescents and often overlooked and misdiagnosed.

[Slide.]

Atypical depression has not yet been studied in children and adolescents, and it usually has an onset in adolescence, and it is manifest by increased lethargy, appetite and weight changes, and reactivity to rejection.

There is hypersomnia and often carbohydrate craving. In adults, it tends to be genetically distinct from major depressive disorder.

[Slide.]

Seasonal affective disorder usually has its onset in adolescence in those living in regions with distinct seasons. The symptoms are similar to those of atypical depression, but are more episodic. They do not include increase reactivity to rejection.

This disorder should be differentiated from depression precipitated by school problems and school stress since it usually overlaps with the

school calendar.

[Slide.]

Treatment-resistant depression is not clearly defined for children and adolescents. It occurs in approximately 6 to 10 percent of depressed children and adolescents who suffer chronic depression.

In adults, treatment resistance is defined as patients who have had at least two trials with two different classes of antidepressants which are administered at approximately similar doses for at least six weeks each.

[Slide.]

Another issue that needs to be thought about in understanding the mood disorders and especially major depression is that they may be affected by the complexity of comorbid disorders which may affect the recognition and diagnosis of major depression, the types and efficacy of treatments, and various psychosocial outcomes.

[Slide.]

Comorbidity tends to be present in 40 to 90 percent of youth with major depression. Two or more comorbid disorders tend to be present in approximately 20 to 50 percent of youth with major

depression.

Comorbidity in youth with major depression involves dysthymia or anxiety disorders with a rate of approximately 30 to 80 percent, disruptive disorders with a rate of approximately 10 to 80 percent, and substance abuse disorders with a rate of approximately 20 to 30 percent.

Major depressive onset is usually after the comorbid disorders except for substance abuse in which major depression tends to antedate substance abuse disorders. Conduct problems may be a complication of major depression and may persist after the major depressive episode resolves.

Children may manifest separation anxiety comorbid disorders, while adolescents may tend to manifest social phobia, generalized anxiety disorder, conduct disorder, and substance abuse.

[Slide.]

In terms of differential diagnosis of major depressive disorder, the complexities tend to be with an overlap of symptoms with other nonaffective disorders, such as anxiety states, learning problems, disruptive disorders, and personality disorders and eating disorders.

The overlapping symptoms may include poor

self-esteem, demoralization, poor concentration, irritability, dysphoria, poor sleep, appetite problems, suicidal thoughts, and being overwhelmed.

[Slide.]

One should consider in the differential diagnosis the nonaffective psychiatric disorders, which include anxiety disorders especially separation anxiety, generalized anxiety, and other anxiety states, disruptive and attention deficit disorders, learning problems, substance abuse, eating disorders especially anorexia nervosa, personality disorders, and premenstrual dysphoric disorder.

[Slide.]

Another disorder that needs to be considered and understood is an adjustment disorder with depressed mood. This includes a mood change and impairment of functioning within about three months of a stressor, and this does not meet the criteria for major depressive disorder.

Adjustment disorder with depressed mood tends to be self-limited, there are less mood disturbances associated with it, fewer symptoms, and no relapse, which is an important issue.

Consider other disorders if the symptoms

last more than six months or meet the criteria for other disorders, for example, dysthymia.

[Slide.]

General medical conditions may be another complexity in understanding and diagnosing major depressive disorder. These medical conditions may be accompanied by symptoms of depression. They may also impact the course of major depressive disorder.

Major depression can be diagnosed if the depressive symptoms preceded or are not solely due to the medical condition or to medications used to treat the medical condition.

The incidence of major depression tends to be higher in certain medical illnesses. Chronic illness may affect sleep, appetite, and energy. Guilt, worthlessness, hopelessness, and suicidal ideation are usually not attributed to the medical illness, but do suggest the symptoms of major depressive disorder.

Medical conditions that are often associated with major depressive disorder include cancer, hypothyroidism, lupus erythematosus, AIDS, anemia, diabetes, and epilepsy.

Chronic fatigue syndrome is another

disorder that needs to be considered, but its symptoms are similar to major depression, but there tends to be more somatic symptoms, less mood, cognitive, and social symptoms.

Medication-induced symptoms involve those induced by stimulants, neuroleptics, cortical steroids, and contraceptives.

[Slide.]

Bereavement is another issue that needs to be considered because there are a similarity of symptoms with major depressive disorder. The diagnosis of major depression can be made if the bereaved child or adolescent has moderate or severe functional impairment, psychosis, suicidal thoughts or acts, and a prolonged course.

Following bereavement, a predisposition to major depression may be related to prior major depression or a family history of major depressive disorder. In general, uncomplicated bereavement often remits in 6 to 12 months after a death.

[Slide.]

I would like to focus now on some issues of clinical course for major depressive disorder. The median duration for clinically referred children and adolescents tends to be 7 to 9 months,

and in community samples it has been reported to be shorter, approximately 1 to 2 months.

Predictors of a longer course or duration involve the severity of depression, the degree of comorbidity, the presence of negative life events, parental psychiatric disorders, and poor social functioning.

Remission of major depression is defined as a period of 2 weeks to 2 months in which there is one clinically significant symptom only. Ninety percent of children and adolescents with major depression remit in 1 to 2 years after the onset of the major depressive episode.

[Slide.]

Approximately 6 to 10 percent of those with major depression have a protracted course. A relapse is an episode of major depression during the period of remission, and predictors of relapse include the natural course of major depression, namely, the nature of the way it manifests, lack of compliance with interventions, negative life events, rapid decrease, or discontinuation of therapy.

Forty to 60 percent of youth with major depression tend to have a relapse after successful

acute therapy, it's a high rate. This indicates the need for continuous treatment.

[Slide.]

Recurrences occur also, and this is an emergence of major depressive symptoms during a period of recovery, which is an asymptomatic period of more than two months. Clinical and non-clinical samples have a probability of recurrence of approximately 20 to 60 percent within one or two years after recovery, and 70 percent after five years of recovery. So, this is a chronic disorder.

Predictors of recurrence include the earlier age of onset of major depressive symptoms, increased number of prior episodes of major depression, the severity of an initial episode, the presence of psychosis, the degree of psychosocial stressors, the presence of dysthymia and other comorbidities, and the lack of compliance with therapy.

[Slide.]

In terms of the clinical course, children with major depression, 20 to 40 percent develop bipolar disorder in 5 years after the onset of major depressive disorder, and predictors for the bipolar disorder onset would be early onset of

major depression, the presence of psychomotor retardation, psychosis, a family history of psychotic depression, a heavy family loading for mood disorders, and psychopharmacologically-induced hypomania.

[Slide.]

Other factors that affect the clinical course of major depression is that the risk for depression increases 2- to 4-fold after puberty, a very important developmental issue, and that various genetic, as well as environmental, factors influence the pathogenesis of major depression.

For example, shared family environmental or not extra-environmental non-shared issues tend to be very important in affecting the course, as well as those youngsters who have high genetic risk are more sensitive to various environmental stressors.

Children with depressed parents are three times more likely to have a lifetime episode of a major depressive disorder.

[Slide.]

The prevalence of children's first-degree relatives when children have major depression tends to be 30 to 50 percent. In addition, parents also

may have major depression and anxiety disorders, substance abuse, as well as personality disorders.

[Slide.]

The clinical course of children with major depression is also associated with poor school success, low parental satisfaction with the child, a very important parent-child problem, learning problems, other psychiatric disorders that interfere with the child's learning.

The course may also be affected by various personality traits, such as the child being judgmental, having angry outbursts frequently, poor self-esteem, and dependency. Cognitive styles and temperament, such as negative attributional styles, may affect the course of major depressive disorder.

Early adverse experiences, such as parental separation or death, may affect the course. Recent adverse events may affect the course, family conflicts, neglect, and abuse, biological factors, such as inability to regulate emotions, and/or distress.

[Slide.]

The relation of dysthymia in major depression is quite important because dysthymia is associated with an increased risk for major

depressive disorder. Seventy percent of youth with dysthymia tend to have major depressive disorders.

Dysthymia has a mean episode of approximately 3 to 4 years for both clinical and non-clinical in community samples. A first major depressive episode usually occurs 2 to 3 years after the onset of dysthymia, which may be considered a gateway to the developing recurrent major depressive disorder.

The risk for dysthymia is associated with chaotic families, high family loading for mood disorders particularly dysthymia.

[Slide.]

Another important issue in terms of course of children with major depression is that they are at very high risk for suicidal tendencies. There are a few studies, some of which I will highlight, one by Marika Kovacs, which is a 9-year follow-up of prepubertal children. She had various groups that she studied.

At the time of follow-up, children who had major depression had a 74 percent rate of suicidal thinking and a 28 percent rate of suicide attempts. Those who initially had dysthymia, also had a 78 percent rate of suicidal thinking, and close to 20

percent rate of suicide attempts.

Compared to children with adjustment disorder or other types of psychiatric disorders that are not mood disorders, these rates for children with mood disorders, namely, major depression and dysthymia, are significantly greater for suicidal thinking and suicidal attempts.

Our own follow-up study of 6 to 8 years for prepubertal inpatients indicated that there is a 5 times risk for suicide attempt when the prepubertal children reach adolescence if they had a prepubertal mood disorder.

[Slide.]

A community sample study indicated that the 1-year incidence of suicide attempts in adolescence was associated with a 12 to 15 times greater risk if the youngster had major depressive disorder.

[Slide.]

There are various concerns about treating major depressive disorder. The treatment research, first of all, is relatively sparse in children and adolescents. There are varied opinions about whether psychotherapy or pharmacotherapy, or a combination should be the first-line treatment.

The initial acute treatment often depends on the severity of symptoms of major depression, the number of prior episodes, the chronicity, the age, contextual issues in the family, school, and other environmental features, the degree of negative life events, the compliance with treatment, prior treatment responses, and the motivation for treatment.

[Slide.]

Some general principles that clinicians have thought about is that psychotherapy may be considered for the more mild or moderate major depressive symptoms. Empirical effect of psychotherapies that we now know of include cognitive behavioral therapy and ITP, interpersonal psychotherapy.

Antidepressants may be used for youngsters who have symptoms of major depressive disorder, nonrapid cycling by polar states, psychotic depression, depression with severe symptoms that prevent effective psychotherapy or that fail to respond to psychotherapy.

Also, due to the psychosocial context, frequently pharmacotherapy alone may not be effective.

[Slide.]

The treatment of children with major depression, there are very few studies of acute treatment using medication. There are few pharmacokinetic or dose-range studies with children and adolescents.

The SSRIs are thought to perhaps induce mania, hypomania, behavioral activation, which might include impulsive behavior, silly or agitated daring, and there are no long-term studies for the treatment of major depression.

I am going to actually conclude, and not go over some of these studies, which you will hear about I am sure today, and to say again that major depressive disorder in children and adolescents is complex and heterogeneous regarding its clinical course, comorbidities, predictors, of course, need for specificity of treatment, and the developmental variations.

It is a chronic condition that recurs with serious morbidity including suicidal tendencies. There are few treatment studies, which limit our knowledge of the methods to reduce these symptoms and the morbidities.

There is a need to clarify the indications

for pharmacotherapy, as well as psychotherapy whether alone or used in combination, as well as that to maintain youngsters who have already exhibited major depressive disorder.

Thank you.

DR. RUDORFER: Thank you, Dr. Pfeffer.

We will now turn to Dr. David Shaffer of Columbia University who will speak on the topic of Suicide and Related Problems in Adolescents.

Suicide and Related Problems in Adolescents

DR. SHAFFER: Good morning.

[Slide.]

I am going to review the epidemiology of youth suicide and also some of its phenomenology as it may be relevant to the discussion that you are going to be having for the rest of the day. It is a topic that I have been involved in for a number of years, and I hope that it is helpful.

[Slide.]

In the United States, in 2001, the last year for which we have statistics of this kind, about 1,600 15- to 19-year-olds committed suicide. You will see that that is the third leading cause of death in the United States, and in most countries, it is the second leading cause of death,

but in the United States and a few other countries, homicide comes between that.

You can also see that suicide accounted for more deaths, over twice as many deaths as from cancer, in fact, more deaths than all of the other major physical conditions combined.

[Slide.]

The methods by which children commit suicide are, by and large, very similar to those -- with children, young people -- are very similar to those which are used by adults. The main difference is that hanging is somewhat more common in young people, and the figures that I have got here on the left are the 5- to 19-year-olds, on the right, over the rest of the population.

You will see a few other things of interest. Ingestion is primarily a cause of death in females, firearms are more common in males than in females, and carbon monoxide poisoning is one of the few conditions where there have been any changes in causes of death, so that the proportion of suicides attributable to carbon monoxide poisoning has declined since the introduction of catalytic converters. The proportion of suicides attributable to firearms, even though there has

been a general decline in access and use of firearms, has not declined.

You can also see from this slide that cutting, which there is often a lot of debate about cutting, whether that is or is not a form of suicide, in fact, accounts for a very negligible number of deaths. I think most people would view cutting as not being part of the suicide syndrome.

[Slide.]

This is a chart which shows the distribution of suicide by different genders and ethnic groups across the life cycle, and the top line represents white males. That is followed by African-American males, then white females and black females. Where the vertical arrow is, is the rate for adolescents.

You can see several things from this chart. First of all, I should say that this chart is remarkably similar in one country to another, so there is something about this pattern of mortality which seems to be almost independent of cultural influence.

You do get very big differences in parts of Asia, but apart from that, it is remarkably similar. That is to say that there are very, very

few suicides that occur before puberty, that adolescents occupies an intermediate position between childhood and adulthood, and then one gets this very striking increase in the rate in elderly males and relatively little variation by age in females.

[Slide.]

If we deconstruct this a little more and thus look at adolescents, what you can see is that here, most 10- to 15-year-old suicides actually are occurring amongst 14- and 15-year-olds, and that suicide before puberty is very, very rare.

Sometimes you will read about big increases or big changes in the young child rate, but the rates are very low and very unstable as a result of that, and I don't think that one can draw very many conclusions about suicide before puberty.

That may also be relevant to the matters that you are considering today, because both suicide and depression are relatively uncommon, very uncommon before puberty, and that may mean that what we should be looking at is what are the differences between adolescents and adults.

[Slide.]

The United States ranks around about in

the bottom of the top tier of rates in the world. Most countries with the highest rates of suicide are in Northern/Eastern Europe, but the United States is 16th as far as males are concerned, and ranks 22nd as far as females.

There are quite big differences in gender mainly in China, where suicide is the 7th country for female deaths, but much lower for male deaths, but, in general, the United States is not distinguished by having a particularly high or a particularly low rate.

[Slide.]

We know quite a lot about the frequency of suicidal ideation and attempts from large community studies, particularly the Youth Risk Behavior Study, which is a study that is carried out by the National Center for Health Statistics every two years, for which different states volunteer, and a broad population of between 15- and 20,000 high school students are interviewed using self-report measures every two years.

[Slide.]

What one has been able to see from that really was a big eye-opener. That is to say, that suicidal ideation in high school students is

extraordinarily common. Almost 20 percent of American high school students will think about suicide during the past year.

Suicide attempts are also very common, so that the overall rate is about 9 percent, and if you track these YRBS results, they don't show an awful lot of variation from one year to another.

I have highlighted by color the difference between the self-reported attempts and attempts that received medical attention, because only about a quarter of attempts do receive medical attention or are brought to medical attention.

I think what is important about this is that adolescents may not disclose even suicidal attempt behavior, let alone suicide ideation, and that is frequently not known to either their parents or to others, and that also has to be a consideration, I think, in what you are considering.

Both ideation and attempts, and attempts which receive medical attention, are far, far more common than completed suicide, and if you were to array these out by gender, we estimate that there are about 4,000 suicide attempts for every female suicide death, but about 400 male attempts for

every male death, so that you do get these big gender discrepancies with attempts being more common in females and deaths being more common in males, but you can see that the ratio of attempts to deaths is extreme particularly in females.

[Slide.]

Not only do many adolescents attempt and think about suicide, but they do it quite often, so that from the studies that we have, about half of suicide attempters will make only one attempt a year, and nearly a half will make two or more, in many instances, four or more deaths per year.

We get similar findings in clinical or community studies, and we do know from follow-up studies that having made one attempt will increase the probability of another 15-fold, so that can be quite an important consideration if you are planning a medication study or any other kind of therapeutic study, because maybe what you need to find out about is not so much the state of suicidality at the time of inception into the study, but the history of suicidality as well because that could be an important factor in either stratifying for suicide risk or for filtering it out or filtering it in.

The episodes of ideation, again, you can see that most youngsters who think about suicide do so more than once a year, and in many instances, it is several times a year.

[Slide.]

With respect to how suicidal adolescents are excluded from psychopharm studies, because in general, the studies of depression have excluded suicidal instances, there have been variations in the techniques that have been used, there has been no uniform approach, and that may be a consideration that the committee would want to look at in weighing up different studies and trying to compare them.

[Slide.]

Finally, with epidemiology, I just want to show you how the suicide rate has changed over the last century. This is the 20th century youth suicide profile.

What you can see is that starting I guess in the late '50s, the top line are males and the bottom are females, the male youth suicide rate started to increase, and it increased and increased 3-fold, finally, reaching some sort of asymptote around in the late '80s, peaked a little bit more

towards the end, and then started to decline.

So, starting in 1994, we have had an extraordinary decline in the youth suicide rate, which is very interesting. It has been parallel twice before, once coinciding with World War I and once with World War II. We don't know what this could be due to, and that will be something that I am going to return to in a second or two.

[Slide.]

As far as the causes of suicide, far and away the most common finding in psychological autopsy studies, which interview friends and family after a death has taken place, are the very high rates of diagnosable psychiatric illness that are present, and in studies done in a variety of locations, 90 percent of completed suicides were diagnosable with a DSM diagnosis prior to their death, and the rates are extraordinarily similar from location to location.

[Slide.]

The most common diagnoses are depression, antisocial behavior, substance abuse, and some form of anxiety, and most teen suicides occur in 16- to 19-year-olds, and in that group, in 16- to 19-year-old male suicides, it is important to know

that two-thirds meet the criteria for substance or alcohol abuse.

So, the occurrence of completed suicide is very closely linked to the occurrence of particularly alcohol abuse.

[Slide.]

As Cynthia Pfeffer outlined, and I won't repeat this, suicidality is extraordinarily common in depressed children and teens, both at the time of diagnosis -- and this is a meta-analysis from six studies -- ideation was present in about 60 percent, a previous attempt in 30 percent, and during the follow-up period, attempts also occurred frequently, so that when you find ideation and attempts during the course of treatment of depression, as I say, this is a well-reported phenomenon.

[Slide.]

There are other factors that predispose to suicide. Imitation is one that is particularly worrying because it means that public information campaigns may have a double-edged sword, because we do know that you do get suicide epidemics in the young.

There is a contagion factor, and the

Centers for Disease Control are very actively engaged in trying to find ways of reducing this, and there are now a host of studies in adults, but not yet in children or adolescents, that show that biological abnormalities may predispose to impulsive responses to stress and a family history of suicide.

[Slide.]

We can devise a schema, which you have got in your handout, which can show the route from any of these disorders to suicide ideation and from there to suicide, but I don't think that there is time to get into that model in this presentation.

[Slide.]

I just want to go back to changing rates, because they may be very relevant to today's discussion.

[Slide.]

As I showed you, there has been this very striking and encouraging reduction in male suicide males amongst young males 15 to 24. It is even more striking actually if you look at 15- to 19-year-olds.

What is important is that this has not been a United States phenomenon only. It has been

reported in a large number of other industrialized nations.

In the list that I have given here, three nations, Austria, Germany, and Switzerland, have been experiencing a decline which well predated the introduction of any of the newer groups of antidepressants, but in all of the other countries, the decline started sometime after 1988.

There is only one country which seems to have a stable or rising rate, which is Scotland, and there are a number of possible reasons that have been debated to explain these reductions.

One is that during the '90s, at least in the United States, there was economic prosperity, a decline in unemployment, and other social indices tended to improve, but rates also started to decline in high youth unemployment countries in Europe, and the relationship between SES and suicide is not strong, and, in fact, it hasn't really been established.

The first thought was if so many suicides are associated with drug and alcohol abuse, maybe exposure to drugs and alcohol would have been reduced during this time, and this is certainly my first guess. However, use and abuse rates have not

changed, if anything, they have continued to inch up.

[Slide.]

Reduced firearm availability, the Brady Act was introduced in 1994, and there is evidence from tracking studies that ownership and use of firearms started to decline around about 1980, but the proportion of suicides by firearm has gone unchanged, and although there have been very striking declines in accidents attributable to firearms, it is not clear that we can point to the reduction in suicides as being caused by that.

Also, the declines have been noted in countries in which there are almost no firearm suicides, so this doesn't seem to be a very plausible explanation.

[Slide.]

More psychotherapeutic treatment is a possibility, but, in fact, the data seem to suggest that visits for psychotherapy have declined consistently over the past 10 to 12 years, more psychopharmacologic treatment, and you will have heard that there has been an enormous increase in exposure to antidepressants during this period in many countries, or it could be a nonspecific

finding, a better recognition of adolescent suicide with some nonspecific interventions or some combination of the above.

[Slide.]

A word or two about treatment. There have been some useful Cochrane analyses looking at effective treatments for suicide attempts. These have mainly been done in adults, and only two treatments emerged as being successful.

One is dialectical behavior therapy, which is a very specific form of therapy which is hard to come by because very few people are trained in it, and one study looking at flupenthixol, which is an antipsychotic or neuroleptic, in multiple attempters.

There have also been studies showing lithium or at least discontinuation of lithium results in an increase in the suicidality, and Clozaril seems to have a specific suicide sparing effect in schizophrenia.

But apart from that, we don't have much to guide us, and there is nothing out there which tells the clinician what to do with this very common problem.

[Slide.]

Maybe that is why, but, in general, teens who do commit suicide tend to be relatively undertreated compared to adults, so that, for example, the top three lines show that between 30 and 60 percent of adults who commit suicide will have had mental health treatment, but in adolescents, very few have had that, so it is getting between 7 and 21 percent, they are an undertreated group.

[Slide.]

Furthermore, one of the things that has been interesting to epidemiologists over this current debate is do you find antidepressants in toxicologic studies of completed suicides, and Exen [ph] in Sweden has done a study showing that the findings in autopsy studies suggest that suicides are significantly undertreated with SSRIs compared to the rest of the population.

There has only been one study in youth, and that is from the Utah Youth Suicide Study by Dr. Gray, and he has looked at 50 psychological autopsies, all of whom had careful toxicology investigations.

A quarter of those had been prescribed antidepressants, but in none of those cases were

antidepressants found at autopsy, so we know that teenagers often don't take their medication, and certainly they didn't seem to be taking it in this case.

[Slide.]

So, I would just like to conclude with some cautions and considerations. Ideation and attempts are very common in depressed teens, and they recur frequently, so finding them in youngsters being treated for depression is, of course, not surprising. That doesn't address any treatment effect that might be found.

A methodological point. Teenagers often conceal ideation and attempts unless they are asked about them directly. Self-report facilitates disclosure. It is my understanding that we are heavily dependent upon event reports in these data, and event reports may be influenced by the mode of elicitation.

They are not used with a glossary which precisely defines how things should be classified, so misclassifications can occur.

Self-harm is a term that is used by some, but not others in the mental health profession. It is a very heterogeneous descriptor and not all

types of self-harm are associated with suicidal intent.

There have been no direct studies with frequent and careful measurement examining whether SSRIs increase, decrease, or have no effect on suicidal ideation and behavior, so that we are dependent very much on inference, but maybe that is always the case.

I just would like to conclude with the following. After increasing for 35 years, teen suicide rates have been declining consistently in many countries. During this period, there has been a marked increase in exposure of teens to SSRI antidepressants.

These trends could be related. This is ecologic, and we don't know whether they are related, but at the moment we don't have a better explanation for the turnabout of a condition that led to the death of tens of thousands of young people.

I would like to stop at that point.

DR. RUDORFER: Thank you very much.

At this time, just before our break, I have one announcement to make. Any open public hearing speakers who have not yet signed in, please

do so immediately. We will only be able to call upon speakers who have formally signed in, so we wouldn't want you to miss your chance.

We have time for a 15-second break, but I am told that may not work, so why don't we take 5 minutes or as close to that as we can work, and we will come back for our open public hearing. Thanks.

[Break.]

Open Public Hearing

DR. RUDORFER: There is specific guidance from the FDA that I would like to read. This applies to all meetings or considered general matters meetings, and as we heard earlier from Anuja, since we are not focusing on one specific product here, that encompasses this joint meeting.

Both the Food and Drug Administration, or FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing sessions of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason -- and I am addressing the

speakers this morning -- FDA encourages you, the open public hearing speaker, at the beginning of your oral statement to advise the committee of any financial relationship 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 any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

As I mentioned earlier, the clock dictates only a limited amount of time for each speaker. I would like to run all night, but I hear an ice storm is coming, so in the interest of time, we have a light warning system, and each speaker, please be advised, when you see the yellow light, you have 30 seconds remaining, so please start to wrap up.

The flashing red light means you are out of time and the microphone will go off. I have asked them to let you finish your sentence for three or four words, but it is out of our hands.

We have two speaker-ready chairs, so I am asked to remind you that when your two away from your number, please be sure you are in one of those.

Speakers are assigned by number and we will begin with Number 1.

Irving Kirsch and David Antonuccio

DR. KIRSCH: My name is Irving Kirsch. Baum, Hedlund has paid for my air tickets. I decided to come before knowing that.

Dr. David Antonuccio, Amanda Drews, and I are reviewing the published literature evaluating the efficacy of antidepressants in depressed children. A total of 12 randomized, controlled clinical trials have been published.

Two-thirds of these trials failed to find any significant benefit of medication over inert placebo. Only 4 trials reported significant differences, and these did so only on clinician-rated measures, not on patient-rated measures.

When the data from these trials are combined, the placebo response is found to be 87 percent of the drug response. This means that the drug effect is only 13 percent of the drug response. This is not a clinically significant effect.

Many children get better when given antidepressants, but the data indicate that this is largely a placebo effect. These conclusions are consistent with those found in 7 previous published reviews.

To summarize, the published clinical trial data show that the therapeutic benefits of antidepressants for children is negligible at best.

David.

DR. ANTONUCCIO: These results were drawn from studies with design flaws that typically favor the study drug. For example, they frequently exclude placebo responders before random assignment, rely on ratings by clinicians who have a vested interest in the outcome, and are likely to be unblinded by medication side effects.

Furthermore, these results are drawn from the published literature which is subject to publication bias and file drawer problems meaning

that many studies with negative results do not get published. Adding unpublished studies, most of which have negative results, will surely shrink the difference between antidepressants and placebo even further.

In order to evaluate the cost effectiveness of antidepressant use in children, the committee must consider the benefits, as well as the risks. Clinically meaningful benefits have not been adequately demonstrated in depressed children, therefore, no extra risk is warranted.

An increased risk of suicidal behavior is certainly not justified by these minimal benefits. Neither are the established increased risks of other commonly reported side effects, which include agitation, insomnia, and gastrointestinal problems.

The highest possible standard should be applied to scientific data involving drug treatment of children, because children are essentially involuntary patients. Those of you on the committee who are parents know this to be true because when your children have prescription medication for something that ails them, you make them take it as prescribed whether they want to or not.

Children given antidepressant medication often do get better, but so do children given placebo. Thus, the clinical data suggest the improvement is due primarily, if not entirely, with placebo effect.

Please be careful to ensure that our children are not exposed to risk without commensurate benefit.

DR. RUDORFER: Thank you.

May we have the next speaker, Number 2.

Lisa Van Syckel

MS. SYCKEL: Good morning, ladies and gentlemen. My name is Lisa Van Syckel, and my daughter, Michelle, at the age of 15, was placed on Paxil. She was diagnosed with depression and anorexia nervosa. It turned out that that diagnosis was wrong, she actually had Lyme Disease.

My daughter self-mutilated, became psychotic, became violent, attempted suicide twice. My daughter survived those two suicide attempts, not because of the drug, because of the police officers who were summoned to my home.

Michelle has suffered severe withdrawal. She is constantly ill with flu-like symptoms. She has had rectal bleeding, she has vomited blood.

She has had her friends at school call her "Psycho," all because she was misdiagnosed and all because everyone has withheld from the public the adverse effects of Paxil.

I am a parent. It is my right to make an informed decision on behalf of my daughter. You did not allow me to make that informed decision and she was harmed. We are blessed because Michelle did not die, and Michelle is now attending university and doing beautifully.

Please, have respect for our children, make sure that you put proper warnings on these medications. Our children's lives are at stake here, because not only does it cause suicide, it also causes them to become violent, very, very violent.

Thank you.

DR. RUDORFER: Thank you.

May we have the next speaker, Number 3.

Ann Blake Tracy, Ph.D.

DR. TRACY: I would like to say, first of all, that this is a meeting that should not be taking place today. I testified at an FDA hearing similar to this in 1991, and these drugs should have been banned at that time in my opinion.

I am Dr. Ann Blake Tracy, a Ph.D. in health sciences with emphasis on psychology. I have spent the last 14 years researching the SSRIs and working with patients who are having adverse reactions to these medications. I am also the author of Prozac: Panacea or Pandora, Our Serotonin Nightmare.

I have testified in criminal and civil cases for 12 years concerning these medications, and I am greatly concerned about the use of these drugs among children, with developing brains, who have far more reactions than the general public would, as I am the elderly who are having severe adverse reactions.

What I presented to the FDA in 1991, I would like to present again. Each of you will get a copy of this. This is a 31-year-old patient on Prozac for six months, shows the patient, although appearing alert and functioning, in a total anesthetic sleep state while dreaming. I believe technically, you could call that a REM sleep behavior disorder.

The research now shows, this many years later, that 86 percent of the cases being diagnosed with this REM sleep behavior disorder are patients

on antidepressants, 80 percent of those on SSRI antidepressants.

There are some very famous cases that I believe manifest that very clearly, and in representing those families today, I would give you Andrea Yates, who drowned her five children while taking Effexor and Remeron.

DR. RUDORFER: Thank you. I am afraid we are out of time now.

DR. RUDORFER: Thank you.

Number 4, please.

Tom Woodward

MR. WOODWARD: My name is Tom Woodward. My wife Kathy and I have been married for 19 years and until 6 months ago had 4 children. Our oldest child, Julie, hung herself after 7 days on Zoloft, and she was only 17, was a cautious child, and had no history of self-harm or suicide, nor was there any history of depression or suicide in our family.

The doctors we spoke with stressed that Zoloft was safe and had very few side effects. The possibility of violence, self-harm, or suicidal acts was never raised. The two and a half pages we received with the Zoloft never mentioned self-harm or suicide.

Julie began experiencing akathisia almost immediately. We now know from a blood test from the coroner's office that she was not metabolizing the drug.

We are 100 percent convinced that Zoloft killed our daughter. We are here because we believe the system we have in place is flawed. It is clear that the FDA is a political entity and its leadership has protected the economic interests of the drug industry. Under the Bush administration, the FDA has placed the interests of the drug industry over protecting the American public.

Dr. McClellan understands how important political contributions are particularly since his mother has headed up the Republican fund-raising in Texas. Eighty-six percent of the $14 million in political contributions given by drug companies has gone to the Bush administration Republican candidates - what did Pfizer, Eli Lilly, and GlaxoSmithKline Beecham buy?

The FDA should be a jealous advocate in protecting the American people. Those in leadership positions within the FDA must be beyond reproach. FDA's chief counsel Daniel Troy has spent his career defending the drug industry.

Suppressing unfavorable data may be legal, but is it ethical?

If the trials don't favor a drug, the public never hears of them. Legal maneuverings have thrown out the scientific method. The drug industry must be compelled to produce all of their findings and studies. I also believe public funding of these trials is warranted.

Our daughter, Julie, had been excited about college and scored 1,300 in her SATs several weeks before her death. Instead of picking out colleges with our daughter, my wife and I had to pick out a cemetery plot for her.

Instead of looking forward to visiting Julie at school, we now visit her grave. The loss we have experienced is horrific. We don't want another innocent child or family to suffer this tragedy.

DR. RUDORFER: Thank you, Mr. Woodward.

May we have the next speaker, please.

Mark Miller

MR. MILLER: My wife Cheryl and I desperately hope that our story, along with others that you will hear today, and I so proud of the teens and the young adults who you will hear from

today, that they have the courage to come forward and talk with you personally. I wish our son could, he cannot.

There is a serious problem with the way SSRI medications are being prescribed today and how, in many cases, they can directly cause violence and suicidal behavior in those we love and treasure the most, our children.

You see, we lost our 13-year-old son, Matt, in the summer of 1997. He died after a psychiatrist we did not know gave him three sample bottles of a pill we had never heard of, for a perceived illness that his doctor could only guess at.

We were advised with great authority that Matt was suffering from a chemical imbalance that could be helped by a new, wonderful medication called Zoloft. It was safe, effective, only two minor side effects were cautioned with us - insomnia, indigestion.

Now, I don't know if Matt had a chemical imbalance. I do know this. We had moved into to a new neighborhood a year before, a new school setting, he was uneasy. He didn't have the friends he had grown up with in our old neighborhood. Yes,

our son was unhappy.

So, Matt's doctor, a man we know through court testimony to have been a well-paid spokesman for Pfizer, gave us Zoloft. He said, "Take these for a week, call me back when you know how Matt is doing."

Matt didn't have a week. He became agitated on the pills. He did not sleep. He did not eat. He could not sit still. That night, a Sunday, before leaving on vacation, after taking his 7th Zoloft tablet, he took his own life.

This is important for you to know. Matt hung himself from a bedroom closet hook, barely higher than he was tall. To commit this unthinkable act, something he had never attempted before, never threatened to any family member, never talked about, he was actually able to pull his legs up off the floor and hold himself that way until he lost consciousness and forced himself to leave us.

Matt's autopsy showed the levels of sertraline in his blood were three times the therapeutic minimum levels.

You have an obligation today, this panel, to prevent this tragic story from being repeated

over and over and over again. I hope you will do the right thing.

DR. RUDORFER: Thank you, Mr. Miller.

If we could have the next speaker, please.

Corey and Jay Baadsgaard

MR. COREY BAADSGAARD: Good morning. My name is Corey Baadsgaard. Four years ago I was diagnosed with having social anxiety disorder, and my family practitioner doctor, he prescribed Paxil 20 milligrams.

After about 8 1/2 months, I started taking 40 milligrams of Paxil because it was not working at 20 milligrams. A few months after that, I went back. The same problem, it wasn't working, and he suggested I start taking a new medication called Effexor.

He abruptly discontinued the Paxil and put me immediately on Effexor at 75 milligrams, and I was supposed to work up to 300 milligrams over a 3-week period. The day that I took the 300 milligrams, I didn't feel very well and I stayed home from school.

I went back to sleep and that evening I woke up in a juvenile detention center. Unaware of what I had actually done, I asked one of the

members of the juvenile detention center, and I found out that I had taken my high-powered rifle that I use for hunting to my third period class, took 23 of my classmates hostage and 1 teacher hostage.

I spent 14 months in jail, not really knowing why I had been there, not really remembering anything that I had done.

This whole thing has changed my whole family, it changed me, myself. We were forced to move. I cannot even go back to the same town that I lived in, I have to stay at least 25 miles away from city limits.

These drugs are ridiculous. They should not be prescribed unless it's absolutely last resort.

MR. JAY BAADSGAARD: These drugs are hell. Look at what they have done to my son.

DR. RUDORFER: Thank you.

May we have the next speaker, please.

Joyce Storey

MS. STOREY: My son, Brian Storey, was 17 years old in 1997. Our family doctor diagnosed him with severe depression. He took blood, checked for drugs or any medical condition. He found

neither. He gave me 14 Zoloft pills and said come back in two weeks. He never told me they had side effects and he even said if a person is drinking or doing drugs, that Zoloft works well with them.

Five days later, my son killed a woman. When they arrested him, he was drug-tested. They found no illegal drugs, he was only on Zoloft. During his trial, the kids that testified with him and against him said he did no drugs or alcohol.

The psychiatrist that examined him was Dr. James Merkangis from Connecticut. He is also a Doctor of Neurology and is on the faculty at Yale University. He said Brian had a manic reaction to Zoloft. He testified Brian told him it was like being in a dream.

The news media called my son the All-American boy, and he was. He is now serving life without parole. Six months later, another boy at my son's high school, Jeff Franklin, 17 years old, on Prozac, took an ax to both his parents and three of his brothers and sisters. Both of his parents died. He is serving two life sentences.

This is not a coincidence. There is a common denominator, teenager, severely depressed, on an SSRI antidepressant. What is scary is that

you are only hearing from a few of us that this has happened to, and there are a lot more out there.

I am praying you will look at these drugs very closely and, at the very least, take them out of the hands of pediatricians and GPs. These doctors are not psychiatrists, and they do not have the knowledge and experience in treating mentally ill children.

My son never had a chance. There are 13 million people on these drugs, 6 to 8 million are children. The question is why are we handing these drugs out like candy, and the answer is $17 billion a year business. It is always about money. Please help before more families are destroyed.

Thank you.

DR. RUDORFER: Thank you.

Next speaker, please.

Jame Tierney

MS. JAME TIERNEY: Good morning. My name is Jame Tierney. I was 14 years old when I was prescribed 75 milligrams of Effexor for migraine headaches. I took this for about a year. At the time, the drug lost its effectiveness and my doctor doubled the dose.

For the next 9 months, my life as I had

known it was gone. I thought daily about suicide and hurting myself. I felt void of normal emotions. I was so belligerent, agitated, and filled with hate - hate for my family, my friends, and most of all myself. Rage consumed me. I felt trapped.

I said and did things I had never done before and never would do now. I had little control and little inhibition. It was as if I was watching a movie and some villain was destroying all the relationships around me. I spent my time alone and viciously fighting with my parents. They would ask what was wrong and what had happened to me. I could not answer them because I did not know or understand myself. I was terrified.

I thank God my parents knew that wasn't really me and continued to search for answers. They found the answer to my uncharacteristic behavior. It was the Effexor that my neurologist had prescribed for my migraine headaches. I was not, repeat not, prescribed this drug for depression. I have had no history of depression prior to or after I was off the Effexor. For me, this drug caused the very symptoms it's supposed to alleviate.

Due to the severe withdrawal symptoms,

Prozac was used to get me off Effexor. It worked, but the same personality and behavior problems reemerged. Effexor and Prozac affected me the same way. I had never had these feelings before I took Effexor, I have never had these feelings since I stopped taking the Effexor and Prozac.

Effexor took three years from me and I will never get them back. The horror of what these drugs did to me is ineffable. These drugs are destroying lives everywhere.

I implore you to please protect the children from these drugs.

DR. RUDORFER: Thank you very much.

If we can have speaker Number 9, please.

Donna Taylor and Mark Taylor

MS. TAYLOR: Hi. My name is Donna Taylor. My son was shot at Columbine. He took 7 to 13 bullets though his chest and nearly died. I also have other members of the family that have died since then on these drugs, but we can't get into that right now, and many, many people that we know, that families have been divided and separated, and there is just all kinds of divorces and all that going on from these drugs.

I will let Mark speak.

MR. TAYLOR: First of all, I would thank you for allowing me to come and speak on behalf of the thousands of innocent Americans that have died as a result of these drugs.

I would like to start with an opening, very famous statement, and it says, "The measure of a man is not his strength or how much money he has, or how good he looks or how strong he is, or how powerful he is. The measure of the man is how noble he is."

I want to ask you guys, are you really being noble with your choices, or are you just allowing the drug companies to squeeze by you just because they have a big pocketbook. This is ridiculous.

Do you people have children, do you, do any of you? Have any of you had anyone that has died on these drugs? If you have, I am amazed that you guys are even standing here supporting these drug companies.

I mean this has never happened in the history of America. This is a shame and it ought to be stopped today, not next week.

MS. TAYLOR: And God says the same thing. It's in the Bible, Revelations 18, 19 through 24

makes it clear, sorcery means anarchy in the last days and blood will be running all over the streets.

MR. TAYLOR: Say yes to America's health and no to the drug companies.

DR. RUDORFER: Thank you both.

We are going to move on to speaker Number 11, Shannon Baker.

Shannon Baker

MS. BAKER: My name is Shannon Baker and I have no financial ties to the pharmaceutical industries, nor am I here to complain about my daughter's side effects, adverse reactions, or withdrawal symptoms. I am here because she is no longer alive.

I know you have all got pictures. I am here because today, I am representing the love that my daughter had for life and to be her voice and the voice of all the other children who their voices have been silenced by these drugs.

Their deaths have been so senseless and needless. I am here speaking in front of you, hoping that you will go the right direction and ban these drugs for children. There needs to be no more senseless and needless deaths because of these

drugs.

Thank you.

DR. RUDORFER: Thank you.

Our next speaker, Number 12, please.

Dawn Rider

MS. RIDER: My name is Dawn Rider and I am here to tell you my story, and I represent, as president of ASPIRE, more than 11,000 persons who are all named on the Eli Lilly and Prozac petition, which a copy has been given to the panel.

We have been educated to believe that mental, emotional, and behavioral disorders are caused by chemical imbalances in the brain. The fact is that this is only theory, and this theory is pushed on us as if it were the absolute truth.

The reality is that the best of scientists do not completely understand the complex inner actions of the myriad chemicals in our brains. Those of us who elect to believe this theory and subject ourselves to treatment become guinea pigs in an ongoing experiment.

I know this from personal experience. I trusted our family doctor when he explained that depression is caused by a chemical imbalance. We trusted him when he determined that Paxil was right

for my husband, and Prozac for my son.

We weren't educated enough at that time to ask him to provide us with the test results that proved which chemicals were being balanced.

I am not going to go into details of what happened to our family. I have given you all documentation, it's very painful. Suffice it to say that my beautiful 14-year-old son is now dead, and when we discovered the problems with these drugs, we decided it would be better for my husband to suffer through depression than end up dead like our son, and we found out that he could not get off of Paxil.

He went through over a year of hell before he was able to finally withdraw from the drug, and in the process it destroyed our marriage of over 20 years.

I say with no apology whatsoever that these SSRI drugs destroyed what was once a loving and vibrant family. Why do we believe that street drugs like heroin and LSD can lead to outcomes such as this, yet, we won't accept that legally prescribed drugs, working on the same neurochemicals, can result in horrific crimes against persons and property?

Why do we accept that a drug like penicillin, beneficial as it is for some, can prove fatal for others? We fail to accept that these drugs can have paradoxical effects. These drugs are not safe for everyone.

They should be labeled with the strongest of precautions and dispensed only by trained physicians who have time to adequately monitor the patient. Most doctors do not have time for this level of care.

Also, patients should be required to sign letters of informed consent. Please carefully consider the documentation that I have left with you and look at the faces of those that are here today and the faces that out in the hall, those children who cannot speak for themselves because they are dead. They are not merely anecdotal evidences.

There is a preponderance of evidence that will be presented before you today. Please consider it carefully and do the right thing.

Thank you.

DR. RUDORFER: Thank you.

We are up to Number 13.

Sara Bostock

MS. BOSTOCK: I have slides, so please look at the screen.

My daughter Cecily had only been taking Paxil for two weeks before she died, during which time her condition greatly worsened.

By the day of her death, was pale, unable to sleep, almost unable to converse, and in a frightened, agitated state, jumping at the slightest noise. That night she got up and without turning on any lights, went into our kitchen only 40 feet from where I was half asleep. She stabbed herself twice in the chest with a large chef's knife. The only noise was a slight yelp and a thump when she fell on the floor.

This was a young woman who had everything to live for. She had just completed applications to grad school and received a large pay increase the month before.

She had a boyfriend who loved her and scores of wonderful friends. She had never been suicidal. To die in this violent, unusual fashion without making a sound after the marked worsening of her condition led me to believe that Paxil must have put her over the edge.

Her autopsy revealed she had a very high

blood level of Paxil, which reflects poor metabolization and is a feature common to many of these suicides. I believe this induced an intensely dissociative state, perhaps even sleepwalking. SSRIs suppress rapid eye movement and block the muscle paralysis which occurs in this stage of sleep.

The whole regulation of waking, sleeping, dreaming occurs in the brain stem where the serotonin neurons are clustered and where SSRIs are having their impact. Patients taking SSRIs had rapid eye movement during non-REM sleep and while awake when they were not paralyzed. This atypical REM is often associated with strange behaviors including hallucinations.

The effects of SSRIs on sleeping, waking, unconsciousness itself are ill understood. From accounts of people under the influence of these drugs, I believe SSRIs can alter consciousness in some mysterious and frightening way that is not normally seen even in mental illness. I am certain this is what happened to my daughter.

Untold thousands have died because of the drug companies and the FDA's failure to heed the evidence over the past 17 years.

DR. RUDORFER: Thank you.

Again, I apologize for the short time.

Number 14, please.

Vera Hassner Sharav

MS. SHARAV: I am Vera Sharav and I am president of the Alliance for Human Research Protection.

The family testimonies that you are hearing today are not anecdotes. They are corroborated by a Harvard review of children's medical charts, which found that within three months of treatment on an SSRI, 22 percent suffered drug-induced adverse psychiatric effects, and overall, 74 percent of children suffered adverse events during the course of treatment.

The FDA has known for years, but failed to reveal that antidepressants consistently fail to demonstrate a benefit in children. At least 12 of 15 trials failed. The FDA has known and failed to warn physicians and the public that SSRIs increase the risk of suicide and hostility in children.

FDA's 1996 Zoloft review found "7-fold greater incidence of suicidality in children treated with Zoloft than adults." The British Drug Regulatory Authority reviewed the evidence, which

is not being shown in this meeting, and they determined that the risks far outweigh any benefits. They took action to protect children. When is the FDA going to take action?

The FDA is foot dragging, equivocating, and tinkering with definitions while children are dying. The San Francisco Chronicle reports that the FDA has barred its own medical reviewer who reviewed more than 20 trials involving 4,000 children, and his findings confirmed the British finding, which is that SSRIs increase the risk of suicide.

DR. RUDORFER: Thank you.

If we could have speaker 16, please.

Cynthia Brockman

MS. BROCKMAN: Thank you for allowing me to address you about the 1999 Zoloft-induced drug reactions that my son Chris had at 16, resulting in a woman's death and a life sentence for him.

My son and I want to express sincere sorrow for that death. Our sympathies also extend to all victims of SSRI's deadly mind-altering effects.

The medical community has tolerated mental health care in which patients are worse off after

treatment than before with the worst cases ending in death.

I urge you to ban SSRI use in children, and not to let another life be destroyed by lack of adequate SSRI regulation.

Chris took Zoloft or Adderall, deteriorated from drug-induced akathisia, could not bear adverse symptoms of inner turmoil, loss of conscious behavior. He described overpowering drug effects, his uncontrollable fits of anger, pitches and voices setting him off, not wanting to be touched, feeling horrible all over his body, not being in reality.

After his offense, his drug reactions stopped, went off all SSRIs for about a year, but restarted when depressed and put on Zoloft again. Prison doctors ignored warnings, forced him to take harmful drugs drugging him into hallucinating, irrational, suicidal state.

May 2002, I met with the Texas House Committee on Corrections who ordered prison doctors to correct this health crisis caused by these drugs. Various drugs had triggered severe suicidal, homicidal symptoms for about two years in a clinical setting of doctors starting and stopping

his meds.

When doctors stopped all drugs, all symptoms disappeared. Doctors released Chris as recovered from the prison psych hospital to a regular unit May 2003. Chris has not had any psych drugs since.

These clinical events show dangerous reactions caused by SSRI-induced psychosis through challenge, de-challenge, re-challenge. Medical experts said Chris would not have been suicidal, homicidal had he not been reacting to SSRI drugs.

Dr. O'Donnell concluded Chris' offense was from combined toxic drug effects which altered behavior, enhanced violent thoughts and actions, impaired judgment, was unable to form intent.

Citizens Commission on Human Rights confirmed SSRIs caused his symptoms. Now Chris take omega-3 fatty acids and fish oil to restore his mental health that was damaged from SSRIs. He is doing well without medications, and I thank Jesus Christ for that.

Please ban these drugs and their use in children.

Thank you.

DR. RUDORFER: Thank you.

We will move on now to Number 18, please.

Todd Shivak

MR. SHIVAK: Good morning. We are Todd and Eileen Shivak. We do not have any financial relationship to anyone here.

Our story is much like the cases everyone else here today is bringing forward to you.

Our son Michael was 11 when he was prescribed Paxil for what was diagnosed as depression. The consequences of this still live with us today. Thank God he is alive and with us today, but Michael is afraid of his doctors, how can he trust what they will give him next.

He is afraid of the police. He has been wrestled down, handcuffed and taken to jail. The police are supposed to protect us and look what they have done to him.

It is difficult for him to trust his teachers. They still look at Michael as a troublemaker even though he currently is an A/B student with much improving grades. His peers still think of him as a freak, the kid who tried to slash his wrists while in class.

As parents, our most important job is to protect our kids. We thought we were doing the

right thing. The doctors convinced us that taking these drugs was the only thing that we could do for Michael. Now, Michael wonders whether we are going to have him arrested, sentenced, physically restrained and punished again. If he can't trust his parents, who can he trust?

Our daughter, Catherine, was 5 years old at the time. She witnessed firsthand some of the most terrifying sights that I have ever had to deal with. Our family is finally getting back to the loving family we once were, but the fear of what happened still haunts us.

Worse yet, how could all the doctors not recognize what was happening? Michael saw three different social workers, two different psychiatrists, and went through at least four different emergency room psychological evaluations in two different hospitals.

We are here to plead that you do something to stop the prescriptions of these drugs, so that no one else has to go what we are all going through. It is impossible to describe the pain and utter helplessness we all felt watching Michael suffer, watch him cry, take up weapons against us, and beg us to let him die. How do you erase the

picture of your child trying to run in front of a moving car?

Please save our children from this drug.

DR. RUDORFER: Thank you.

If we can have speaker 19, please.

Andy Vickery

MR. VICKERY: Good morning. My name is Andy Vickery and I am a trial lawyer from Houston, Texas. For the last eight years, I have represented parents who lost their children to suicide induced by these drugs. You have heard from two of my clients this morning already and will hear from another.

I only have two minutes and I can tell you a lot more than two minutes. The title of the paper that I filed with you is "Needle in the Haystack." I applaud your desire to look at the randomized clinical trials comprehensively to see if they confirm the signal that Dr. Katz acknowledged exists.

I applaud that, however, I am concerned as Lilly was told in 1990 that you are looking for a needle in a haystack, you are off on a wild goose chase. These trials were not designed to detect suicidality, they did not use the Beck Suicide

Ideation Scale which would make the kind of refined measurements that the epidemiologist gentleman who spoke earlier said are needed. They did not use the Barnes Scale, as Dr. Mann himself had recommended in a '91 article to measure treatment emergent akathisia.

They weren't designed to answer the problem, and in 1990 or '91, when Lilly met -- and you have the handwritten notes of this in the materials I gave you -- when they met with outside consultants including Dr. Jerold Rosenbaum, he said, "There is a data problem, you are looking for a needle in a haystack."

Find these vulnerable people and rechallenge them. Please look at the way Lilly sought to study this issue in 1990. They followed a protocol by Charles Beasley that said don't use RCTs, don't use epi studies, find these people and rechallenge them. That was done by Anthony Rothschild who said these patients need to be reassured it's not them.

In the meantime, because the signal is there, please issue warnings; while you look at the data, issue warnings.

DR. RUDORFER: Thank you.

We are up to speaker 20.

Rosie Carr Meysenburg

MS. MEYSENBURG: My name is Rosie Carr Meysenburg. I am from Dallas, Texas. I have no financial ties with anybody but my husband of 40 years.

In my handout, I have highlighted what I am speaking about here.

The first paper is a personal letter from Dr. Peter S. Jensen. At that time, he was the head of Child & Adolescent Disorders Research Branch of the NIMH, the National Institute of Mental Health. He said that research indicates that antidepressants for depressed adolescents are not very effective.

The second paper is a personal letter from Dr. Larry S. Goldman, Director of the AMA, the American Medical Association. He writes physicians have known for many years the dangers of giving any antidepressant to patients with certain disorders. There is a substantial risk of precipitating mania or psychosis.

The last item is a journal article from the Journal of Clinical Psychiatry researched at Yale University. It states that 11 percent of all

psychiatric hospital admissions were from antidepressant-induced mania and psychosis.

It also states another area of research that would be relevant to this issue is the work of Winter and colleagues showing that Prozac and other SSRIs can simulate the effects of LSD. In other words, this is saying for some people, taking an SSRI is the same as taking LSD.

About two million people enter a psychiatric hospital every year, 11 percent then is over 200,000 people a year who have an antidepressant-induced psychosis and who are hospitalized. Not all are hospitalized. Some of them have either committed suicide, a homicide, or a murder/suicide.

DR. RUDORFER: Thank you.

Number 21, please.

Rachel Adler

MS. ADLER: Mr. Chairman, I respectfully request that my entire remarks be entered in the record. My name is Rachel Adler. I am on the board of directors of the Child and Adolescent Bipolar Foundation, CABF, a parent-led, not-for-profit organization, that is the leading source of public information for pediatric bipolar

disorder.

Board members Sheila McDonald and John Adler are here with me, as well.

Bipolar disorder may emerge with an episode of major depression, an illness which often causes suicidality even in preschoolers. Children with depression are at a high risk to switch to bipolar disorder.

We surveyed 17,000 members last month and received a 15 percent response rate over a 5-day period. Eighty-nine percent of the respondents report that their child had been treated with an antidepressant.

We have received favorable comments, but some responses indicate that in some subgroups of children, suicidal ideation and behavior may emerge for the first time or worsen when a child is given an antidepressant. Some of these children perhaps have a vulnerability to a bipolar disorder.

For these reason, CABF urges the FDA to require manufacturers to add a black box warning on the labeling for antidepressants to alert clinicians and parents to the possibility that antidepressants can trigger and worsen suicidality, as well as mania or rapid cycling bipolar disorder

in some children.

CABF opposes any ban on the off-label use of these or other psychiatric medications in children because many of our members report them to be necessary and even lifesaving for their children with mood disorders especially when used in combination with a mood stabilizer.

CABF also urges the pharmaceutical industry and the Federal Government to fund research to analyze what factors are shared by those children who, according to parent reports, became suicidal shortly after taking an antidepressant.

Finally, CABF calls upon the pharmaceutical industry and the National Institutes of Health to make public all safety and efficacy data from unpublished studies in children.

I would also like to say that what I am hearing is a lot of people blaming a medication for what happened to their children, and have a direct blame. What I would sort of like to see is more trained psychiatrists who actually know the side effects as well themselves and who are talking to the parents, telling them about the possibility of side effects, about that depression inherently, you

know, can result in suicidality and that the medication might increase that.

But to blame the medication itself that has helped so many people and has also prevented so many suicides, I don't think is the right way, but we do need to have much more clinicians guiding our patients and parents, so that they know what kind of side effects are possible.

Thank you.

DR. RUDORFER: Thank you.

We are going to move on to Number 23.

Pepper Draper

MS. DRAPER: Good morning. My name is Pepper Draper. I am a Director of the International Coalition for Drug Awareness. I have absolutely no financial gain. I do this completely 100 percent voluntary, and the reason for that is because of my own son's problems.

My child was prescribed Ritalin, which became very depressed, and we bought into the whole serotonin theory, so we were naturally raising that serotonin, which unfortunately started causing him to become severely depressed and suicidal.

Unfortunately or fortunately I should say is that we were able to finally understand the

truth about serotonin, that raising serotonin and stopping the metabolism of it has caused suicide and aggression, and that is well documented.

Unfortunately, Dr. Tracy was not able to talk about that, but what I want to share with you is that there is going to be others here from Arizona who are going to share with you how wonderful these drugs have been for the State of Arizona, but I am here to tell you that I deal with these people every day who are tired of their mental health workers putting them on another medication and another medication and another medication, until these children are now being put in mental hospitals at an enormous rate.

They are being given electric shock therapy and it is very tragic what I am seeing, and I just want to share with you that I know that if we will teach them the right ways to take care of their bodies and cut out the things that are addictive, like these medications are, that we can help our youth learn to deal with what is going on in their lives, and I just want to share with you one last thing.

I am really saddened that the fact that every single parent cannot share what has happened

to their child because if they could, my mother would be here, standing up here, sharing what has happened to her adult son.

DR. RUDORFER: Thank you.

If we could have speaker 24, please, Dr. Marks.

Donald Marks, M.D., Ph.D.

DR. MARKS: Good morning. My name is Dr. Donald Marks and I address your subcommittee as a prescribing physician, as a father, and as a former associate director and director for clinical research for two multinational pharmaceutical companies. I am here at my own expense because I believe in the importance of these issues.

SSRI manufacturing and sales is serious business with tens of millions of patients in the U.S. and a market in the tens of billions of dollars.

My experience working for pharmaceutical companies is that any attempt to decrease sales by increasing warnings will be met with severe organized resistance. SSRI drugs are mostly prescribed by primary care physicians who have limited time with patients, limited training in childhood and adolescent neuropsychiatry and

neuropsychopharmacology, and minimal time to evaluate properly patient suitability and response to pharmacologic versus non-pharmacologic interventions.

The seriousness and severe adverse event effects of SSRI drugs make their use hardly justified in the majority of cases because SSRIs are well known to have limited efficacy over placebo and against non-pharmacologic treatments.

There are many studies in the peer reviewed medical literature supporting the causal role of serotonin in disinhibition and violence. My own prescribing experience with SSRI drugs and evaluation of numerous cases referred to me has revealed significant agitation and aggression, akathisia, activation of mania and hypomania, increased depression, serious dependency and withdrawal difficulties, suicidal ideation, and toxic interactions with other drugs.

It is important to be aware that these symptoms of SSRI toxicity can be mistaken for the progression of the underlying mental state being treated, leading to use of more of the same and other offending SSRI drugs rather than to withdrawal of the causative SSRI agent.

This creates coding problems for physicians, coding problems by clinical researchers and sponsoring companies reporting adverse events in SSRIs.

SSRI manufacturers, such as Glaxo and Pfizer, have conducted clinical trials in depressed children, many of which show no efficacy against placebo, and this has led to an increased warning in England that Paxil should not be prescribed as new therapy for depressed children under the age of 18.

DR. RUDORFER: Thanks. I am sorry we are out of time, but thank you, Dr. Marks.

We are going to move on to speaker 25.

Leah Harris

MS. HARRIS: Good morning. My name is Leah Harris and I am here at my own expense.

The two minutes I have to speak will not permit me to go into the details of what I suffered while taking Prozac, Paxil, and Zoloft from age 12 to 18. I provided additional information in my submitted written statement.

I went from being a shy and mildly depressed, but never suicidal kid to being overcome with thoughts of hurting and killing myself while

on the SSRI drugs, thoughts which I acted on.

Since quitting SSRIs over a decade ago, I have never again self-mutilated or had suicidal thoughts. All other things being equal, the suicidality simply vanished. For me, this is clear proof that the drugs must have played a role, and I am one of the lucky ones, I have survived to tell the tale.

I am not an anecdote and my story is not anecdotal evidence. As a tax-paying American citizen who was hurt by these drugs throughout my childhood, I demand that the FDA take seriously the British decision of December 2003 banning all SSRIs except Prozac for use in children.

Please consider all the evidence especially that which the pharmaceutical industry does not want you to see. The FDA must take action now regarding this grave issue of public health.

Yes, many people claim to be helped by these drugs, and that is wonderful, but what about those of us who are harmed? Medical professionals and the public must be informed of the very serious risks that are associated with SSRIs.

In light of these risks, at the very least, isn't it time for the FDA to require that

the drugs be labeled with clear warnings that might save lives? Such warnings may negatively affect sales, as Dr. Marks referred, which may not please the pharmaceutical industry, but the FDA was created as an independent regulatory agency to serve the interests of the American public, not Big Pharma.

American children are no less precious than British children, and they are in need of our protection, too.

Thank you.

DR. RUDORFER: Thank you.

We are up to speaker 26.

Donald Farber

MR. FARBER: I am Donald Farber of Marin County, California. I am a plaintiff's attorney. I have represented antidepressant victims for five years.

As a lawyer, I look at the evidence, too. I hear the emotional stories, but I look at the evidence.

On January 27th, six days ago, I got a writing that I have been waiting for the FDA for 15 years, from GlaxoSmithKline. Attempted suicides on Paxil during all premarketing testing were

frequent, placebo, it was actually rare, but due to the fact they manipulated the figures in the re-analysis of the data, it was infrequent. So, even by this standard, we should have had a warning 12 years ago. What do we have to do to get a warning?

Dr. Katz mentioned the re-analysis of the data. I call it tinkering with the data.

Here is what happened to Paxil to get it approved. Dr. Laughren knows about these figures. Here is what happened with the tinkering of the data before and after.

Look at the difference. These are not lawyer figures, these are their figures. They manipulated the data, Paxil suicides went down, placebo suicides, which is the key figure here for you mathematicians, went way up, so that the result was statistical insignificance by the time the PDAC met in October of '92.

Whether the drugs go on the market or not, they have to be given a warning. I am for full disclosure. I am not for banning these drugs, but I want full disclosure, and the FDA doesn't need a citizens' petition to do their job.

Finally, I do object to this entire

meeting. I would venture that 95 percent of you are pro-industry and it is time for people like Joe Glenmullen and Peter Breggin to sit on this committee as well as you distinguished people.

Thank you.

DR. RUDORFER: Thank you, sir.

Could we have speaker 27, please.

Lorraine Slater

MS. SLATER: Informed parental consent is only possible as long as full disclosure is made by the pharmaceutical companies, the FDA, and the medical community.

How can you imagine I feel as Dominique's mother knowing now that I was slowly poisoning my daughter every day as I was dispensing her antidepressant medication including Celexa and which she made her first suicide attempt after being on it for almost one month, and effects of the last medication she was on when she did commit suicide?

Yes, Dominique's mind and behavior were slowly being altered to the point that she became very agitated, irrational, ultimately suicidal, because none of the so-called medical professionals acknowledged the drug's role in her irrational and

suicidal behavior or properly withdrew her from their suicidal effects.

Our lovely 14-year-old daughter is dead. Dominique has been denied the unalienable right by her creator of the pursuit of life, liberty, and happiness. She will no longer be able to pursue her dreams of becoming either a computer software engineer, computer graphics engineer, or marine biologist, and someday an entrepreneur, she had hoped.

Gone, too, is the ability to be able to watch Dominique blossom into womanhood, as well as motherhood, as she expressed the desire to someday have five kids. Now, we will never have the opportunity to continue sharing our lives with Dominique, whom we loved and cherished so much.

She was not only very intelligent, humorous, delightful, insightful, and innovative, she was also very caring and thoughtful. Dominique had a way of making others feel special and loved. She touched so many lives. For example, Dominique made 1,000 paper origami cranes and sent them to Governor George Pataki of New York for the first anniversary of 9/11.

It was because of Dominique's very loving

and genuine nature that around 300 people showed up to her memorial service. They couldn't believe that for someone who was so loving and caring, she would herself take her own life.

I submit to you today, ladies and gentlemen, that Dominique's life was taken from her as a result of drug-induced psychosis and suicidal ideations, not to mention the probability of experiencing akathisia, extreme agitation. As a 14-year-old adolescent, her brain was experiencing the second largest growth period, and her hormones were unbalanced.

How can teenagers be allowed to be given antidepressants that were never approved for adolescent consumption, only for adults? How come the medical profession doesn't fully disclose the possible harmful and fatal effects of medication as well as watch carefully for diverse effects on its adolescent population?

DR. RUDORFER: I am sorry that we are out of time, but thank you very much.

If we could have speaker 28, please.

Matthew Piepenburg

MR. PIEPENBURG: Well, there are very impressive credentials around this room and

certainly at this panel, and impressive schools and qualifications and professorial positions at very elite institutions.

There are also a number of impressive terms of art tossed around - morbidity, idiosyncratic. I like Mr. Katz's term controlled data or controlled trial data.

What I would like to suggest is behind me is a number of things that do not show up in controlled trial data that need to be heard, that are as important as what can be achieved statistically.

I don't think for parents who spend a great deal of time in cemeteries, controlled trial data is as pervasive or persuasive.

I do not suggest or believe that everyone here has a negative or a grotesque motive or is all greedy. I do think there are legitimate motives here, and I think these things do need to be discussed without being incendiary.

Nevertheless, it is important to recognize the human dimension here. We had prepared a two-page speech full of FDA talk papers, adverse reporting events on Paxil in particular, my family friend, Paul Domb, has suffered as a victim of

Paxil. It is just very hard to go over that when you hear these stories.

Last night, we were at a restaurant. We gave the waiter our speech to print out for us off of a disk. He came back. He had suffered Paxil side effects that led to suicidal thoughts, violent thoughts after a 40-year marriage, and he saw our speech and sat down for 20 minutes and basically cried before us.

It is a pattern and epidemic that is pervasive and has more importance to me than the statistics we were going to read. Let me just suggest also that this individual had been to Vietnam, lost most of his platoon and most of his body in Vietnam, crawled for two and a half days through the jungle to survive.

None of that caused him the depression or the desire to jump off a bridge like Paxil did. If he could handle Vietnam with poise, how are 13- and 12-year-old kids supposed to handle Paxil?

Thank you very much.

DR. RUDORFER: Thank you.

Could we have speaker 29, please.

Terri Williams

MS. WILLIAMS: My son, Jacob Williams, was

born on October the 15th, 1986. Jacob was an exceptional athlete who participated in football on both the varsity and junior varsity football teams in his school.

In September of 2000, Jacob experienced a loss of interest in his school activities. He maintained his interest in football, however, there was a conflict with his grades and his attendance.

As a result of this issue, his father and I attended a conference at his school on October the 11th, 2000 with various representatives from the school. The school administrator suggested that Jacob may be depressed and that we should seek medical help.

I contacted Jacob's pediatrician and made an appointment for 3:45 that afternoon. On October the 11th, 2000, his pediatrician prescribed 10 milligrams of Prozac, which was increased to 20 milligrams three weeks later.

Shortly after starting the initial dose, Jacob began to complain of having strange dreams, which he had said were bad. Shortly after the dosage was increased, I began to notice an aggressive behavior, which had not been there before. Jacob also became destructive and

destroyed some of his favorite things.

His friends would later tell me they had noticed the same behavioral change. He also showed a verbal aggression and short temper, which had not been present before.

When questioned about this behavior, he stated I don't know what is making me do this. At this time, I thought this could be a part of normal adolescent behavior and did not pursue the matter any further.

On December the 5th, 2000, I discovered Jacob's body hanging from the rafter in our attic. He had hung himself with his own belt. A letter was placed on the ladder leading up to our attic thanking us for giving him 14 years of a happy life.

Something had to have gone wrong in the thinking process to have brought this about. Had I know that this was a potential side effect, suicide, I would have never allowed my son to take the drug Prozac.

Thank you.

DR. RUDORFER: We are now going to go to speaker 32, please.

MR. McINTOSH: I would like to introduce you to my daughter, Caitlin Elizabeth McIntosh. Well, it is actually only a 2-dimensional image of her, but it is all I have left. She died of suicide at age 12 years, 3 months, just 8 weeks after being put on Paxil, and then Zoloft.

Caitlin was a straight "A" student in the fifth grade, a talented musician, artist, and poet, who loved animals and wanted to be a veterinarian. The sixth grade began, and that, combined with the onset of puberty, this bright, sensitive girl who had once loved going to school, started having some trouble coping, as many kids do in the sixth grade, it's a tough adjustment.

She was also having some problems sleeping due to a mild seizure disorder. We wanted to help, of course, so we took her to our family physician, who prescribed her Paxil. He said it would help with her coping and her sleep.

She didn't do well on it at all, so he took her off it cold turkey, which you are not supposed to do. When we saw a psychiatrist a week later, he put her on Zoloft. She then started having strong suicidal ideations, along with severe agitation known as akathisia and hallucinations,

and she was put in the adolescent ward of a mental hospital to "balance her meds."

Well, there, things only got worse, as she was put on other strong psychotropic drugs to treat the symptoms that we now know were actually caused by the SSRIs, and let me be very clear about something. The dramatic and severe symptoms that led to my daughter's suicide manifested only after she started taking antidepressant drugs.

The downward spiral continued until January 5th, 2000, when she hung herself with her shoelaces in the girl's bathroom in the middle school she was attending.

We were told that antidepressants like Paxil and Zoloft were wonder drugs, that they were safe and effective for children. We were lied to. The pharmaceutical companies have known for years that these drugs could cause suicide in some patients. Why didn't we?

I implore you, ban the use of antidepressants here in the United States so that other parents will not have to endure the pain I felt and other children might be saved.

DR. RUDORFER: Thank you.

Speaker 33, please.

Delnora Duprey

MS. DUPREY: My name is Delnora Duprey, and it has been well over two years since I have seen my grandson play ball, ride a bike, talk on the phone, or run in to say, "Hey, grandma, what's for dinner?"

All the normal everyday things in his life are lost. He is not here to get his restricted license in April, see his little sister start school, to ride with his big sister when she started driving, or just to go out and have pizza and see a movie.

A tall, thin boy, quiet and well liked and respectful to everyone, a big heart and a smile that made you ask what are you up to, a boy who loved his family dearly, had hopes and dreams for a future. A future of uncertainty now - he is locked away in a detention center awaiting trial for the murder of two people who he loved most in the world.

A nightmare that started with a diagnosis of depression and placed on medication that was never tested on children and never meant for their use. He had no say in this. We, as adults, trust our doctors and the FDA to know what they are

doing. Even when we get complaints, we say the doctor said it will help you.

A sweet boy who never hurt himself or anyone else went to live with his grandparents. His medication was changed from Paxil, which he had been on a very short time, to Zoloft.

From a family physician, this medication was increased to 200 milligrams for an 80-pound child. Within 48 hours, his grandparents were dead, and he is sitting, facing a life of uncertainty, a life of maybe total incarceration for the rest of his life, a child that does not even know what has happened to him.

I don't want to see any more families go through this nightmare that we have all endured. The child's life changed forever. Next time it might be one of your own family. We must stop these drugs for children and strengthen our restrictions on the doctors who prescribe them.

DR. RUDORFER: Thank you.

Number 34, please.

Joe Pittman

MR. PITTMAN: Hello. My name is Joe Pittman.

My son, at the tender age of 12, killed my

parents. I am going to read you a letter he wrote to me to you all.

"Dear FDA: My name is Chris Pittman. I am now 14 years old. I would like to tell you what happened to me, what the medication did to me and how it made me feel.

"When I was taking Zoloft, I took the lives of two people that I loved more than anything, my grandparents. I went to the doctor and he gave me a sample pack of Zoloft. He told me to take 50 milligrams once in the morning and another 50 at night.

"I didn't notice a change in my behavior until I was completely off the medication. It made me hate everyone. The smallest things made me blow up, and I started getting into fights, which was not me. I would usually avoid fights. Before the medication, I had only been in two fights my whole life. I just hated the whole world for no apparent reason.

"A week after the doctor gave me the sample packs, he increased my dosage to 200 milligrams a day. Everything just kept getting worse. Then, I snapped. I took everything out on my grandparents who I loved so very much.

"When I was lying in my bed that night, I couldn't sleep because my voice in my head kept echoing through my mind telling me to kill them until I got up, got the gun, and I went upstairs and I pulled the trigger. Through the whole thing it was like watching your favorite TV show. You know what is going to happen, but you can't do anything to stop it. All you can do is just watch it in fright.

"Because of my own personal experience on the medication, I would not want anyone to go through what I have then and now, losing the lives of my loved ones for the effects of homicide or suicide, or both, due to the medication.

"Thank you. Christopher Pittman."

DR. RUDORFER: Thank you.

Number 35, please.

Richard Mack

MR. MACK: My name is Richard Mack. I am a retired law enforcement officer and sheriff from Arizona.

My expertise in that field was juvenile delinquency, school violence, and narcotics investigations.

My first experience with SSRIs was when I

was a parent of a second grader, my wife and I were called into the school, our son had a problem staying in his chair. What was the government school's answer? Drug your son into submission, so he will stay in his chair.

We refused and we thank God now that we did. Our son turned out just fine, played basketball, baseball, and excelled at school and sports.

I was a sheriff of a small community in Arizona. We had an abnormal amount of high rate of suicide and teen violence. I am just an investigator, I just present the facts. One thing that we could not ignore was the circumstantial evidence that the common denominator in all of these cases was the victims or perpetrators were on SSRIs.

In investigating these events, it became quite commonplace for all of us to ask the same question as we got to the next event of horrified and traumatized people and families. You have heard from many of them today.

Some people don't have the adverse reaction to these drugs, some do. I learned the same with LSD when I investigated that as an

undercover narcotics officer. I can only say that the evidence is mounting over and over as did our investigations.

We cannot, as law enforcement officials, ignore such circumstantial evidence. I doubt very seriously if you could either. I am an advocate for state's rights and I do believe that if the FDA fails to take action, the state and local authorities will have to.

Thank you.

DR. RUDORFER: Thank you.

Speaker 36.

Noah Wright Smith

MS. SMITH: My name is Noah Wright Smith and I am a 15-year-old victim of legalized drug abuse. My mother had me put on Ritalin when I was 5. I felt sick all the time on Ritalin and it was just the beginning of bad things happening to me because of drugs.

My grandparents won custody of me last year. When they won, they got upset because I was in bad shape and on a lot of drugs. They picked me up at Broughton Mental Hospital in Morganton, North Carolina, and learned I was on 1,000 milligrams of drugs a day. In my lifetime, I have been on 16

psychotropic drugs including Zoloft, Paxil, and Effexor, and all of them made me feel sick and do very bad things.

I wasn't a bad kid. I was a badly abused kid, abused by my mother and my stepfather. The Department of Social Services knew I was being abused, but they didn't do anything except put me on more drugs.

The drugs made me sick and do bad things like trying to stab my teacher with scissors. Sometimes it made me want to kill my parents, and I told them that, and was put in a mental hospital.

Some drugs made me have bad nightmares, so I tried very hard not to sleep every night, so they gave me drugs to make me sleep. Some of the drugs made me want to kill myself. I couldn't stop thinking about killing myself. When I told the doctors, they sent me to still another mental hospital.

One day I tried to jump off a very high railing to kill myself. I was put in a mental hospital again for doing that, but I really wanted to die. I really did want to, and I was so scared and mad, too. In those mental hospitals, they kept giving me more drugs, and I got depressed. I got

diabetes and high blood pressure.

My grandparents won my custody and took me to a new psychiatrist. We have worked hard together and he found I really don't need any drugs. Last year he took me off all of them, one at a time. No more nightmares or wanting to hurt or kill other people, and I don't want to kill myself anymore.

Drugs almost ruined my life and almost killed me. What about the kids that have to take these drugs? I don't want kids to kill themselves. Who is taking care of them? Who really cares about us kids? I don't even know if you care, do you? Somebody had better listen to kids who say the medicines make them want to kill themselves, and make them sick, and do bad things, because they are telling you the truth.

Thank you for listening to me. Now, please, help the other kids, so that they don't get hurt by drugs, and so they don't kill themselves. I almost killed myself and I am glad I am alive.

DR. RUDORFER: Number 37, please.

Marion Goff

MS. GOFF: I do not have any financial ties. I am her with my daughter, Alex. We are

here to tell you about her twin sister, Devon, when she was 9 years old. We are also joined by Senator Lincoln Chafee's wife Stephanie who is a friend of ours.

In 2002, Devon developed an obsessive-compulsive disorder very suddenly and very severely. In a three-month period, she lost 10 pounds. We consulted a specialist who prescribed Zoloft on her second visit with him. Soon thereafter, he increased the Zoloft to 50 milligrams or more, but it didn't help, so he changed her prescription to Paxil.

She was hospitalized and Devon's medical condition was compromised in that she had developed a cardiac arrhythmia and had to be placed on a heart monitor. She was in the hospital for one month, and she was on the heart monitor and bed rest for the entire time.

During this time, her Paxil was increased to 20 milligrams. A few days later she was started on Zyprexa also. Devon was not getting any better, in fact, her behaviors grew worse. She began hitting her head against the metal hospital bed. She threatened to jump out of the window on two occasions.

On two other occasions, we found a pair of sharp scissors in her bed. Our child was never suicidal before these medications. At one point, my 9-year-old child, who weighed little more than 60 pounds, was on 30 milligrams of Paxil and 10 milligrams of Zyprexa.

Our gentle daughter would now fly into a rage several times each day. It became part of our life to have my husband and myself restrain Devon at times for fear that she would truly hurt herself.

During these times, she would try to inflict injury upon herself by banging her head on walls, beds, floors. She would punch herself in the legs and arms. She grew extremely violent toward us. She would run to the silverware drawer and get a knife and attempt to stab herself.

The worst moment happened when I looked in on her, in her room one night, to find her by her open second floor bedroom window with one leg out the window in a position as if she appeared she would jump.

Devon is presently being treated for Lyme Disease. In summary, our experience has been one of absolute terror to watch your 9-year-old

daughter suffer so much, so suddenly, and to be so lost in helping her.

So often we would ask why this was happening, and we were told to forget about the etiology.

DR. RUDORFER: I am sorry, we are out of time. Thank you very much.

Number 38, please.

Gary Cheslek, M.D.

DR. CHESLEK: Actually, my wife is speaking later.

My name is Gary Cheslek, and I am a practicing dentist from Vicksburg, Mississippi, and I am speaking today, not just as a health care professional, but also as a parent.

I am here today to tell you an anecdote. Webster defines an anecdote as a short narrative of an interesting or amusing biographical event, an anecdote or anecdotal. That is the euphemism the manufacturers of Prozac, Paxil, Effexor, and Zoloft use to describe the thousands of reported out of character, violent, homicidal, suicidal events that occur in a vulnerable subset of patients who ingest their SSRI antidepressants. They would have us believe that these are mere coincidences and don't

prove anything.

My son, Justin, was a 20-year-sophomore at the University of Southern Mississippi when he went to the Student Health Clinic complaining of insomnia. He was given a thorough examination including bloodwork. Significant in the doctor's note at that initial visit is the notation, "No suicidal ideation."

Complaining that the sleep medication he was prescribed made him feel sedated and depressed, he was put on Paxil for two weeks. During those two weeks, he repeatedly told his doctor he didn't like the way the Paxil made him feel, so he was switched to Effexor.

Within 24 hours of the switch to Effexor, he had a seizure. Five days later he hung himself in his apartment. He didn't leave a note. Beneath him was his laptop computer and a glass of Coke. It was as if some sudden impulse had made him do this.

We grilled his girlfriend about his mood and behavior in the months prior to his death. She said his demeanor changed dramatically around her birthday, February 22. Justin started taking Paxil February 21.

Last June, regulators in the UK and Canada banned Effexor and Paxil for use in children and adolescents, and recently expanded that ban to all SSRIs except Prozac. Last August, Wyeth issued a Dear Doctor letter alerting the health care professionals that the clinical trials had not established the safety and effectiveness of Effexor in children, and revealed an increased risk of suicidal ideation and self-harm.

The letter does not, however, indicate that some of these trials were done seven years ago.

DR. RUDORFER: Thank you very much.

Sherri Walton

MS. WALTON: My name is Sherri Walton and I am here as a volunteer advocate. This is my 14-year-old daughter, Jordan. We have traveled here from Arizona at our own expense because we know that public forums, such as this, usually only hear from those who have had negative experiences. We felt it was important for us to share our story.

Jordan was diagnosed with Tourette's syndrome when she was 7 years old. As is typical of Tourette's syndrome, she also has OCD and ADHD. She was originally prescribed an SSRI medication to

relieve the anxiety that consumed her because she could not control her thoughts or behaviors.

This medication allowed her to participate in, and understand, the cognitive behavior therapy that gave her some semblance of normalcy. In fourth grade, Jordan was still being hampered by the obsessive thoughts caused by her OCD. In the classroom, this was overwhelming and extremely frightening for her.

Her medication was changed to a different SSRI and within a few months, her obsessive thoughts became less and less intense. They were still there, but now she was able to recognize what they were and usually work through them.

Dance is Jordan's passion. It is what she wants to do with her life. In November of 2002, she announced she wanted to quit dance. As she burst into tears, she said that she wanted to die, she wanted to kill herself.

She was diagnosed with clinical depression and her medication was changed from the SSRI she had taken for four years to a different SSRI to treat both her OCD and depression.

As Jordan has struggled to find success in school and in her relationships with peers, her

meds were sometimes the only thing she could count on to help her. The daughter I have here now standing next to me is a happy, healthy, successful teenager. There is no doubt in my mind that the SSRI medication saved her life, and like the other SSRI antidepressants she is taking gave her a chance for a full and complete life.

With the greatest sympathy for any families who have lost children to suicide, I ask that you identify and fix any breakdown in the system that could lead to such tragedy. At the same time, I ask that you appreciate and take into account the enormous benefits that these medications have had for children and their families.

Please urge the FDA not to take away the tools that have allowed my daughter and millions of other sons and daughters out there to be successful in life, and, in fact, to have lives.

As a parent, I call on the FDA to take no action that would harm my child.

DR. RUDORFER: Thank you.

We are up to speaker 40.

Peter R. Breggin, M.D.

DR. BREGGIN: Hello. I am Dr. Peter

Breggin. I am a psychiatrist and one of the few experts in the world on medications who isn't involved in any way with the drug industry. I think there are handful of us.

I have given you a peer-reviewed article that came out just a few weeks ago that I wrote, which is the most extensive review to date on violence, suicide, and mania caused by the SSRIs, and it has just, I don't know, maybe hundreds of citations.

Back in the 1980s when Prozac was being approved, Richard Kapit, the chief medical officer at the FDA, identified a stimulant syndrome in association with Prozac, and he repeatedly warned in in-house documents that this stimulant effect would turn depression into agitated depression and cause a deterioration in the individual.

Since then, we have been able to identify a continuum of stimulation that has at least four syndromes involved, that I have now seen produce violence and suicide in dozens of patients in my clinical consultations and in my medical/legal work.

The syndrome, first and foremost, includes manic-like behavior. We know that Luvox, for

example, just in its label has a 4 percent rate of mania. From Emslie's study, hidden in the fine print, we know that Prozac, controlled clinical trials, 6 percent rate of mania.

The second syndrome is the agitated depression, it is hard to tell often clinically from mania.

The third syndrome is this obsessive suicidality and violence, and the fourth syndrome is akathisia, which we now know, and is even in the old DSM, can produce psychosis and agitation, and a variety of other problems leading to suicide and to violence.

The literature is extensive. You have got to go beyond the needle in the haystack. Please look at my review.

DR. RUDORFER: Thank you, Dr. Breggin.

Speaker 41.

Robert Fritz

MR. FRITZ: People have been pleading with the FDA for 11-plus years to put warnings on prescriptions for antidepression medication to no avail. The FDA has had people present information about suicidal tendency increase and numerous completed suicides, and still no warnings of

increased risk of suicide were issued.

The people of the United States have a right to know what risks are associated with taking these drugs. I have a right to know what risks are associated with taking these drugs, so I can make an informed decision as to whether or not I want my children to take these drugs.

The need for a warning is compounded by the fact that doctors are prescribing these medications off label. My daughter, Stephanie Raye Fritz was taking Zoloft. We weren't told of any risk of increased suicidal tendencies or increased suicide attempts.

She hung herself on the evening of November 11th in her bedroom after finishing her homework. She showed no signs of increased depression or imminent suicidal thoughts, and, in fact, was still recruiting people to see her sing the following month.

We had no warning of what Zoloft could do to our daughter, but you people, the FDA, certainly did. On October 27th, two weeks before she took her life, you put out a Public Health Advisory and notified physicians about preliminary data from studies suggesting an excess of reported suicidal

ideation and suicide attempts for pediatric patients receiving certain of these antidepressant drugs.

Why weren't we, the parents of the kids taking Zoloft, notified with this advisory? It is too late for my daughter, but for the FDA to continue to sit on this information and not let the public know the risks associated with these drugs is a gross misuse of power.

I am not asking that these drugs be taken off the market. I don't know enough about their safety to recommend that. What I am seeking is that when the drugs are prescribed off label, or when drugs are prescribed after an advisory is issued suggesting new adverse side effects, that the FDA make it mandatory that the physicians prescribing such drugs explain in plain English what the risks are and that an informed written consent be received from the parents or the patient's guardian.

I hope that you will agree that all Americans deserve to know what risks they are assuming when they take medication. I believe that most Americans, including most elected officials, agree with that.

How many more people have to die before a warning gets issued?

DR. RUDORFER: Thank you.

We are going to move ahead to speaker 43.

Lawrence Greenhill, M.D.

DR. GREENHILL: My name is Lawrence Greenhill. I am a child psychiatrist, Professor of Child Psychiatry and Pharmacology at Columbia. I am speaking today on behalf of the American Academy of Child and Adolescent Psychiatry where I serve as Chairman of the Program Committee and as Chair of the Pediatric Psychopharmacology Initiative Committee.

First, I want to extend my sympathy to all the families who spoke so moving here today about their losses. I think similarly, the membership, who are comprised of 7,000 child psychiatrists at the American Academy of Child and Adolescent Psychiatry, are concerned about these families, and they want to get the results of this review to help their patients with safe and effective treatments.

In that regard, the American Academy of Child and Adolescent Psychiatry supports the review that is going on and it specifically supports the reclassification of suicidal events using patient

charts, that is, patient level analysis, as the category that turned up in Dr. Laughren's report of possible suicide-related events was one most subject to possible methodological bias that might be addressed by patient level analyses and reclassification.

Furthermore, I support the mandatory registration of all clinical trials as advocated in JAMA by Dickerson and Rennie in July of 2003. That is because one of the greatest roadblocks to understanding the safety and efficacy of trials is the lack of public access and its disclosure of these data sets due to laws that treat some of the data as proprietary trade secrets.

I join my colleagues at Columbia in encouraging the field to carry out further prospective placebo-controlled trials using methods such as we have heard today, the randomized withdrawal discontinuation or challenge, de-challenge --.

DR. RUDORFER: Thank you, Dr. Greenhill.

Number 46, please.

Suzanne Vogel-Scibilia, M.D.

DR. VOGEL-SCIBILIA: I would like to have my remarks into the written record, and I want to

let you know I am here at my own expense.

Good morning. My name is Dr. Suzanne Vogel-Scibilia. I a member of the NAMI board of directors. As a person diagnosed with bipolar disorder, I am proud to serve on the NAMI Board and proud that NAMI is the nation's voice on mental illness representing both consumers and family members. I am also proud to be the mother of five children, two who are diagnosed with mental illnesses and one who is currently being treated with an SSRI.

I am also a practicing clinical psychiatrist with no financial ties to the pharmaceutical industry. I represent thousands of families across the country.

My son, Anthony, had a very severe mental illness primarily depression and attention deficit disorder as a manifestation of his bipolar disorder, and another son has had treatment with numerous antidepressant medications including several SSRIs.

My children have had tremendous improvement with their illnesses and lead very full and functional lives because of SSRI medication, along with other psychotropic medications. I

shudder to think of their plight if these medications were not available.

One of my sons has had suicide attempts and violent incidents with knives. He has also run out of our house - in a fit of terror --in subzero weather only to be found freezing and hypothermic by our local police department in the next town. These incidents all occurred while his illness was not adequately treated with an antidepressant medication.

My other son suffers from disabling obsessive- compulsive disorder symptoms and depression, and has had his life dramatically improve from treatment with SSRIs.

I want to talk and speak about suicide and the consequences of untreated mental illnesses.

We are pleased that the FDA is looking closely at the data related to SSRI use and suicidality. NAMI is deeply concerned with the public health crisis and the number of youths who commit suicide. The U.S. Surgeon General reports that up to 80 percent of our youth who need mental health treatment receive none at all.

In summary, I would like to thank the committee for allowing 200,000 members of NAMI to

share our views on this critically important issue. I hope and pray that this committee will render a decision based, not on emotion-filled pleas of individuals whose experience are not supported by adequate research.

Thank you very much.

DR. RUDORFER: Thank you.

If we could have speaker 48, please.

Dennis Winter

MR. WINTER: I am Dennis Winter. I am here today with Karine Winter and Mary Lou Winter, Beth's mom.

Four months ago or less than four months ago, Beth, a 22-year-old recent graduate from the University of Rhode Island, she graduated summa cum laude, she was a child who was loving, from a very tight, close family, never any instance of alcohol or drug abuse, never any problems, a wonderful student, a wonderful girl, a loving sister to her brothers and sisters, committed suicide after being on Paxil for seven days.

Now, what I think is critical here is the fact that she can go to her general practitioner on the first visit and be prescribed Paxil. I think it is clear that you need to come out with warning

labels for practitioners and doctors, so the lawyers in this room, when those labels are out there, if the doctors continue to do it, will be able to bring actions. If you bring out the warning labels, there is enough legal community in this world that will police itself.

Let me go on. As we are sitting here today, we heard a lot about idiosyncratic data, all permitted data, requested data available, data we are permitted to evaluate fully, and it comes down to this data stream that we don't know that happened 15, 20 years ago, the data stream you are trying to analyze.

I don't know, like Mr. Farber said, if you are going to be analyze all that data and come out with that data. You should put out warning labels because you are not going to get a clear answer.

I am running out of time, but Dr. Healy provided testimony in federal court on May 22nd, 2001. Everybody needs to be read that testimony. He gave it under oath, under threat of perjury, and that is very enlightening to anybody involved here, and you really need to read it.

Also, you need to look at confidentiality agreements. A lot of families of people who commit

suicide are embarrassed. When the lawyers come, they sign confidentiality agreements, and you don't hear about what is really happening out there.

DR. RUDORFER: Thank you very much.

We are going to move along to speaker 51.

Steve Cole

MR. COLE: I am Steve Cole. I am here at my own expense.

My father committed suicide after 13 days on Prozac. He has absolutely no history of mental illness, in fact, quite the contrary. He and my mom had just built a new house, a lot of the work he did himself. He and I and a friend built a cabin out of raw lumber.

These are not the type of things that you do if you are planning on dying. Let me repeat that. You do not do that.

He was looking forward to his new house. He was planning many activities. He was upbeat, he didn't drink or gamble, and he did not have any recognized prerequisites for suicide unless you want to consider all 70-year-old men suicidal, and I just don't buy that. Generally, he was in very good health.

Next slide.

He experienced some chest pains about a month and a half after moving into the new house. As a precaution, he went to his cardiologist. His heart tested perfectly well. He was upbeat and had a new grandbaby on the way.

He was prescribed Prozac off label for the chest pain. The doctor, who is an outstanding, wonderful man, stood behind us on this, and stated that he has no doubt that it was Prozac induced. Eleven days after he started, he demonstrated symptoms of akathisia, he was jittery. His fingers and his skin felt odd, he was easily agitated.

He told me, "I cannot stand the way this drug makes me feel." Two days later he committed suicide.

Growing up, he watched a lot of westerns. He loved westerns, but he would turn the channel if a man was hung or lynched. This is the way my father died. He hung himself. It was completely out of character. He died by means of his own nightmare.

Thank you very much.

DR. RUDORFER: Thank you.

Number 52, please.

Allan Routhier

MR. ROUTHIER: I am here to request that Wellbutrin be recognized as another dangerous drug. Information was sent to this committee by some researchers and myself as to the reasons for inclusion. There are too many cases of suicide and deaths caused by this drug. It is known to cause akathisia, depression, psychosis, serotonin syndrome, seizures, hallucinations, and many other serious adverse effects.

One suicide while on Wellbutrin for ADHD was 9-year-old Carey Brooks, who had to kneel down to hang himself with his shoelace. There are many reasons these drugs are prescribed, and they can cause suicide in non-depressed people.

Do not blame acts of drug-induced psychosis on depression especially when this is happening to people given these drugs for other purposes. It is not only SSRIs. SSRI is a misnomer. None of them are selective to serotonin. When you affect one neurotransmitter, you affect others.

Remeron, Serzone, Effexor are not SSRIs. Effexor works on serotonin, norepinephrine, and dopamine, as does Wellbutrin. FDA Med Watch reports hundreds of suicides on Wellbutrin.

Wellbutrin is structurally similar to amphetamine and overstimulates many people.

Six months ago my wife went to the doctor sick and was sent home with Wellbutrin. After six days of serious adverse reactions and insomnia, she shot herself. This was not her. Forty years old, beautiful, with two boys, she was a perfect wife and mother, married for 18 years, almost 25 years working in the Welfare Office.

She was never depressed. She was the most loving, unselfish person anyone could know. Immediately after starting Wellbutrin, she was not herself. This was an act of psychosis. This has been happening for too long. People are worth more than profits.

How many more have to die before something is done? Don't be fooled by manipulated studies. This was whitewashed in 1991, now they are trying to do it again. This happens to adults, as well as children, prescribed for any reason, not just MDD.

My wife was murdered. The FDA is supposed to protect us from these pill pushers.

Thank you.

DR. RUDORFER: Thank you.

Number 53, please.

Daniel J. Safer, M.D.

DR. SAFER: I am Daniel Safer. I am a child psychiatrist, and I have no conflict of interest in coming here.

I think the major finding of the British Committee on the Safety of Medicines was that most of the data that they got were unavailable to them prior to the company coming in for an indication, so when they found the data, they were surprised to see that most of the studies were negative or failed for the treatment of depression in children using SSRIs. So, that was I think the major finding as far as I am concerned of the British Committee.

The second finding indeed was that most of the studies, the vast majority of the studies they looked at were either failed or negative for the treatment of depression in children.

The third finding had to do with the side effects of particularly the suicidality issue, which I consider a minor finding of the British report. It was about 1 and a quarter percent rate for placebo and about 3.5 percent for the active medication.

I think that is fairly understandable

because the medication, the SSRIs are known, and have been known, to increase the risk of agitation and activation and children. In fact, the rate is about 15 to 20 percent when you look over about 40 or 50 studies on SSRIs.

It is a high rate, so you would expect that children who were depressed might have an increased rate of suicidality if they are agitated or anxious or activated under medication.

Now, there is a lot of concern about the fact that a lot of these studies are not published, they simply are put in a file drawer. I think that is a big concern, it's a big concern for Eric Kahn [ph] and Michael Thase and Norman Sussman, some of the major people in the field of psychiatry.

So, I think the focus of the meeting is sort of unfortunate by focusing on suicidality because I think the big issue here is that we don't have access to the data that we need from the controlled trials, that are simply put in a file drawer by the companies.

So, I would like to close by quoting Daniel Conner in the American Journal of American Academy of Child and Adolescent Psychiatry this month. Oh, I will leave the quote out.

DR. RUDORFER: We will look it up. Thank you.

Speaker 54, please.

Julie Zito, Ph.D.

DR. ZITO: I am Julie Zito from the University of Maryland/Baltimore, and I bring to my comments this morning 20 years' experience in psychiatric pharmacoepidemiology.

I would like the committee to consider the following drug safety issues in making their recommendations.

First, symptoms like activation and agitation are reported very inconsistently, anywhere from no incidence in a clinical trial to as many as 55 percent of the children in an SSRI trial. This information suggests a lack of standardization of measurements and methods with which to assess these events.

Second, we need research on behavioral toxicity in order to separate symptoms associated with drug from those associated with the underlying psychiatric disorder. I don't think we can just assume it.

Third, because suicide is a very rare event, we need research that requires active

surveillance, not passive surveillance, active surveillance in large, well-defined populations. We have the capacity to do that with research methods in pharmacoepi, but as yet, there is no federal mandate to go beyond Med Watch.

Thank you.

DR. RUDORFER: Thank you.

Speaker 55, please.

Joseph Glenmullen, M.D.

DR. GLENMULLEN: I am Joe Glenmullen. I am a psychiatrist and clinical instructor in Psychiatry at Harvard Medical School and the author of Prozac Backlash, which describes my experience seeing patients become suicidal on SSRIs.

I am here at my own expense because there is a specific side effect of SSRIs called akathisia that can make some patients so agitated that they feel death would be a welcome relief.

This side effect is so well established that it is clearly described with SSRIs in the Diagnostic and Statistical Manual, the DSM, the American Psychiatric Association's official diagnostic manual.

If you look at the transcript of the FDA hearing on this very side effect 10 years ago, you

will see the FDA saying repeatedly we don't know what to do, we need more research. It is a tragedy to be here 10 years later and hear the FDA saying the same thing.

The industry's response to this side effect has been to blame the underlying psychiatric conditions of patients, to dismiss legitimate medical case reports as anecdotes, and to scare the media away from the subject, claiming that it would frighten patients away from treatment.

Indeed, there is a prevailing authoritarian attitude don't warn patients, you might scare them.

Well, I prescribe SSRIs and I warn patients, and they are not frightened away from treatment. Let's stop blaming patient's underlying psychiatric conditions. Let's stop blaming the victims and deal with this very real side effect.

Thank you.

DR. RUDORFER: Thank you.

Speaker 56, please.

Linda Cheslek

MS. CHESLEK: Hello. My name is Linda Cheslek. I am a pediatric nurse practitioner and I have prescribed medications for pediatric patients

for 25 years.

In the past, I thought that when an FDA drug was approved, that it had gone through a rigorous battery of independent tests and trials under the auspices of the FDA, but I can longer believe this.

Why? Well, this summer I received this letter from Wyeth. It is a Dear Doctor letter. It goes to all health care professionals, and it told me an update on Effexor, that the safety and effectiveness in pediatric patients had not been established, but there were reports of increased hostility, suicide, adverse events, suicidal ideation, and self-harm.

This letter that came to my home confirmed what I already knew, that my son, who had a three-week trial of Paxil and Effexor became very much worse. He developed the akathisia you have been hearing about. He developed serotonin syndrome symptoms and a seizure.

Wyeth had this information for almost seven years. Why did not the FDA require this trial data to be submitted along with the other data? The FDA allows the drug sponsors to manipulate and massage the data, to present it in a way that they

feel is promoting their drug, and not the truth.

I ask you to require them to submit all the data and to give a warning about these medications. When you go to bed tonight, I hope you will see my face, the face of my son, and maybe of other faces of these people, and give a warning.

Thank you.

DR. RUDORFER: Thank you.

We are to speaker 57.

Jeff Avery

MR. AVERY: Hello. My name is Jeff Avery.

My 16-year-old stepson, Brandon Ferris, committed suicide on July 22nd, 2001, about three weeks after he began taking Zoloft. Brandon was a bright and socially outgoing teen who got along well with others. He was a black-belt instructor in Tai Kwon Do, active in the church's youth group, and held a part-time job.

His mother home-schooled Brandon and worked at the Tai Kwon Do School, so she was very active in Brandon's activities.

In June of 2001, Brandon expressed that he was feeling down, and not his usual energetic self. It was decided that he should take some time off and see a counselor.

The counselor suggested that he see a doctor. The doctor, who found no physical problems, prescribed Zoloft.

Sunday, July 22nd, Brandon and I went to church. On the way home Brandon volunteered to make a cake for his mother's birthday. He asked permission to go on a boating trip. He spent the rest of the day with his friends and an older brother Randy.

When he came home from his youth group meeting at 9:15, he seemed fine. At 9:45 he asked his mother about the boating trip. At 10:30 he went to check his e-mail, but his brother was using the computer. At 11 o'clock, he was found in his room hung by the neck from a belt in his closet. We called 911, we performed CPR to no avail. He was pronounced dead at the hospital.

Reflecting on the day's events, I could not detect any indication of forethought to suicide. However, later conversations with others close to Brandon inferred that he may have been having problems with the medication.

The obvious question is what happened in Brandon's mind between 10:30 and 10:45.

This was not the end of unspeakable

tragedy. Five months later, Barbara, unable to cope with the loss of her youngest son, took her life.

Since then I have collaborated with Brandon's biological father, Dan Ferris, to obtain information that would point to the cause of Brandon's death. We believe, after having done much research, that the drug Zoloft had a causal effect in Brandon's final actions.

Thank you.

DR. RUDORFER: Speaker 58, please.

Harry Skigis

MR. SKIGIS: What can I say that hasn't really already been said, but I had a speech prepared and decided to revamp it while sitting here in the audience.

I tried to kill myself and luckily didn't succeed. I am still on Paxil because I am hooked on a nonhabit-forming drug. I don't know if I will live long enough to see how this thing ends up, but I am going to try.

I have always believed that do unto others as you would have done to yourself. Would you people put your children on this drug? Would you take it yourselves? I doubt it.

Probably not all the statistics in the world can't bring back the people that are dead because of the irresponsibility of the FDA. How can I put in any faith in a government that still somewhat denies that cigarettes are addictive?

I wonder if you people can sleep at night while your decisions are killing innocent people every day. I leave my life in your hands and hope that you will apologize to all the people here for your decision and ignorance in this matter and how it has shattered so many people's lives.

I really hope you guys can do something about this or at least tell us who will help us, because a lot of people are dead here today, and it's all in your hands. So good luck.

DR. RUDORFER: Thank you.

Speaker 59, please.

Pamela Wild

MS. WILD: On September 9, 2001, in a state of confusion and hopelessness, I put a.38 Special, Smith & Wesson revolver under my chin and pulled the trigger.

In going through withdrawal from Paxil, I lost all ability to cope and reason and without realizing it, became suicidal. I suffered from

sleeplessness, night sweats, light and sound sensitivity, irritability, and dizziness.

I was in a constant state of terrible anxiety and felt as though the only thing holding me together was my skin. I couldn't understand why others weren't seeing things my way, as though I was speaking in another language. I was told by my therapist that I had drifted into a fantasyland.

She said it was though my system had been poisoned somehow, I was told not to worry, the only way to die from this drug was to fill a tub with Paxil and water and drown in it.

The side effects I experienced on Paxil, even though I reported them to my doctor, were dismissed because no one was warned that Paxil could cause what I was experiencing.

If I, at 41 years old, could not articulate what was happening, how do you expect a child to?

There is no real medical explanation for my survival. The front of my face was blown away, leaving a hole large enough to encompass a man's fist. The bullet miraculously only took two-thirds of my tongue, most of my mandible and my cheek bones. The maxilla was shattered.

The orbit of my left eye was broken and forced the eyeball out onto what remained of my left cheek. It completely destroyed my hard and soft palate along with my nose and sinus cavity.

I was blessed, though. I may not able to taste or smell, but at least I lived. I can see, talk, and I can hear. But more surprising than any of those, I have brain function. I truly believe my life was spared for a reason. That reason is so I can prevent others from experiencing what I experienced.

DR. RUDORFER: Thank you very much.

We are up to speaker 60. Thank you.

Karen Barth Menzies

MS. MENZIES: Good morning. My name is Karen Barth Menzies and I am an attorney for Baum, Hedlund. We represent several thousand SSRI victims. We have been doing this for 12 years.

The U.S. Code of Federal Regulations 201.57 mandates that you require the drug companies to warn when there is reasonable evidence, not causation, reasonable evidence of an association of a serious risk.

The clinical researchers who did these trials on kids and the drug companies themselves

confirmed that there are multiple events of suicidality caused by the drug. The methodology that you are going to be using is designed to explain away those events.

Even Dr. Laughren admits in the memo he gave you for this hearing today that there is evidence in these trials of an increased risk of suicidality, reasonable evidence is there. If there is reasonable evidence, you must make them warn.

Serious risk, we certainly have that. Akathisia, psychosis, mania. When you are looking at this data, you are not just looking at the suicide, also look for signs of akathisia and psychosis and mania. These aren't as easily explained away by the drug companies, by blaming the disease, by blaming the victims.

When you take the potentially fatal risk and couple that with lack of efficacy of these cases, why take that risk especially when it comes to our kids.

Paul Leber [ph] predicted this day when he said that the FDA would come under attack because they weren't as demanding as they ought to have been when they were looking at the efficacy of the

antidepressant products.

Put me out of business for the right reasons, warn about these drugs and disclose.

DR. RUDORFER: Thank you.

Speaker 61, please.

Amy Coburn

MS. COBURN: Hi. My name is Amy Coburn. I have flown here from Salt Lake City, Utah, at my own expense.

I am here on behalf of my father, myself, and my family. My father's name was Wayne Coburn. Most people remember him as a man full of life and willing to help anyone in need.

I remember my dad as a man who loved his family very much and was very loved in return, a man full of ideas and hope for the future, but like many people, he found he got a little down in the wintertime. He was diagnosed with seasonal depression without suicidal tendencies.

When I was 13 years old, he was put on Paxil. Three weeks later he pulled his car into an old factory garage, started his engine, and there waited until he died of carbon monoxide poisoning.

This naturally shocked me and my family and we all had a hard time coping with his death.

I started going to a counselor to work through my grief, and I was put on Paxil, the same drug my father was on.

I started acting differently, then very soon after I started having suicidal thoughts, mood swings, I was fighting with my friends, and the one thing my mom noticed is that I wouldn't talk about how I was feeling. The only thing she could get out of me was "I am fine, leave me alone."

Six weeks after I was put on the drug, I stayed home from school, wrote my good-bye letters, and swallowed a cupful of poisonous bathroom cleaner. I immediately got scared and ran to my neighbor's house. She called 911 and luckily I survived and I am standing here today.

We soon found out that we weren't the only ones who had problems with these drugs. Hundreds of families have lost people they love because they had no idea of the effect they could have on a person's mind. All me and my family want are warnings on these drugs.

DR. RUDORFER: Thank you. I am sorry, we are out of time. Thanks.

Speaker 62, please.

Sharon McBride

MS. McBRIDE: I am here as a mother and I am here at my own expense.

When our daughter was 13 years old, she came to me and said that something was wrong with her. After discussion, I took her to the emergency room where she was diagnosed with depression.

After three years of intense psychotherapy to discover and help the cause, she experienced her first manic episode. She was hospitalized and given lithium and a mild dose of antipsychotic medication for a brief period of time.

The resulting acne and weight gain caused her further depression thereafter. Due to my inability to accept the diagnosis, we took her to a psychologist rather than a psychiatrist to get a middle-of-the-road opinion.

Because she was so depressed, we did eventually see a psychiatrist again, and she was prescribed one of the SSRI medication, Zoloft. Shortly after beginning this treatment, she had a serious suicide attempt. The doctor at the hospital first thought that it was just another attempt trying to get attention, but after he interviewed her, his opinion changed.

While she had been depressed, she had

never attempted suicide before this time. Eventually, she was prescribed three medications, one of which was Paxil. Three different times in her life she abruptly stopped taking the medications including Paxil, which resulted in manic episodes.

Before her last episode, she had been stable for five years. Then, during a very stressful time with her grandmother dying, she abruptly stopped the Paxil and experienced her worst manic episode with hallucinations and other health problems.

She finally had to be court-ordered into the hospital and it devastated her life. She lost her job as a security assistant at a hospital, and her roommates could no longer live with her because this was not the person that they had known and loved.

That was two years ago and she is just beginning to put her life back together. I would encourage the committee to look very closely at the suicide attempt ratio for children and teenagers taking these SSRI medications.

Thank you.

DR. RUDORFER: We are up to I believe our

final speaker of the morning session, and that is Dr. Thomas Moore.

Thomas Moore, M.D.

DR. MOORE: Good afternoon. I represent Drug Safety Research. I have completed two studies that raise additional questions about the safety of antidepressant drugs, and both of those studies should be in your binders.

The first of those concerns the medical use of these drugs, who are taking them, and the headline finding is that in the four-period 1998 to 2001, use of antidepressant drugs in children doubled.

The second finding is that less than 10 percent of these cases were these drugs being prescribed for FDA-approved use, and the remaining 90 percent of the cases, they were for unapproved use or ones that raised safety concerns. Let me give you some examples of what I found.

Among boys 6 to 12 years old, 52 percent of the use was for treating attention deficit or conduct disorders typically in combination with an antipsychotic or a stimulant, such as Ritalin.

Now, I know of no scientific evidence that says that combination therapy is effective in these

disorders, and I know of no evidence that it is safe either.

As you go on, combination therapy was very common in the real world. Twenty-two percent were taking two antidepressant drugs, 17 percent were taking drugs that were ineffective in clinical trials, 42 percent were taking two of more antidepressant drugs.

So, what we are seeing is when drugs are ineffective, rather than abandoning them or trying alternatives, doctors increase the dose or combine the drugs in ways, the safety of which we are not aware.

The second major study that I submitted to you today is of the adverse event experience, largely the same data set, but different criteria from what the FDA has conducted.

The two key findings there are, number one, it appears based on the medical use of these drugs that these drugs cause suicidal and related behaviors at double the expected rate compared to adults. So, they seem to be being reported more frequently in children.

The second finding is there appeared to be no difference in adverse event reports between the

two drugs for which there were warnings, and those four drugs for which we do not have warnings.

DR. RUDORFER: Thank you, Dr. Moore.

We will now end our morning session. I want to thank all our open public hearing speakers for raising very important issues for the committee. I believe we will have two additional public speakers during the afternoon session, but we are now going to take our lunch break.

We will reconvene at 1 o'clock.

[Whereupon, at 11:59 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.

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

[1:10 p.m.]

DR. RUDORFER: Good afternoon.

We are going to begin this afternoon's session with several speakers from the FDA. What we are going to do is hear a total of six speakers from the FDA, as well as our two remaining public speakers. There will be a break along the way.

I am going to ask the committee to save your questions until the end. We will have a lot of time for discussion later this afternoon.

First, I would like to introduce Dr. Gianna Rigoni from the Office of Drug Safety of the FDA.

Pediatric and Adolescent Antidepressant Drug Use in the U.S.

DR. RIGONI: Thank you, Dr. Rudorfer, and good afternoon.

[Slide.]

Today, I would like to describe for you antidepressant drug use trends in children and adolescents in outpatient settings to provide a context for further discussions this afternoon.

[Slide.]

First, I will describe the use of selected

antidepressant products by prescriptions dispense in the United States, followed by the proportion of those prescriptions dispensed to 1- to 17-year-olds.

Next, I will examine the specialties of the physicians responsible for prescribing these products to children and adolescents.

Finally, I will identify the primary diagnoses for which these products are used in these populations.

[Slide.]

The antidepressants examined in this analysis include the selective serotonin reuptake inhibitors, or SSRIs, as we refer to today, and the atypical antidepressants seen on this list here. Atypical include nefazodone, venlafaxine, and mirtazapine.

These products will be presented at the molecule level, therefore, fluoxetine will refer to Prozac, Prozac Weekly, Sarafem, and all generic fluoxetine equivalents, and so on, for each product.

All references to the term "antidepressants" in this talk will refer only to these 10 products. Tricyclic antidepressants,

MAOIs, and other products used to treat depression were not examined for this analysis.

[Slide.]

At this time, only three SSRI products have FDA-approved labeling for use in pediatric population. Fluoxetine is the only product approved for the treatment of pediatric major depressive disorder at this time, while fluoxetine, sertraline, and fluvoxamine are approved for the treatment of obsessive-compulsive disorder in this population.

Although only three products have FDA-approved labeling for the treatment of MDD and OCD, use of SSRIs and atypical antidepressants outside of current FDA labeling in pediatrics is endorsed by many in the medical community through various clinical practice guidelines.

[Slide.]

I will now describe the methods that were used in this analysis.

[Slide.]

Since data for 2003 was not complete in time for this presentation, we will look at drug use trends from 1988, the year fluoxetine was launched, through 2002.

When examining trends and prescriber specialties and diagnoses related to prescribing these products, trends over a five-year period of time, from 1998 to 2002, were used. Data on drug utilization will be presented from sources FDA has available under various contracts. For this analysis, outpatient data was obtained from two IMS Health audits.

IMS is a source of marketing data commonly used by the pharmaceutical industry and government agencies, and is used to obtain numbers of prescriptions dispensed, as well as diagnoses related to the recommendation of pharmaceutical products in physicians' offices in the U.S.

[Slide.]

The first IMS Health Audit examined the National Prescription Audit Plus, or NPA Plus, as I will refer from now on, measures dispensed prescriptions from the outpatient pharmacy settings seen here. We have chain, independent, mass merchandisers, food stores with pharmacies, mail order and long-term care pharmacies.

The number of estimated prescriptions dispensed are obtained from a sample of approximately 22,000 pharmacies in the U.S., and

are projected nationally.

[Slide.]

Next, we examined data from the National Disease and Therapeutic Index Audit, or NDTI, from IMS Health. NDTI collects data on drug products and diagnoses mentioned during office-based physician visits.

A mention is a physician's treatment intention where they believe one of the selected antidepressants is appropriate, and important to remember is it could result in either a prescription, a refill authorization, or samples given to the patient.

Information on trends of diagnoses, patients, and treatment patterns occurring during these visits are linked to each drug. NDTI data are obtained from a sample of 2,000 to 3,000 physicians representing approximately 100 specialties in the U.S., and are projected nationally to reflect national prescribing patterns.

The exact distribution of the specialties participating in the sample each year is unavailable at this time, but is roughly proportional to the distribution of office-based

practice specialties in the United States.

[Slide.]

We will now examine antidepressant prescription trends, prescriber specialties, and diagnoses from 1988 through 2002. I will first describe antidepressant use in the U.S. for all ages and then zoom in more specifically on the younger pediatric and adolescent age groups.

[Slide.]

It was estimated that over 157 million prescriptions for SSRIs and atypical antidepressants were dispensed in the United States for all ages in 2002. The market leaders among these 10 products were sertraline, accounting for over 31 million prescriptions, followed closely by paroxetine, with 30.5 million.

[Slide.]

I will now graphically show you the use trends of these products since the launch of fluoxetine. This graph has a lot of information on it, but it displays the national estimates of antidepressant use in the U.S. in millions of prescriptions dispensed for all ages, so this y axis here is in millions, and each product is represented by a different color line.

Here, we see how the four products on the previous slide make up the highest volumes dispensed. Here, you see paroxetine, sertraline, fluoxetine, and citalopram. But more importantly, we see that for the past 15 years, there is an increasing and substantial number of prescriptions dispensed in outpatient pharmacy settings for these products.

We will now examine the estimated use of these products in the younger pediatric and adolescent populations.

[Slide.]

First, I must describe how we estimated these numbers. Since NPA Plus data does not include the demographic information about the patients receiving each prescription, we used NDTI to estimate the number of prescriptions dispensed to 1- to 17-year-olds.

NPA Plus and NDTI were designed by IMS to be comparable in terms of volume of prescriptions dispensed and the proportion of office visits mentioning products dispensed in larger volumes.

So, to estimate the number of SSRI and atypical antidepressant prescriptions dispensed to 1- to 17-year-olds, the proportion of office visits

in that population that involved the mention of one of these products were applied to the total number of prescriptions dispensed for that year.

[Slide.]

Applying the proportion of office visits to the national prescription estimates for 2002, I present to you the top five selected antidepressants in thousands of prescriptions dispensed to 1- to 17-year-olds.

Approximately, 10.8 million total prescriptions were dispensed for all SSRIs and atypicals in this population, representing a substantial 7 percent of the market in 2002.

Sertraline accounted for the highest volume of prescriptions dispensed, at 2.9 million, and paroxetine followed closely with approximately 2.2 million, and this is for 2002.

Next, I will more closely examine these patterns by breaking the 1- to 17-year age group into the younger pediatric population, which will represent 1- to 11-year-olds, and the adolescent population, which will represent 12- to 17-year-olds.

[Slide.]

When we examined use in these

subpopulations, we can still see substantial use of these products in both groups. The younger pediatric population accounted for approximately 2.7 million prescriptions dispensed in 2002. Sertraline again was the most commonly prescribed product, accounting for about 31 percent of dispensed antidepressants, followed by paroxetine and then fluoxetine.

The adolescent population accounted for approximately 8.1 million prescriptions dispensed in 2002, and this is close to about 5 percent of all antidepressants dispensed in that year.

Again, sertraline was the most commonly prescribed, accounting for 26 percent, but this time followed closely by paroxetine, with 22 percent.

[Slide.]

Now that we better understand the trends in prescriptions dispensed for these products to children and adolescents, we need to better understand the specialties of the physicians most often prescribing these products.

The top prescribers of SSRIs and atypical antidepressants in 1998 were compared to those of 2002, and the top ranked specialties are listed

here by age group and by year.

Here, it makes sense to see psychiatry as the top prescribing specialty over time since it is hard to diagnose mental illness in younger populations. There does appear to be some shifting in prescribers over time, though, as the pediatric specialty becomes responsible for a more substantial proportion of mentions of these products in 2002.

As you can see, the proportion of pediatricians prescribing doubles over that five-year period in both populations, or nearly doubles in adolescents.

[Slide.]

Now, we will examine the diagnoses most commonly associated with these products in office-based practices. All diagnoses naturally fell into the following four categories:

Mood disorders, represented here by the blue portion of the bar, include bipolar affective disorders and all depressive disorders; anxiety disorders are represented by the red portion of the bar, and they include anxiety, obsessive-compulsive disorder, and phobias.

Attention-deficit disorder is represented

by the yellow portion of the bar, and Other disorders are represented by the green portion.

Now, these Other disorders include other diagnoses for psychiatric illnesses, such as adjustment disorder, personality disorder, and psychotic disorders, as well as including diagnoses for autism, migraine, convulsions, menstrual symptoms, eating disorders, and drug and alcohol dependency.

We see nearly 900,000 physician office visits involved the mention of an antidepressant in the younger pediatric population in 2002. This represents approximately 1.6 percent of all visits in the U.S. for these products across all ages.

We also see that anxiety and mood disorders were the most common diagnoses in 2002, accounting for 30 percent and 26 percent, respectively, in this population.

Office visits involving the mention of one of these products in adolescents is much higher, at 2.6 million visits for 2002, and that represents about 5 percent of the visits in the U.S. Mood disorders were the most common diagnoses treated with this product, accounting for nearly 60 percent.

Next, we will look at these bars more in depth as we examine diagnoses trends for specific drugs in younger pediatric and adolescent populations.

[Slide.]

This slide contains a lot of information, but I believe it is important to show that not all of these products are used in the same way in the younger pediatric population.

The following graph displays the distribution of diagnoses for the top five antidepressants mentioned in 2002 to this population. Notice here the percent scale on the y axis. Each bar represents all mentions for these products to this age group, and the percent is what percent of the mentions for that drug were for each disorder.

In the younger pediatric population, we see some variation in how these products are being used, and from the previous slide, we saw that both anxiety and depression or mood disorders were primarily treated with these products. It is seen right here in the graph.

When we look at the top five, we also see that bupropion has the distinctive use in treating

attention deficit disorders in this population, so that middle bar signifies bupropion, and the yellow portion is ADD.

[Slide.]

In the adolescent population, we see there is not much variation in prescribing of these products. Mood disorders were the primary diagnosis being treated with all five products, but we do, however, once again see this distinctive use of bupropion for attention deficit disorders.

[Slide.]

Next, we wanted to determine if prescribing trends for these products has changed over the last five years. In the younger pediatric population, we saw a shift in prescribing from 1998 to 2002, from these antidepressants being used primarily to treat mood disorders, which were identified before as bipolar and other depressive disorders, to being used more to treat anxiety disorders, such as OCD and other anxiety or phobia disorders.

We saw that in the adult population, there was no change in prescribing from 1998 to 2002, and that continuously over this time period, these products were used to treat mood disorders in this

population.

[Slide.]

Some limitations of our drug use data analysis are, first, data on prescriptions dispensed include prescriptions filled in outpatient pharmacies only. Inpatient and institutional use of these products was not included in this analysis.

Secondly, prescriptions dispensed to 1- to 17-year-olds were extrapolated from the proportion of these populations visiting a physician and receiving a prescription sample or refill authorization for one of these products, and this methodology has not yet been fully validated.

Finally, data on diagnoses related to the use of these antidepressants reflects office-based physicians prescribing based on a small sample of physicians. The small sample size may make these numbers unstable and could underestimate the prescribing patterns of certain subspecialists.

Also, since these patients are not followed into the pharmacy after their appointment, a patient may not actually fill the antidepressant prescription.

[Slide.]

In conclusion, use of SSRIs and atypical antidepressants is substantial in children and adolescents, and appears to be increasing rapidly every year. Pediatric specialists, pediatricians, and primary care providers continue to be the leading prescribers of these products, and over the past five years, the proportion of pediatricians prescribing these products has nearly doubled.

Finally, diagnoses related to the use of these antidepressants are slightly different among the younger pediatric population who are being treated for mood and anxiety disorders, and the adolescent population who are being treated mostly for mood disorders.

Thank you.

DR. RUDORFER: Thank you very much.

This morning we heard from Dr. Murphy about the mandated adverse event review associated with one-year post-exclusivity for some medications. Now, I am pleased to welcome Dr. Solomon Iyasu from the Division of Pediatric Drug Development who will give us a review of that information for paroxetine and citalopram.

One-Year Post-Exclusivity Mandated Adverse Event Review for Paroxetine and Citalopram

DR. IYASU: Good afternoon.

Today, I am going to be presenting adverse event reports that have been received by FDA and reviewed as mandated by the Best Pharmaceuticals for Children Act.

[Slide.]

The Best Pharmaceuticals for Children Act was enacted January 4, 2003, and Section 17 mandates to FDA to review all adverse events for one year post-exclusivity determination, and then report to the Pediatric Advisory Subcommittee for their review.

[Slide.]

The data source for my presentation, as well as Dr. Mosholder's presentation following mine, is the FDA's Adverse Event Reporting System, which is a spontaneous and voluntary reporting system.

FDA maintains an electronic database of postmarketing reports of adverse drug reactions, and reporters to this system include health care providers, pharmacies, consumers, and pharmaceutical manufacturers. A large majority of these reports come from manufacturers.

[Slide.]

To make today's presentation relevant to today's topic, I will be focusing the later part of my presentation on the psychiatric adverse events that have been reported during this one-year post-exclusivity period.

[Slide.]

To give you some background about the drug that I will be talking about today, paroxetine is an antidepressant that belongs to the class of drugs which are called SSRIs, is marketed by GlaxoSmithKline.

Adult indications that are approved by FDA include major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder.

The typical adult dose, which are approved, are 20 to 60 milligrams per day. There are no approved pediatric indications, and the exclusivity was granted January 27, 2002.

I have to point out here that exclusivity to a sponsor can be granted without getting an approved indication as long as they do the study set that have been asked in the written request that FDA issues, and that they have met the

criteria fairly as part of the written request.

[Slide.]

To give you some important information that is on the label already, paroxetine is Pregnancy Category C drug, which means that paroxetine has not been studied in pregnancy and therefore should be used only if potential benefit justifies the risk to the fetus. It also should be used with caution in nursing mothers.

There is also information on the Precautions section of the label, suicide risk is inherent in major depressive disorders especially before remission occurs, therefore, high-risk patients should be supervised very closely especially during the initial phases of therapy.

There are also similar precautions about mania and also about seizures, and recommendations to use this medication with caution in patients who have a history of mania or seizures.

There is also, on the same section, adverse events with abrupt discontinuation, which includes symptoms like agitation, anxiety, dizziness, sensory disturbance, that is related to withdrawal, and therefore, the recommendation is to taper it slowly.

[Slide.]

Now, I would just summarize the drug use trends for paroxetine, extensively discussed by Gianna before me, but paroxetine is the second most commonly used SSRI in children. Both pediatric and adult prescriptions have steadily increased between 1999 and 2003.

The main diagnosis linked with its use include depression, anxiety, and obsessive-compulsive disorders in children.

Pediatric patients account for approximately 3.5 percent of the total U.S. prescriptions of Paxil between July 2002 and June 2003.

[Slide.]

To give you an overview of the adverse event reports that have been received by FDA since the original marketing for this medication, there were a total of 17,000 adult and pediatric reports including domestic and foreign that were received by FDA. This included duplicates, as well, and 68 percent of them were domestic. Less than 5 percent of these reports were in pediatric patients

Looking at the top 20 pediatric adverse events for this entire period, the pediatric

adverse event in the top 20 was similar to those reported in adults. The majority were limited events related to mostly the events that resulted from maternal exposure, prenatal exposure.

[Slide.]

Looking at the annual reports of adverse events for this drug since 1992, there was distinctly an increase in 2002 compared to prior years. These data, the bar graphs represent raw counts of adverse events that were received by FDA, and do not exclude the duplicate reports, and they are unadjusted for use.

You will notice that the last bar graph, which is really representing the first half of the year, the numbers were 87, which seems to suggest that there is this continuing increase that was observed in 2002.

[Slide.]

Just to provide some context, I want to mention the timeline for some important events that may have some importance in this deliberation.

First, the yellow line as you see here is the period of that inclusive post-exclusivity one-year period, and during that period, there was a BBC show, which is "The Secret of Seroxat," that

was aired on October 2002 in the British TV, which subsequently got very widespread media coverage around the U.S. and other parts of the world.

In 2003, the British Government warned against the use of Paxil, and FDA issued a talk paper on Paxil for its treatment of depression in June 2003. Following the post-exclusivity period, in October 27, 2003, there was an FDA public advisory for antidepressants and suicide.

The contents of this will be discussed more fully, I think when Dr. Laughren presents his talk.

[Slide.]

Now, focusing on the mandated period, which is a one-year post-exclusivity determination period, after manual review of the reports, there were a total of 127 unduplicated pediatric adverse event reports. The gender distribution was 61 females and 59 males.

The age distribution for these 127 reports were zero to 2, about 32, which mostly represented maternal exposures or prenatal exposures; 2 to 5, about 6, the majority were actually in the older kids.

The outcomes for the 127, 10 percent of

the reports included outcomes of death, which were 13. Approximately, a third of them also ended up in hospitals or at ER visits.

[Slide.]

The age distribution, to give you a flavor by type of exposure, is that in the maternal/breastfeeding exposure, the majority were in males, and in the direct pediatric exposure, the majority were females.

The age distribution, as expected, in the maternal/breastfeeding group, 32 of them were less than 2 years of age, which actually most of them were in less than 1 month. In the direct exposure, most of the reports came from older kids, mostly 12 to 16, and 6 to 11.

[Slide.]

Looking at the pediatric exposures by reasons for exposure to paroxetine, looking at 127, 33 of them were maternal exposure or breastfeeding exposure, and the rest of them are described in depression/dysthymia, 28; anxiety/panic or posttraumatic syndrome disorder, about 15; ADHD, 2; OCD, 1. There were about 18 of them that had multiple diagnosis of psychiatric conditions, and then Others, which are a smattering of other

conditions which occurred in single digit. Unknown were in 21, we did not have any information in the reports about what the reason for exposure was.

[Slide.]

Looking again at the 127, concomitant medications were described in 55 out of the 127 reports. Specifically, paroxetine was mentioned as the only drug used in 5 cases. In most, it was actually not described whether there was concomitant medication or not.

Reporters for this 127, looking at the type of reporter, one-third of the reports were actually from health professionals, two-thirds of them were from consumers, media, or litigation sources, which is really atypical in the sense that most of the reports that we get at FDA, two-thirds often come from health professionals.

The dose range in the reports range from 5 to 60 mg/day. This excluded the maternal/breastfeeding exposure. This was really looking at the children that were exposed directly.

[Slide.]

The pediatric adverse events, looking at them from predominant events, there were about 68 psychiatric adverse events, and discontinuation

syndrome or decreasing dose was observed in 7, maternal exposure in 33 as previously described.

Today, I am going to be focusing more on the psychiatric adverse events, which are 68 reports that were received, and then the rest of the presentation in terms of describing the other events will be in tomorrow's presentation which I will be doing to the same committee.

[Slide.]

Looking at those 68 adverse events, and looking at labeled and unlabeled events, there were about 9 completed suicides reported, 17 suicide attempts, and suicidal ideation in 11 patients, and occurrence of other psychiatric symptoms that included mania, impulsivity, disinhibition, or obsessive behavior, and so forth.

Then, unlabeled events were self-injurious behavior in about 10 patients, completed homicides in about 4, and then aggression, hostility, homicidal ideation in about 8 patients.

[Slide.]

Looking more closely at the psychiatric events, the gender distribution was 57 percent of them were in females. The age distribution, most of them were in the older children 12 to 16 years

of age, 60 percent of them, and 35 percent in 6 to 11 years old.

Concomitant medications were described only in 24 patients out of the 68, we did not have any information on the rest of them. In 20 of the 24 patients, there were other psychotherapeutic agents being used, as well.

Discontinuation or decrease in dose was noted in about 11 of the 68 patients that were reported.

[Slide.]

Going more in detail as to the discontinuation or decrease in dose with respect to psychiatric events, among the completed suicide, 1 out of the 9, there was discontinuation or decrease in dose involved; suicidal attempts, 5 out of the 17, and 2 out of the 4 for homicides, and then 3 out of the 8 for the aggression/hostility/homicidal ideation.

[Slide.]

Looking closely at the suicide attempts, which were about 17, the majority of them were being treated for MDD or bipolar disorder. Concomitant medications were mentioned in approximately one-third of these patients, and

discontinuation or decrease in dose in approximately one-fourth.

[Slide.]

Pediatric deaths, there were a total of 13 as I mentioned before. Because of the topic today, I will talk about the 9 completed suicides, and the rest of the patients will be discussed in tomorrow's presentation.

[Slide.]

Among the 9, the age distribution was 12 to 16 years, and then the gender distribution of 5 females and 4 males. Initial diagnosis in these patients, 5 of them was major depressive disorder, 1 explosive disorder, in 3 of them it was not known.

Duration of treatment ranged from 14 days to 1 year. Discontinuation was mentioned in 2 patients. Concomitant medications, that included also some psychotherapeutic agents, was mentioned in 4 patients, and there was possible substance abuse in 4 patients, and a history of prior attempts in 3 of them.

[Slide.]

In summary, the causality assessment was very difficult in many of the reviews that we have

done with these reports, and many of the psychiatric events that were described in the reports occurred in patients with underlying psychiatric disorders, therefore, severity of illness/underlying disease may play a role, and it was very difficult to disentangle its effect from what might have been going on.

There is also a prior history of suicide attempts in some of the patients, and in others, there was no negative history of this. The other factors in terms of patient factors are concomitant medications that were mentioned in several of these patients, and also the lack in others. So, there is the variability in terms of the type and the quality of the reports that we got.

In terms of the reporting factors, there was inadequate detail in describing the event. They also varied in terms of descriptions that were in the reports.

The timing of event in relationship to the medication was not always clear in many of these reports, and also ascertainment of reported events by medical professions was absent in many of these reports. The lack of follow-up information also made it difficult to assess.

[Slide.]

I also want to mention the nature of the data system that we have, which is really a passive spontaneous and voluntary system, and it suffers from a number of limitations.

Often there is underreporting of important events, and there may be also the reporting biases that are influenced by either media publicity, and also the well-known variability in terms of reports that we get or the frequency of report related to the length of time that a drug has been in the market. In the early period of the marketing, there are more reports than later.

The report quality, as I said, also may vary, missing details, example, concomitant medications is a common problem. Also, because this is really enumerated data, we could not really estimate true incidence rate of events or exposure risk for many of these medications that we have reports for.

So, the AERS database has some serious limitations in terms of interpreting the data that we have.

[Slide.]

In closing, the psychiatric events

described in the adverse event reports may actually reflect to the underlying disease, because many of these events are also unexpected in other natural progression of the disease or part of the disease picture.

It may also be a drug effect or other concomitant medication, or it may actually be lack of effectiveness of the drug, and it is very difficult from these reports to sort out what is going on.

Therefore, evaluation of the controlled trials is necessary to sort out causality in terms of the observed adverse events.

[Slide.]

I am going to continue with the next drug, which is citalopram, but I would like to acknowledge the following individuals for their contribution for their review.

[Slide.]

Next, I will cover, as mandated by BPCA, citalopram, and will be talking about the adverse events in detail.

[Slide.]

To give you some background again about citalopram, it's an antidepressant belonging to

SSRIs, and marketed by Forest Pharmaceuticals.

Its current approved adult indication is for major depressive disorder. The adult dose ranges from 20 to 40 mg/day. There are no approved pediatric indications.

The original market approval was July 17, 1998, and exclusivity was granted July 9, 2002.

[Slide.]

Again, to mention some of the relevant safety labeling which already exists, Pregnancy Category C, as I mentioned before, and also a caution against the use in nursing mothers.

There is also a Precaution section that mentions, similar to what is observed for Paxil, suicide risk inherent in depression and also the danger of activation of mania and hypomania.

Also, additional events mentioned in the precautions, any psychoactive agent may impair intellectual or psychomotor functions, and therefore, care should be exercised in prescribing these medications when individuals have to operate machinery or other things that may require intellectual and motor functions.

Seizures is another precaution that is mentioned especially in those with history of

seizure.

[Slide.]

Additional safety information in the Adverse Reaction section is about agitation with the use of citalopram, and also additional premarketing reports which are frequent, impaired concentration, depression, suicide attempt, and confusion; and infrequently reported in premarket reports are aggressive reaction, psychotic reaction, delusion, paranoid reaction, emotional lability, and panic reaction.

[Slide.]

To give you just a summary of the drug use pattern, it is the fourth most commonly used SSRI in children. Again, use had been increasing in recent years. Pediatric patients account for approximately 3.3 percent of the total U.S. prescriptions of Celexa.

Pediatric diagnoses most often linked with its use are depressive disorders, obsessive-compulsive disorder, and attention deficit order.

[Slide.]

Since marketing, there were over 6,000 reports which included also duplicates that were

reported to FDA, 79 percent of them were domestic. Less than 5 percent of the reports were in pediatric patients.

The top 20 pediatric adverse events were, looking at that, all adverse events related to in utero exposure were unlabeled, which actually happened to be in the top 20 for pediatric adverse events.

Adverse event reports for children involving direct exposure were generally similar to those reported for adults.

[Slide.]

After a manual review of the one-year post-exclusivity period, there were 42 unduplicated reports that were pediatric. Sixteen of them were in utero exposures, and resulted in unlabeled events and one death.

There were 26 children involving direct exposure, 8 unlabeled events, and no deaths in this group.

Looking at the outcomes, there were 16 serious outcomes, 10 hospitalizations, 4 life-threatening, and 2 was disability. For the direct exposure group, the dose range was typically 5 to 60 mg/day. The median dose was about 20

mg/day in these reports.

[Slide.]

Again looking at the age distribution, in the in utero exposure, most of them female, as well as in the direct exposure group, and age distribution is 0 to 1 in 15 patients, and then most of the direct exposure group, in older children.

[Slide.]

Looking at the reasons for exposure to citalopram, there were 26 direct pediatric exposures and then 16 in utero exposures. I am going to just focus on the adverse events pertaining to psychiatric, but these are the reasons for why they were exposed.

[Slide.]

There were only 5 psychiatric events, in 5 patients where there were psychiatric events, and these are broken down by labeled and unlabeled events.

In the labeled events are the cognitive impairment, aggression, agitation, mania, and delusions, suicidality, and psychotic reaction.

Unlabeled events are the violent/homicidal behavior, which were observed in 2 of the patients.

[Slide.]

Looking at these 5 patients with psychiatric events, there were 4 males and 1 female. The age distribution as 6 to 11 years with 2; 11 to 16, about 3 of them. Diagnosis in 4 of them was MDD, and 1 case was oppositional defiant disorder, ODD.

Concomitant medications were reported in 2 patients, Prozac in 1, and another, Keppra and clonazepam. Symptom resolved once citalopram discontinued in 4 according to the reports.

[Slide.]

In closing, I would like to say there were few psychiatric events that were reported during this one-year post-exclusivity period, unable really to determine causality due to limitations of the AERS database, therefore, we will continue to monitor these adverse events in children.

I would like to reiterate the same limitations that I mentioned before with respect to paroxetine when I talked about limitations of the AERS database.

Thank you very much for your attention.

DR. RUDORFER: Thank you.

Dr. Andrew Mosholder will now speak on the

Office of Drug Safety Data Resources for the Study of Suicidal Events.

Andy.

Office of Drug Safety Data Resources for the Study of Suicidal Events

DR. MOSHOLDER: Thank you very much.

I am very pleased to be here this afternoon. I am going to talk about how we looked at some of our Office of Drug Safety data resources to see if they would be relevant to exploration of this issue.

[Slide.]

It is very much a team effort and I want to start by acknowledging my colleagues who assisted me.

[Slide.]

The objective of my brief presentation will be to describe the data resources we have available in the Office of Drug Safety at FDA that are relevant to this issue, and, in particular, looked at two types of databases, the first being the postmarketing surveillance database that Dr. Iyasu just described, and also some population-based epidemiological databases.

Also, I will be describing the context of

spontaneous postmarketing reports of these types of events with newer antidepressants.

[Slide.]

Turning first to the postmarketing surveillance data from the AERS system as you have just heard about.

[Slide.]

We did a special search for these events, and I will describe the methods. The list of drugs is shown here, and it is the same drugs we have been discussing throughout the day. We limited the age on the report to patients 17 years or younger, and we looked at U.S. reports only.

[Slide.]

In the AERS database, the events are classified under particular adverse event terms according to the so-called MedDRA dictionary. We chose a list of event terms that we thought would capture suicidal behaviors and ideation. I will let you read for yourselves the list, but that was the list of terms that we searched in the AERS data base for those events.

[Slide.]

The results showed for all those drugs over their full marketing history, there was a

total of 524 case reports, of which 110 were death reports. I should add that these are raw counts, which means there was no hands-on review for duplicate reports.

Occasionally, the same case will be reported by more than one health professional or the health professional and the consumer, and those are referred to as duplicate reports. So, these are just the raw counts.

[Slide.]

Here they are broken down by drug, and you see they are ranked in order. You see fluoxetine has the most, and, roughly speaking, the numbers of reports parallels the prevalence of their use in the pediatric population, so that is not too surprising.

[Slide.]

What this displays is the same totals broken down by year of reports. So, we see the year the report was received down here on the x axis, and the number of reports.

A couple of things to observe here. First of all, for most of the drugs, we see that there is between, say, zero and 10 reports annually, and then, of course, there are these two sort of

exceptions to that. There is a peak over here in the early '90s, and that is for fluoxetine, and then in the last two to three years, there is another peak, and that is for paroxetine.

The one thing to point out here relevant to the fluoxetine, as I am sure everyone is aware, this peak coincides with the controversy in the early '90s about whether fluoxetine can induce suicidality. In fact, in 1991, there was an advisory committee about that topic.

To understand this increase with the paroxetine reports, we looked at that in a little more detail, as I will show you.

[Slide.]

This shows the proportion of reports according to whether they were consumer or health professional, and the interesting thing here is that while the health professional reports have remained fairly constant over the years, what we see in the last two to three years is an increase in the proportion of reports that are coming from consumers, which, of course, doesn't mean that they are not legitimate reports, but it does illustrate that there is some influence on the spontaneous reporting that is encouraging consumers to report

more of the these events in the last few years, and that seems to account for this increase.

[Slide.]

To go into things a little more in depth, we decided to look at reports from the first three years of marketing and do an in-depth review.

We took reports for all 10 drugs from the first three years that they were marketed in the U.S. This is a standard way in pharmacoepidemiology of comparing reports across drugs to account for the so-called Weber effect that applies during the first three years of a drug's marketing history.

Even so, during this time period, there was limited pediatric use of these drugs, and because of secular trends, changes in reporting systems, and other variables, it is still very difficult to make quantitative comparisons between drugs.

[Slide.]

So, we looked at these reports, we eliminated duplicate reports, and we chose four suicide-related categories - suicidal ideation, suicide attempt, completed suicide, and self-mutilation, and classified the reports into

one of those categories.

[Slide.]

This shows the results. There were 94 reports retrieved from the AERS system. After review for duplicates, there were 78 unduplicated reports, which gives you an idea of the proportion of duplication. It is something like 15 percent.

This was for 9 drugs, no cases for nefazodone. Out of these 78 reports, most were female, most were over 12 years of age, and that is consistent with what we know about the epidemiology of suicidal behavior in adolescents. Most of the events were classified as suicide attempts.

There were 7 completed suicides, 6 with fluoxetine, 1 paroxetine, 4 males, and 3 females. We found no reports of rechallenge with the same drug, which is sometimes used as an indication of evaluating the causality.

[Slide.]

This slide shows the numbers of reports by category here and by drug. If you look at the total, you see that, as I already mentioned, 67 out of 78 were in the suicide attempt category.

Again, these are ranked in terms of the totals. You see that fluoxetine again has the

most. Again, this sort of roughly parallels the prevalence of their pediatric use.

[Slide.]

So, interpreting these results, we would say that suicidality was reported with all drugs. The drugs with the largest numbers of reports coincided, roughly speaking, with the greatest amount of pediatric use.

The reporting is variable and appears to be influenced by various events and also because of the quality and variability and low pediatric use, the data really do not support quantitative comparison between drugs.

[Slide.]

In general, AERS data are most useful for distinctive or rare adverse drug reactions, such as aplastic anemia. The problem here, as Dr. Iyasu has already described, is that the outcome of interest that we are tracking, which is suicidality, is also an outcome of the indication for which the drug is prescribed, so that it is very difficult to sort out whether the drug played a role or whether it was the underlying disorder from evaluating data of this type.

[Slide.]

I want to move on to look at some other data resources that we have in ODS and tell you about that.

[Slide.]

We looked at four principal sources that could be used, one, the Tennessee Medicaid. That is a health care claims database. We have two surveillance databases. I will let you read the descriptions, but they are maintained by CDC and the Consumer Products Safety Commission.

This one applies to hospital emergency rooms, and this one applies to emergency rooms and also ambulatory care.

Finally, there is the Oregon Adolescent Suicide Attempt Data System. In the State of Oregon, adolescent suicides and suicide attempts are reportable conditions, so that the State Center for Health Statistics maintains a database on those reports.

[Slide.]

To summarize briefly, there are significant limitations in attempting to use these data sources to evaluate this issue. One was rarity of completed suicide, difficulty in identifying individuals with outcome of completed

suicide. It may not generate a health care claim, for example.

There is great difficulty in classifying non-fatal suicidal behavior, as we have already heard about, difficulty obtaining data on drug exposure prior to the event, lack of suitable control groups, confounding by indication, and privacy restrictions.

[Slide.]

In conclusion, for the study of this issue of pediatric suicidal behavior associated with antidepressant treatment, the available pharmacoepidemiological data and postmarketing surveillance data is of limited utility, and randomized, controlled trial data should be superior to these sources.

Thank you very much.

DR. RUDORFER: Thank you.

Open Public Hearing

DR. RUDORFER: We will now turn to the afternoon portion of our open public hearing.

I am mandated to read the ground rules for meetings of general matters, so if you will bear with me for a moment, I need to address our open public hearing speakers.

Both the FDA and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at this 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 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 any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

With that, we will turn to our first

afternoon speaker, David Fassler.

David Fassler, M.D.

DR. FASSLER: Thank you. My name is David Fassler. I am a child and adolescent psychiatrist practicing in Burlington, Vermont. I am speaking today on behalf of the American Psychiatric Association where I serve on the board of trustees.

The APA represents over 35,000 psychiatric physicians across the country. The APA receives funding from a variety of sources including pharmaceutical companies, but no pharmaceutical funding was used in conjunction with my appearance today or the preparation of my comments.

You have already heard lots of testimony today, so let me try and briefly highlight and underscore a few key issues.

First, childhood and adolescent depression is a very real illness which will affect between 3 and 5 percent of all young people. The good news is that we can help most kids who suffer from this disorder. Intervention is most effective when it begins early and when it involves a comprehensive treatment plan individualized to the needs of the child and family.

Because we care deeply about children, we

encourage parents to be advocates for their kids, to ask lots of questions about any proposed course of treatment. We also encourage the FDA to develop mechanisms to enhance access to data from clinical trials including negative trials, as well as unpublished research.

We believe that such access would facilitate scientific discussion and dialogue and help physicians and parents make fully informed decisions about treatment options.

Second, with specific reference to suicidal ideation, it is important to emphasize that such thinking is always a very real concern, and as you have heard this morning, it is also not uncommon.

From the Youth Risk Behavior Survey, we know that 1 adolescent in 5 thinks about suicide each year, and that by the end of high school, at least 1 in 10 has made an actual suicide attempt.

Third, medications can be extremely helpful and even lifesaving for some children, but medication alone is rarely a sufficient treatment for complex child psychiatric disorders such as depression.

Finally, we are concerned that the

publicity surrounding this issue may frighten some parents and discourage them from seeking help for their children. This would be a real tragedy since the reality is that we really can help most of these kids.

DR. RUDORFER: Thank you, Dr. Fassler.

Our next speaker is Dr. Lawrence Diller.

Lawrence Diller, M.D.

DR. DILLER: Last but not least. I am behavioral developmental pediatrician who has prescribed psychiatric drugs to children for 26 years. I have no financial connections to the industry.

I am the author of Running on Ritalin and Should I Medicate My Child.

As a front-line practitioner, I have lost faith in my research academic colleagues to provide me the data information, opinion, and conclusions in an objective and unbiased fashion. I desperately need that information in order to validate and augment the clinical decisions I must make every day on who does and doesn't get medication.

Unfortunately, in my quarter century of practice, I have seen child psychiatry's biologic

revolution hijacked by a for-profit drug industry. Drug companies so pervasively influence academic research, professional education, now direct consumer information, ultimately determining the very way society views its own problems.

I see top research leaders in the field of child psychiatry simultaneously publishing papers in scientific peer-reviewed journals while appearing in press conferences for corporations that have funded the research, which is then reported in the Wall Street Journal.

We learn of nonpublication agreements of negative finding studies and limited access to raw data that potentially allows for completely different interpretations or conclusions based upon the published information.

At this time, the conflict of interest between my academic colleagues and the drug industry rivals that of the stock analysts and the brokerage firms. Doctors are at risk of being regulated by the government, but this is unlikely to happen soon since the public and the Congress have been similarly influenced or bought by these powerful corporations.

Unfortunately, it will take children dying

followed by trial lawyer class action suits to get changes either in the practice or the regulation of the SSRIs. That is a heck of a costly way, both the individual families and the public, for what should be routine formal postmarketing drug surveillance funded by neutral third parties.

Until then, I hope there is more government-funded research, but as long as I only have research funded or suppressed by drug companies, I will remain quite cautious and hypervigilant over what I prescribe the youth of America.

Thank you.

DR. RUDORFER: Thank you, Dr. Diller.

At this time we are going to take just a very quick break and return for further speakers from the FDA. Let's say five minutes if possible. Thanks.

[Break.]

DR. RUDORFER: We have three additional speakers from the FDA who will address some of the important data at hand and that is still emerging.

First, I am pleased to introduce Dr. Thomas Laughren, who is team leader of the Division of Neuropharmacologic Drug Products, who will

discuss with us the regulatory history on antidepressants and suicidality, and give us an update on current plans for the analysis of pediatric suicidality data.

Regulatory History on Antidepressants and Suicidality and Update on Current Plans for Analysis of Pediatric Suicidality Data

DR. LAUGHREN: Thank you, Matt.

[Slide.]

I am going to talk very briefly about the regulatory history of antidepressants and suicidality, and then spend most of my time talking about our current plans for looking at the pediatric suicidality data coming out of the controlled trials

But first I would like to thank the families who came forward this morning to talk about their very personal stories, both the families that talked about tragic outcomes and those who talked about children who appear to have been helped by medications.

It is very hard to do that, and I think it helps us to put all of this discussion in context, but a very important point, and this has been made several times, it is very difficult to assess

causality based on individual cases. That is true both of those cases where the outcome is tragic, but also true of the cases where the outcome is good.

For either of those, we have to turn to controlled trials, so my focus is going to be on the controlled trials.

[Slide.]

What I have given you in this slide is the standard language which is in all antidepressant labeling, and has been in antidepressant labeling for decades. This is in the Precaution section. Essentially, it warns clinicians of the possibility of a suicide attempt in major depressive disorder, and advises clinicians especially early in treatment to watch patients very carefully.

Now, this statement does not explicitly warn of the possible linkage between antidepressant use and the emergence of suicidality, but I think it allows for that interpretation and, in fact, this idea that antidepressants may be associated with the emergence of suicidality early in treatment has been around for a very long time in psychiatry.

[Slide.]

This is a statement from a textbook of psychiatry published in 1960. This was the time at which the tricyclic antidepressants had just come on the scene. Let me read it.

It says, "With beginning convalescence, the risk of suicide once more becomes serious as retardation fades."

[Slide.]

What this statement is referring to is what is commonly known as the roll back phenomenon. This is the observation again of emergent suicidality early in treatment and the belief, the belief that that is in some way linked to the use of the drug, and the view, the mechanism proposed is that antidepressants give patients increased energy, particularly those with psychomotor retardation, that allows them to act on their suicidal ideas before the drug has had a chance to affect mood.

So, this is one proposed mechanism for this observation. In fact, it is only one of several proposed mechanisms. When we met with the advisory committee in 1991, to talk at that time about Prozac and the possibility of suicidal

induction, Dr. Martin Teicher from Harvard University reviewed a number of proposed mechanisms to explain this observation including the roll back phenomenon.

But he also talked about the possibility of actually a paradoxical worsening of depression, in other words, the mood actually becoming worse rather than better.

He talked about the possible role of akathisia, which is associated with many of these drugs, about the induction of anxiety and panic attacks by some of these drugs, about the idea that patients with bipolar depression may experience a stage shift, in other words, moving from depression to a mixed state, and finally, even the induction of insomnia.

All of these ideas, the idea is that once these behaviors are induced, there is then a link from that behavior to suicidality, and all of these proposed mechanisms have some plausibility, but it is quite a different matter between proposing a mechanism and empirically establishing that there is, in fact, a link between the use of an antidepressant and the emergence of suicidality.

[Slide.]

That is really the question that we are dealing with here today and that is the question we hope to be able to address with these clinical trials data for these pediatric studies: Is there a causal link between antidepressant drug use and suicidality in pediatric patients with major depressive disorder or with other psychiatric disorders?

We agree that this is a critically important question to answer, but we also feel that it is important to answer it in a careful and thoughtful manner because to err in either direction has significant consequences.

Clearly, we do not want to miss a signal of increased risk of suicidality, because that would give us greater comfort in the use of these drugs than would be warranted.

On the other hand, we don't want to reach a premature decision on the strength of the signal because that could result either in the overly conservative use of these medications or in their lack of availability all together for treating pediatric depression. So, it is important to get it right.

[Slide.]

In this slide, what I have done is to list the 9 drugs that are involved in our ongoing review. You have seen this list before today. This involves a total of 25 studies in pediatrics, 16 of them in major depression, the others in various other pediatric disorders, involving a total of over 4,000 patients.

[Slide.]

Right now let me talk a little bit about how the signal came onto our radar screen. We had reviewed over the past three to four to five years pediatric supplements for 8 drugs, and we looked at the safety and efficacy data for these drugs.

In the course of putting together a report for FDA, companies code their adverse event data, and they do this in their own ways. We don't tell them how to code the data, they choose their own dictionaries and they set about coding the data before they send it in.

This applied to any events suggestive of suicidality, as well as any other adverse events. We reviewed those supplements over this period of three to four years, and suicidality did not emerge as a matter of concern based on those reviews.

However, the Paxil review did raise a

question about data management in that events suggestive of suicidality were coded under the general preferred term "emotional lability."

This struck the reviewer as rather odd, and so in responding to GSK, we asked them to separate out the verbatim terms suggestive of suicidality under a term specific to suicidality.

[Slide.]

That request to GlaxoSmithKline resulted in additional work and ultimately resulted in a report on paroxetine and pediatric suicidality. That report went first to the MHRA -- that is FDA's counterpart in the UK -- and shortly thereafter to FDA in May of last year.

That report indeed suggested an increased risk of suicidality associated with paroxetine use in particular in one of the three studies done in pediatric depression.

[Slide.]

What I am going to do in the next two slides is to quickly walk you through a timeline of key events that occurred over the past eight months to try and give you a sense of how we got from the time of that initial report up to the present time.

So, that report was issued in May. In

June, both FDA and MHRA issued regulatory responses. As you heard earlier, the MHRA essentially contraindicated paroxetine in pediatric depression. FDA came out with fairly strong language that recommended against its use in pediatric depression, but stopped short of a contraindication, and, in essence, we said that we were continuing to look at the data.

In July, we issued a request to sponsors of the eight other antidepressant products asking them to look at the suicidality data in their databases using an approach similar to that, that had been used by GSK, and I will talk about that approach a little bit later.

So, in essence, we wanted to look at summary data from the other programs, similar to what had been given to us for Paxil. In August of last year, we went back and relooked at the suicidality data in the pediatric supplements.

In August, Wyeth, the manufacturer of Effexor, having responded to our July request and having looked at their data, decided that they did have a signal and they made a labeling change which they are allowed to do under changes being effected without our prior approval, so they changed their

labeling, adding information about that perceived signal, and they also sent a Dear Doctor letter which essentially recommended against the use of Effexor in pediatrics.

Also, at that time, MHRA contraindicated Effexor in pediatric depression.

In September of last year, we held an internal regulatory briefing at FDA. We hold these briefings basically to update upper management on key issues that are before us, and this certainly was a key issue, and we have the briefing.

There were a number of recommendations that came out of that briefing. Two were of critical importance to our ongoing review. One of those was the suggestion that we think about reclassifying the cases, because there was some uncertainty about what this diverse array of events coded under this broad term "possibly suicide-related" actually meant. So, there was a suggestion that we do that.

There was also a suggestion that we think about doing a more refined data analysis, allowing the use of adjustment for covariates.

[Slide.]

In September and October, we began to get

responses to our July requests for summary data for other antidepressants, and it gave us some cause for concern, because we were seeing that sponsors had not used exactly the same approaches that we had suggested in our July request.

In October, we issued an updated Public Health Advisory, at this time essentially broadening the concern to all antidepressants. In essence, we advised clinicians to use caution when using these drugs in pediatric depression, essentially, to pay attention to the language that is already in labeling.

In October, having thought more about a patient level data analysis allowing us to look at covariates, we issued a response to all antidepressant manufacturers asking them to give us patient level data sets to allow us to do this analysis.

Also, in October, having thought more about the reclassification effort, we decided, instead of trying to do this inside FDA, we decided to go outside FDA and get an outside expert group to help us with this reclassification.

In November and December, having thought more about this problem of case finding that I had

alluded to earlier in response to our July request, we issued a second and actually then a third response to companies to give us cases to look at.

Finally, in December, as was pointed out several times earlier today, MHRA, having completed its review of all the pediatric data, decided to go ahead and contraindicate all the other new generation antidepressants except for fluoxetine.

So, as I understand it, fluoxetine is the only current generation antidepressant available for treating pediatric depression in the UK.

[Slide.]

I have used the terms summary data and patient level data several times, and I want to make sure that you understand what it is I am talking about.

By "summary data," I am referring to data tables that are provided to us by sponsors based on their own analyses, that include only numbers of patients with events as the numerators and either total patients exposed or total accumulated person-time as the denominators.

These are the data that we got from Glaxo back in May and that we have since gotten from all the other sponsors. These are summary data.

"Patient level data" are data sets that are provided by sponsors in response to a detailed request from FDA for electronic data sets that are structured to include one row per patient participating in each study, so that we have data for all patients participating in those trials, and we have multiple variable data for each patient.

These data sets allow us to do adjustments for covariates that may be important for any particular event of interest, while summary data of course do not.

In the next slide, I am going to summarize for you the suicidality risk data from the seven programs for the antidepressants that were studied in pediatric depression. Before I do that, I want to clarify what the two event categories are that we are dealing with.

[Slide.]

The first event category is an umbrella term, "possibly suicide related." This is the term that Glaxo developed in looking at its own database, and it is the term that we asked other sponsors to look at in going through their data sets.

Basically, it was intended to capture any

event in their databases that included any thoughts or behaviors that the sponsor considered to represent possible suicidality, so it is a very broad term.

The term "suicide attempt," as defined for these analyses, was the subset of that umbrella term, so a subset of these originally captured events that met the conditions of having any indication of self-harm. So, this is how "suicide attempt" was defined in this analysis.

So, the overall umbrella term "possibly suicide related" and then the subset of those events that had some indication of self-harm.

[Slide.]

This is, I am sorry, a very busy slide. These are the risk data coming out of these seven programs, and I am going to walk you through this.

Again, there were seven programs - paroxetine, fluoxetine, sertraline, venlafaxine, citalopram, nefazodone, and mirtazapine. I have divided these up into different colored rows so you can see the number of studies in each program, two of them involving three studies, the rest all two-study programs.

This is risk data. So, this is simply the

number of patients having one or more of these events divided by the total number of patients exposed. There is no adjustment for time here. This is crude risk. In parentheses, I have got the percent.

The way this is set up, first of all, the overall umbrella category "possibly suicide related," and then the subset of these events that met the criterion for "suicide attempt." Again, that criterion was any indication of self-harm.

Let's just walk through the individual programs. Again, paroxetine had three trials. For the first trial, 329, you see a risk ratio of roughly 6, 6.5 percent for drug, 1.1 percent for placebo, so definitely a signal of something.

However, if you look at the other two studies in this program, 377 and 701, these were also fairly large studies, in fact, this one was slightly larger, the risk ratio was around 1. So, the signal for paroxetine is essentially coming out of one study, a big signal, but the other studies show essentially nothing.

If you look at fluoxetine, there really isn't any signal coming out of the fluoxetine program, the risk ratios are all in the vicinity of

1. For sertraline, again, you have one study which is suggestive of a signal, 4.1 percent versus zero, drug versus placebo, but for the other study, similarly sized, in fact, these were identically designed studies, there is no signal. It's 2.2 percent for both.

If you look at venlafaxine, there appears to be a signal coming out of both studies in that program. For citalopram, again, you have two studies, both large studies. One study, no signal, in fact, if anything, it is slightly in favor of drug. The other study, a weak signal, but many more events, many more events in this study, and a risk ratio of rough 1.6.

The number of events in the nefazodone and mirtazapine programs is so small that it is hard to know what to make of that.

There are two points that I want you to take away from this slide. First of all, I think in looking at these data, there is enough of a suggestion of a signal of something that clearly it is worth pursuing this.

Everyone at FDA concluded that there is obviously something going on here, we need to

pursue this, but one troubling thing about this set of data is the inconsistency in the signal across studies within the programs.

In most of these programs where there is a signal except for venlafaxine, it appears to be coming from one study. So, that is something that we felt that we need to try and explore in some way.

[Slide.]

In the remaining time what I am going to do is talk about the concerns we have had in interpreting these suicidality data.

I should have mentioned at the outset, I am sorry, I made a number of changes in my slides over the weekend, so I apologize. I have had to delete some of the material. I didn't talk about efficacy, and I am not planning on talking about efficacy here, you know, in the discussion section I am happy to do that.

I thought it would be useful if I focused instead on the clinical cases because one of the concerns we have had is what these reported events that are captured under this broad term "possibly suicide related" actually represent.

So, I put together a number of slides over

the weekend to try and give you a better sense of that, and that is why the slide package you have is different than what I am presenting.

In any case, there are three concerns that we have looked at. One has to do with case finding, and that is the first bullet, and I alluded to that earlier. In looking at the summary data that sponsors gave us, it appeared that somewhat different approaches were used to capturing and presenting these cases to us. So, I will talk about how we explore that.

Secondly, there is the issue I talked about of the question of how you classify these cases into meaningful categories for the purposes of analysis and regulatory decisionmaking.

Finally, I have already alluded to the issue of the inconsistency in the signal across individual studies within the programs, and that was one of the findings that led us to want to do a more refined analysis looking at covariates. It is one of several reasons, but that is one justification for that analysis.

[Slide.]

Let me first focus on the issue of case finding. This is a very busy slide, I apologize for

that, but I will walk you through it. This is the algorithm that was used initially by Glaxo and that we then asked the other companies to apply to their databases in finding cases.

In essence, there were two components to this. There was an electronic string search, which I will talk about, and what they were to do is to apply this string search, and they were to blindly look at the events that were turned up with that search and decide whether or not those events were of interest from the standpoint of suicidality and then give us those data.

So, the string search was one part of the search. The other part was to do a blinded review of narratives for any deaths or other serious adverse events in their databases. Now, there were no deaths in any of these trials, so this part of the search focused on narratives for serious adverse events.

So, let go back to the string search. There were two components to the string search. First of all, we asked companies to look at their preferred terms. These are the dictionary terms that companies use in coding data. We asked them to look at the text string "suic" and "overdos" to

pick up any instances of events that were coded under either suicidality or overdose, or any variation of that.

Now, the bullet underneath here suggests that we ask for a separate listing for events coded as accidental overdose. Accidental overdose is usually, just to give you an example, where a patient misses a dose on one day and then on the next day thinks he should take two doses. So, that would not be a suicide attempt, that is what is usually considered an accidental overdose.

So, we didn't want those to be included among the events, but we wanted to be able to see them to see which ones were excluded.

The second part of this was to do a string search for the actual verbatim investigator terms.

Here we used -- again, this is the approach that was used by Glaxo, and we passed this on to the other sponsors -- a variety of terms suggestive of either self-harm or of overdose or suicidality.

So, this was to go through the investigator terms and try and capture any events that were suggestive either of suicidality overdose or some type of self-harm.

Again, we allowed exclusions from that list for what I am calling false positives. A false positive, for example, would be when the text string inadvertently picks up a term that has nothing at all to do with suicidality, so, for example, the test string g-a-s, for gas, would pick up gastrointestinal, so we allowed companies to exclude those events from their lists.

Once they came up with a list of events that they considered representative of suicidality, we asked them to go through and blindly select out from that overall group of possibly suicide-related events, the events that were suggestive of suicide attempt.

Again, the definition of that was any indication of self-harm. So, again, the overall umbrella term and then the subset of suicide attempts.

We asked them then to provide us a narrative of all of those cases that had been turned up. So, that was the algorithm for finding events.

[Slide.]

Now, we had hoped in doing that, that we would get a fairly complete accounting of the

original list of events that had been turned up and the exclusions. Unfortunately, we weren't explicit about that, and it is not what we got.

Often, we got only the narratives for the events that the companies had already decided represented the suicidality set, and did not include the exclusions. Often, there was little explanation for why certain events had been excluded or what the criteria had been in excluding events. So, that was one problem.

[Slide.]

Another problem was that we had failed to ask for narratives on accidental injuries. I had mentioned earlier that we had asked for a listing of accidental overdose, but not accidental injuries. In talking to sponsors about this, and asking them to give us some of the accidental injuries, we turned up a couple of events that caused us some concern.

This was one particular example. This was a child who had been excluded, this event had been excluded from the list. It was a patient who stabbed himself in the neck with a pencil while taking a test.

Now, this probably was an accident, but it

occurred to us that we wanted to see all of these. We wanted to see all of the events that had been excluded as accidental injury, so that our experts -- because at this point, we had already decided to go outside and have an outside group look at these cases, we wanted to have a complete set of events for them to look at, so we asked for all the accidental injuries.

[Slide.]

Another thing that we discovered when we started talking to companies about the application of the search algorithm is that one company in particular acknowledged that it had not done the searching blindly of the narratives for serious adverse events, and this was a problem, because again this had to be done blindly to be done properly.

Another issue that turned up when we started looking at these cases is that some companies had excluded events that were not "treatment emergent."

Now, when looking at adverse event data, it is entirely appropriate to be interested in events that either occur for the first time on assigned treatment, or if present at baseline, are

worse on treatment than at baseline. That is what we mean by "treatment emergent."

So, it is not that it was improper to do that. The problem was that we wanted to see which events were excluded for that reason, so that we could assess ourselves whether or not it was an appropriate exclusion. So, again, in going back, we have now asked for all the events excluded as treatment emergent.

Finally, in looking and comparing the strength of the signal coming out of the pediatric supplement re-review and the signal coming out of the summary data, in one particular case we noted a fairly substantial discrepancy between the strength of the signal. That again raised a question about case finding.

[Slide.]

So, the bottom line is that having looked at these initial summary reports from companies, we did not have complete confidence in the case finding, so we issued, as I mentioned, a second request for clarification both of how the search had been done and then a complete accounting of how the companies winnowed down to the list of events that they considered to represent the suicidality

set, so that we could see what events had been excluded, for what reason, and so that we could be confident that we had a complete set of data to start with.

In addition, we asked for narratives for all serious adverse events rather than just the ones that the companies decided represented suicidality, so again our outside experts could go through all of these data and independently and blindly themselves decide which were representative of suicidality.

So, that is the case finding issue.

[Slide.]

Next, I want to talk about the issue of reclassification. There were two issues that again caused us concern about the approach to classifying these cases.

One was in looking at the events that got captured, we noticed that there was an extremely wide variability in the types of events that got included under either the broad umbrella category or also under the narrower term "suicide attempt."

We also notice that companies appeared to have used very different approaches to capturing the subset of events labeled "suicide attempt."

Some companies used a fairly conservative approach, others essentially labeled all of the events as suicide attempts even though there was nothing in the case report to suggest self-harm.

[Slide.]

So, what I have done, and these are the slides that I put together this weekend, I have gone back to look at the 109 patients having one or more possibly suicide-related events. These were the patients who were included in the numerators for the table that I showed you earlier.

So, these are the cases, and the collection of 109 patients goes across all studies, not just the depression studies.

A couple of points to make. First of all, the point about there were no completed suicides among these 109 cases. As I mentioned, there was very wide variability in the types of verbal expressions and behaviors that were considered by companies to be representative of suicidality.

Another problem with these cases is that the majority of them were not well described. We did not have the level of detail in these cases that one would have liked to do a rational classification.

My goal in doing this is to provide you with a sense of the range of events to consider. You know, this is not a formal classification. Again, we have contracted with an outside group to do the classification, but I wanted you to have a sense of the kind of variability in the case material that we have, so you can appreciate why we consider this a problem.

[Slide.]

There are two key questions. First of all, is it meaningful to subsume such diverse events under this umbrella term "possibly suicide related," and is it reasonable to define "suicide attempt" as that subset of events that have any degree of self-harm, is that a reasonable definition of "suicide attempt."

I want to be very clear about this. I am not attempting to trivialize in any way any of the events that occurred. I mean these are sick kids, all of these events have importance.

The question is what classification approach is most useful and clinically meaningful in preparation for doing an analysis and in preparation for taking regulatory action. That is really my goal here.

[Slide.]

Let me describe how I approached these cases. For a small fraction of them, patients had more than one suicidality event, so for consistency, I focused on the first one. That only applied to about 10 percent of these patients.

Then, I went ahead and I selected a subset of those events where there was any indication at all of self-harm. Again, this is to mimic the approach that the sponsors were supposed to use in defining suicide attempt.

For those patients who had an indication of self-harm, I looked at whether or not they were hospitalized for the event and whether or not there was any indication of suicide intent. By that, I mean either an active expression of intent in that case narrative or I accepted any concurrent indication of suicidal ideation.

For the remaining patients who had suicidal ideation without self-harm, again, I looked at whether or not they had been hospitalized for the event and whether or not there was a suicidal plan, so there had to be an active expression in the narrative of a suicidal plan in association with that suicidal ideation.

[Slide.]

Overall, the hospitalization rate for these 109 patients was 43 percent. The subgroup having suicidal ideation without any indication of self-harm was 39 percent and the remainder -- these were the patients who had some indication of self-harm -- was 61 percent.

Again, there were no complete suicides, all patients were fully recovered from these instances of self-harm. As sort of an interesting aside, in about 30 percent of these cases, the self-harm event appeared to occur in the context of some kind of interpersonal conflict.

A typical situation would be a child had an argument with a parent or a sibling or a peer or a girlfriend or boyfriend, impulsively engaged in some kind of self-harm behavior, and the event was over, and there was no indication of suicidal ideation. That applied in about 30 percent of these cases.

[Slide.]

In going through the self-harm case events in more detail, again, there were a total of 66 of these. Nineteen of these involved cutting behavior. In almost all of these cases of cutting,

it appeared to be a superficial wound. There was one case where a young girl cut herself so deeply that there was actually blood loss. In another case there was an indication that the patient needed three stitches to suture the wound, but in all the other cases, they appeared to be superficial.

There were 37 overdoses. Again, there was a wide range of different types of behaviors that were classified as overdose, ranging at the one end, one patient was classified as an overdose for taking 20 percent more medication than was prescribed.

Ordinarily, this would not be considered a suicide attempt, and there was no indication in that case of suicidal ideation, but that was classified as an overdose.

At the other extreme, there were patients who took fairly substantial quantities of either study medication or usually over-the-counter medication, so a very wide range in terms of amounts of drug that was taken.

There were two cases characterized as hanging behavior. In both of those cases, what they really were, were interrupted attempts. These

were children who, in the presence of family or parents, engaged in what was described as hanging behavior, it was immediately interrupted, and so in neither case was there any actual self-harm. So, these were interrupted cases.

The case of burning was similar. This occurred in the context of family, and the child was immediately interrupted although in that case there was some minor burns.

One case that was classified as a suicide attempt was the case of a young girl who slapped herself in the face, and that was it. That was all there was in that case, and there was no suicidal ideation described in that case.

Then, there were six other cases where all that the case indicated was minor self-mutilation. It was not specified what the self-harm behavior was.

[Slide.]

Now, let me give you a breakdown of what I found when I looked at, first of all, the cases of cutting.

There were 19 of these. In most of these cases, in 16 out of the 19, there was no indication of either suicide intent or even any concurrent

suicidal ideation, and 4 of those 19 cases actually ended up being hospitalized.

So, most of those cases did not involve hospitalization and did not involve suicide intent or ideation.

[Slide.]

For the 37 cases of overdose, there were more hospitalizations here, but again, if you notice in this column, in almost every case there was no indication of suicide intent or suicidal ideation.

A number of the hospitalizations could be characterized as an overnight hospitalization for observation.

[Slide.]

Finally, for the remaining 43 patients who had suicidal ideation without self-harm, again, I looked at whether or not there was a plan, an expressed plan, and in most of these cases there was not a plan.

In the 7 where there was a plan, they were hospitalized, but nevertheless, a majority of these patients with suicidal ideation without self-harm were hospitalized.

[Slide.]

So, I hope that gives you a little bit better sense of the range of behaviors that we are dealing with here and the difficulty we had in including all of them under this one umbrella term of "possibly suicide related."

As I said, we have gone to an outside group. What I want to do in this slide is talk a little bit about the Columbia University Suicidality Research Group and why we picked them.

I talked to a number of people about who should help us with this, and most everyone I talked to said that this group has the expertise to do this. They do have expertise, they have been doing this for almost 20 years.

In the last 5 years alone, they have more than 40 funded grants to do this kind of research. They are in the business of developing measures and manuals and methodologies for evaluation of suicidality.

They are a center for training on suicide assessment, and research on both reliability and validity. They are currently involved in the NIMH study looking at adolescent suicide attempters. This is the TASA study. They are doing the suicide assessment or the suicide classification for that

trial. As you can see, they have a very large number of publications over the 20 years they have been doing this.

So, we think this is a good group to help us with this problem.

[Slide.]

I have two more slides left. What I want to do in this slide is again remind you of what Dr. Katz said earlier, is that we view this meeting today as a preliminary meeting. We are hoping to, you know, once we have had these cases reclassified, and have done the analysis, to come back to you with more definitive answers later in the summer.

You are going to hear next from Dr. Kelly Posner from Columbia. She is going to tell you about the way they think about classifying suicidal events and how they plan to approach these data.

Following that, you will be hearing from Tarek Hammad from our Safety Group. He is going to tell you about our preliminary plans for an appropriate patient level data analysis.

[Slide.]

Finally, these are the five topics for which the Neuropharm Division would like to have

feedback from you. First of all, three topics pertinent to the analysis of suicidality data.

Again, I alluded to our concerns about the approach to case finding and how we attempted to resolve that, but we would be interested in knowing what you think about that and whether you think anything more needs to be done in terms of case finding.

Secondly, you will be hearing from Dr. Posner about approaches to classifying these events into appropriate categories before we do the analysis. Since we are actively engaged now in discussing this with them, this would be a good time to give us feedback on that.

Thirdly, if you have thoughts about our plans for the patient level data analysis, we would be interested in hearing about that.

In terms of future concerns, again, one of the striking things about these cases is how poorly they were described, and this may also indicate a less than optimal approach to ascertainment in these studies.

So, if you have thoughts, we are beginning to talk with Kelly Posner and others about developing a guidance document for ascertaining

suicidality in future studies, if you have thoughts about that, we would welcome them.

Finally, I didn't get a chance to talk about efficacy, but obviously, the largely negative results from the short-term trials in pediatrics is clearly a concern.

We would be interested in knowing what your thoughts are about that and whether or not you think there are other possible designs that might help us get at whether or not there are benefits with these drugs.

One design that has been used in adult studies is the randomized withdrawal design. This is a design where you take patients who have responded to medication acutely, have been stable for some period of time, and are then randomized to either continue on drug or assignment to placebo, and you look at time to relapse as the event, as another approach to trying to establish whether or not there are benefits.

I am going to stop there.

Thank you.

DR. RUDORFER: Thank you, Dr. Laughren.

As Dr. Laughren said, we will now hear from Dr. Kelly Posner of Columbia, who will

describe in more detail the suicidality classification project.

Suicidality Classification Project

DR. POSNER: Thank you.

[Slide.]

So, why is a methodologically sound, research-supported classification warranted? Let's back up a second and talk about the problem.

[Slide.]

The problem, as the cases that Dr. Laughren discussed exemplified, there is a clear lack of conceptual clarity about what suicidal behavior means and a corresponding lack of agreement on common terminology both in clinical descriptions of suicidal acts, as well as research descriptions of suicidal acts.

Given this lack of generally accepted terms for referring to even the most basic suicidal behaviors, the importance of using definitions that are both reliable, meaning we all define them and assess them the same way, and valid, meaning there is some truth to them seems quite clear.

[Slide.]

So, what are these standardized research-supported definitions? I think it is

important to note that there really is generally agreement among suicide assessment experts on the basics of these terms. So, we are going to start with the suicide intent.

A self-injurious act committed with at least some intent to die. Intent doesn't have to be 100 percent. If there is any intent to die, we consider it an actual suicide attempt.

Intent does not have to be explicit and can be inferred. For example, if a patient denies intent to die, but thought that the behavior could be lethal, intent can be inferred.

A real case example includes a 12-year-old who is angry at her mother. She took 6 to 7 prescription pills, said she was aware that taking that much medication might kill her, but she didn't know if she intended to die by taking the pills. That would clearly be categorized as a suicide attempt.

Once again, it is important to note that once there is any possibility of injury, the act is defined as an attempt, meaning that if someone pulled the trigger of a loaded gun, but fortuitously missed, it is still a suicide attempt.

[Slide.]

Other classifications: suicidal behavior without injury. Interrupted attempts are defined as the individual is stopped by an outside circumstance from starting the self-injurious act. Examples of these: someone has pills in their hand, but they are stopped from ingesting. Once even one pill is ingested, the event becomes an actual attempt.

They have a gun pointed toward themselves, the gun is taken away by someone else or somehow they are prevented from pulling the trigger. They are poised to jump, they are grabbed, taken down from the ledge. All examples of interrupted attempts.

The next classification is what is called an aborted attempt in which an individual takes steps toward making a suicide attempt, but stops himself before engaging in any potentially self-destructive behavior.

Remember, holding a loaded gun but not pulling the trigger is a good example. This could not possibly result in injury, therefore, it constitutes an aborted attempt. It is still suicidal behavior, but it is not an actual attempt.

[Slide.]

I think it is worth focusing a moment on suicidal intent, because again, intent here is the determining factor when you are classifying suicidality. It is the presence of intent to die that differentiates suicidal acts from self-injury.

One must determine whether the self-injurious act was thought of as a means of causing or facilitating death. Of course, we do have research support for the validity of using intent to define suicidality.

One example is that completed suicide is predicted by previous intent measures, which was demonstrated by Beck and his group in 1989.

[Slide.]

Some more case examples. These are real cases again. These are examples of non-suicidal self-injury.

A teenage girl reported her mother was being cruel and neglectful and she wanted to escape from her mother's home. She states that she researched lethal doses of ibuprofen to make certain that she took an amount that would not be life-threatening. She took 6, feeling sure it was not enough to kill her. She definitely did not want to die, only to escape from her mother's

house. She was taken to the ER and then admitted to a psychiatric hospital.

Another is the more common case of self-mutilation where the person described 12 incidents of cutting himself, stated he did this only "to relieve tension" and "to play with danger to see how far I would go" and no part of him wanted to die. Thought about it for hours before acting on the urge and felt relieved of tension afterwards, did not feel pain.

[Slide.]

So, what is our research support of these classifications? We will start with reliability. We have been able to demonstrate excellent reliability utilizing these definitions and this classification system in NIMH-funded treatment, biological, and genetic trials across the life span.

We have also been able to demonstrate multi-site reliability with other expert centers in family genetic studies and treatment trials, and again particularly the treatment of adolescent suicide attempters trials.

In short, across domains, across the life span, and across institutions, we have been able to

demonstrate excellent reliability.

[Slide.]

Validity. How much truth is there to these definitions? Individuals classified as suicide attempters have as much as 2.5 times risk of future attempts or completions. So, we know this is a real category.

Similarly, interrupted attempters are reported to be 3 times more likely to commit suicide than uninterrupted attempters.

Finally aborted attempters are at risk for eventual attempts and were more likely to have made an actual attempt in the past.

Again, all validating the classifications that we are using.

[Slide.]

So, what is the classification methodology that we are proposing here?

To begin with, the data will be blinded by experts not on the panel. It will be blinded not only to pharmaceutical information, but also to any relevant clinical information that would bias an event rating. For example, a family history of suicidality. An event classification should stand on its own, and we want to make sure that it is

blinded in both domains.

Next, we have to determine the event classifications based on these reliable and valid constructs.

We are then going to do a training on the classification system to establish reliability of panel members who are all experts in the field.

Once the reliability study is done, the expert panel will be divided into three subgroups, and the data will also be divided into three groups in order to do classifications.

There will be additional cases, and the reason for the additional cases is to demonstrate that the classifications are all being done in the same way and to prevent what we call stratification bias.

You want to exhibit a relationship between the groups and make sure it is not some other factor that is causing a group to rate things in a similar way, and then we will generate the classified cases.

[Slide.]

What are the classifications that we are proposing? Suicidal, non-suicidal, and indeterminate. Subclassifications of suicidal

would include suicide attempt, suicidal behavior without injury, which would include aborted and interrupted attempts, suicidal ideation related events.

Non-suicidal subclassifications would include self-injury or mutilation again with no intent associated, and other categories, accidental injuries or other psychiatric symptoms that we have been hearing a lot about today, disinhibition, akathisia, agitation.

Then, finally, the indeterminate category either by non-consensus or inability to classify due to a paucity of data.

So, if, in fact, there is a signal, the point is we just don't know yet what it is a signal of, and that is why a logical research-supported approach is warranted. We want to be able to look at the data consistently and logically across trials in order to make some clinically meaningful sense of it.

[Slide.]

I think it is also worth mentioning for a moment future directions. We want to develop guidelines as to how to better capture data, enabling appropriate classification and description

of suicidality.

We will demonstrate, based on this conceptual clarity, how to utilize research assessment tools, what questions to ask, how to ask them, and what measures aid in this, which will then lead to consistency of terminology and classification, as well as to improved, more valid identification and documentation of suicidality.

In addition, as was mentioned earlier, that will also enable more active appropriate surveillance of suicidality, which is a great need clearly.

Thank you.

DR. RUDORFER: Thank you, Dr. Posner.

Our final formal speaker of the afternoon will be Dr. Tarek Hammad from the Division of Neuropharmacologic Drug Products, who will discuss plans for analysis of patient level data for pediatric studies.

Plans for Analysis of Patient Level Pediatric Studies

DR. HAMMAD: Good afternoon, everyone.

I am here today to talk about our analysis plan for the pediatric patients data.

[Slide.]

These are some of the elements that I will cover in my talk. After a brief description or a statement of the objective of this work, I will describe the data that we have and then I will go on to discussing the analysis plan.

[Slide.]

The objective of this work is to evaluate the risk of suicidality associated with the use of antidepressants in pediatric patients using the results of the blinded reclassification of cases.

I think you have heard enough about the value of this reclassification.

In the process, we will address the possible sources of imbalance in the data, for example, trial design, duration of exposure, et cetera, and also other potential confounders. These efforts will help us understand the sources of inconsistency between trials or between drugs, if any.

[Slide.]

The source of all data is controlled trials conducted in pediatric patients in nine drug development programs. These are the drugs that you have seen before, that is the list of drugs and the number of trials involving each drug.

For the analysis or at least for some stages of the analysis, they will be grouped into two categories, an SSRI group and an Atypical Antidepressant group.

[Slide.]

These trials were not done in one indication, and for purpose of analysis again, they will be categorized or divided into three different subgroups - MDD, anxiety disorders, and attention deficit hyperactivity disorder assuming, of course, we have enough cases within every category of indication.

[Slide.]

As far as individual patients data that we are requested, we developed a standard format to guarantee the compatibility between data coming from various sources. We actually specified every aspect of the desired database down to the variable name and some description to clarify the contents, and some coding notes as appropriate.

In addition, we requested descriptive information about every trial to evaluate the similarity of these trials, which as you can imagine is very important to determine if these trials can be pooled or not to gain more power

while you are investigating this question.

[Slide.]

This is a list of the requested variables that can be categorized in many subcategories - demographics variables, disease-related variables, drug-related variables.

[Slide.]

Outcome-related variables, psychiatric history variables, and some treatment emergent adverse events. As you can see, this is not just about having a second look at the data. It is about trying to understand and appreciate and characterize the signal, if there is any.

[Slide.]

This is a list of some challenges we have with the data, I wanted to mention here because of the important implications of these challenges on the proposed analysis and on the actual interpretation.

They can be divided roughly into two categories, a quality-related component and an analysis-related component.

The first issue in the quality-related component, which is pertinent to what Dr. Laughren was talking about, the case ascertainment, so I

will not belabor the issue more, but a similar issue is pertinent to the other pieces of information being collected, which is other variables that we requested.

The mechanism of capturing these data might be different from trial to trial or from sponsor to sponsor, so we will investigate this, and that is part of the challenge, trying to see if these data can actually even be comparable or not. But for now, the rule that we will use is that we will not use data with missing information more than 10 percent. The second issue is somewhat detailed and I will address in the next few slides

The first point under the analysis-related component is using the trial or the patient as the unit of analysis. Pooling data from different trials, treating them as one large trial fails to preserve the randomization effect and might introduce bias and confounding.

That is because maintaining the randomization guards against the foreseen and unforeseen imbalances between different treatment groups in various trials.

The issue of trial similarity is not only pertinent to having the same protocol, but it is

also pertinent to the implementation of those protocols in reality. That is why I believe the trial-based approach is more appropriate.

However, we might be using some information using the trial as the unit of the analysis, because if we have zero events in one of the arms, for example, we have to impute some data, but if we have zero events in both arms, we will not be able to drive the information in this trial.

So, it depends on the eventual count of the actual cases that we would have. If we are losing too many trials, we might use the patient as the unit of the analysis, of course, after doing the appropriate adjustments.

[Slide.]

The second point is pertinent to the limitations of pooling data in general whether we use the trial or the patient as the unit of the analysis, because these trials have different designs, patient populations, sometimes duration of treatment, et cetera, and pooling them together with the appropriate adjustment gives you an average effect that is really dependent on the proportions of different subpopulations in these data.

This effect will be different subsequently if these proportions are different, so careful evaluation of this has to be conducted and then adjusting for it.

There is also the inherent class effect assumption that is implied by pooling data across drugs or within groups of indications even. Mind you, we do this to try to gain more power, try to see some gathering of data instead of just looking at it trial by trial, but by doing this, if we pool data from drugs within certain class assumption here, the risk of suicidality is equal in all drugs.

The problem comes in when we realize that we do have different size of data for different drugs, and the smaller opportunity to observe an event in one drug might lead to none being observed or very few.

The question becomes whether this is because this drug is generally different from the rest of the class or because we simply don't have enough power. Unfortunately, this will always be an open question, but I would report the results both ways by individual drugs and by group data.

[Slide.]

The analysis plan would follow a standard approach with initial exploratory phase, where we will check for the compliance with our request and the completeness of data, check for coding errors, and the like, and then we will list all the risks and rates by drug, by indication, and by trial just to see what is going on in data, in all aspects of the subgroups before we pool anything, so we know where the signal is coming from if there is any afterward.

Then, we investigate the data separation, which is an important component. For example, if all cases were among men, for example, then, this variable we will not be able to evaluate, and so on. That is just part of the process of evaluation.

Then, we go to investigate interactions and potential confounders to try to understand what is going on and try to characterize the risk, as I said before.

[Slide.]

This is just a sample of one of the tables that will be produced, the rates and percentages and the risks of suicidality by drug and by indication for every trial.

[Slide.]

To evaluate the estimate, to actually try to relate an overall effect, an estimate for an overall effect, two approaches that I discussed are options that we have. First, which I believe is the more of an optimal approach, is using the trial as the unit of analysis.

In this analysis, I will adjust the confounders on a trial level. We are basically looking for a randomization failure in if all of these randomized trials, but in case there might be some failure in randomization, any small imbalances can actually be reflected on the apparent risk.

Then, I will have done everything by trial and by drug. In this particular analysis, I will pool trials for drug groups that I should do initially within indication groups. Trials will be excluded if there are no cases reported in both arms.

Now, depending on the heterogeneity of the trials' findings, the variability between trials will be considered in a fixed effect order in random effects model.

The premise behind the fixed effects model is that the real effects we are trying to evaluate

is fixed, and the observer variation between trials is just by chance. The premise behind the random effects model is that there is an average of these effects that is the full distribution with a variation affected by the observer trials.

Many times you will have both approaches yielding the same results, but I am going to do it both ways with some of the conditions for which approach is more appropriate given the actual data or the heterogeneity of the data.

Now, if we opted to use the patient as the unit of analysis in the situation I mentioned before, which is a situation where we will not have that many cases, and we would be losing trials right and left, so we will try to pool and get some slightly more power, pooling patients as the unit of the analysis.

We will use the Poisson regression to model the rates of suicidality, adjusting for potential confounders, and then again will pool patient data for drug groups within indication groups, and, of course, will adjust for trial in the model because these patients are coming from different trials.

[Slide.]

As you know, these trials were not designed to capture these particular events, so there is some inherent uncertainty about the finding. It depends on what kind of feedback we get from our experts in the Columbia University.

Some sort of sensitivity analysis might be warranted, stratifying by the amount of uncertainty in this particular finding.

[Slide.]

There are some limitations on the interpretation of data that we should know upfront. Just to put the limitations in context, I have here the first bullet to remind you about the goal of this particular effort, which is to evaluate the risk of suicidality associated with the use of antidepressants in pediatric patients.

Now, after everything is said and done, the observed rates will not reflect the actual patients in the general population. Why? Because there are some exclusions in some trials of patients with some baseline suicidality, so the observed rates will not reflect what is going on in real life, and this might hamper our efforts in trying to investigate the risk because it will lead to underestimation in all the arms, so we might not

have enough power to be able to detect the actual thing.

Now that we only have short-term exposure data, we will not be able to extrapolate this to what happens after long-term exposure to these drugs.

Now, we don't really have any information. The next bullet is that we don't have any information on the patterns for discontinuation. Considerably, there might be some informative censoring going on with patients with suicidality tendencies, might be likely to be discontinued. If that happened more in the placebo group, then, there might be some apparent underestimation of the signal in the placebo, and this might lead to some spurious finding, but we don't have information on this which would be very hard to overcome.

My last point is that it remains to be seen if we have enough statistical power to detect differences in the risk of suicidality among various drugs because of the issue that I alluded to before, which is there is no data for some of the drugs.

[Slide.]

In closing, there are our ideas and some

of them were informed by our experience analyzing the data on the completed suicides in adults.

So, your feedback on our approach will be greatly appreciated.

DR. RUDORFER: Thank you, Dr. Hammad.

At this point, we are going to open up for discussion by the committee. If anyone has questions for our speakers, now is the time to raise them.

Dr. Laughren.

DR. LAUGHREN: Matt, I had in my original talk planned on giving a brief summary of the efficacy data, and it sounds like a number of people are disappointed that I didn't do that. I have those data and I could, if you wanted me to take five minutes and do that, I would be happy to do that.

DR. RUDORFER: Yes, please do so.

[Slide.

DR. LAUGHREN: What this slide does is summarize very briefly the outcome on the 15 trials that we looked at for the 7 programs in pediatric major depression.

Again, there are 3 studies in the paroxetine program and 2 studies in each of the

other programs, and what this slide does is to simply summarize in very crude form what the outcome was on the primary endpoint. The protocol specified primary endpoint for those trials, and this gives the age range in these studies here.

So, for example, for the paroxetine program, there were 3 studies, all negative. For sertraline, 1 trended in trend, for the purposes of this slide, indicates a p value on that primary endpoint of between 0.05 and 0.1. A negative trial is indicated by a p value of greater than 0.01.

So, for paroxetine, all 3 studies were negative, fluoxetine, both were positive and, as you know, this was the one program for which we concluded that there was sufficient data to support a claim.

Our standard, and I believe the standard of most other regulatory agencies for pediatric major depression, is 2 positive studies.

For the sertraline program, 1 trended and then 1 negative. Venlafaxine, both were negative. For citalopram, 1 positive and 1 negative. Nefazodone, 1 trend, 1 negative, and both negative for mirtazapine.

Now, the one point I want to make in this

slide is that this was our fairly conservative view of these data. Others have looked at these same data and have reached different conclusions.

For example, for the paroxetine study 329, this was the basis for a publication by Keller, et al. They acknowledged that that trial was negative on the primary endpoint, however, they pointed out that it was positive on virtually all secondary endpoints, and on that basis, they and many others consider that to be a positive study.

Similarly, for the sertraline program, although if you look at the individual trials, neither one makes it. One of the secondary analyses in the plan for these identically designed studies was to pool them, and when that is done, the pooled analysis is very positive, so some view that -- and again this was the basis for a publication by Wagner, et al. -- some view the sertraline program as providing support for efficacy in major depression.

Again, as I pointed out, the citalopram program had 1 of 2 studies that was clearly positive.

[Slide.]

Now, I want to talk a little bit about

this largely negative outcome. If you look at adult major depression studies, and if you look at drugs which we believe work and which have been approved for depression in adults, about half the time studies that on face look like they should make it, fail.

These are studies that are done in what appears to be the right population. The sampling size is appropriate, the doses appear to be appropriate, assessments are appropriate, but for whatever reason, about half the time, these studies fail.

Now, if you assume that that failure rate can be applied to pediatric major depression studies, and you look at the possible outcomes for 2 trials, for programs that involve 2 trials, you can very quickly reach the mathematical result that only about 25 percent of the time would you expect to get 2 positive studies.

Most of the time you would expect either 1 or both trials to fail if the failure rate were the same as is true in adults. So, in retrospect, it perhaps was not as surprising as it turned out to be here that you get a lot of negative results.

On the other hand, the overall success

rate here of 3 out of 15 studies making it at 0.05 on the primary endpoint is clearly, clearly a concern.

[Slide.]

There are a couple of other things to keep in mind. If you look at the history of short-term trials with tricyclic antidepressants in pediatric depression, it is uniformly negative, and there are several possible interpretations of that.

One is that the drugs don't have any benefit. Another possibility is that the extent of heterogeneity in pediatric patients who are captured under these major depressive disorder criteria may capture patients who are even more heterogeneous than we believed to be the case in adults, and the greater the heterogeneity in that sample, the more likely you would end up with negative studies. So, that is one possibility.

Another thing to keep in mind is that the regulatory context for doing these studies was somewhat unusual. In every other case, when a company does a study, the only gain they are going to get out of that study is if it turns out positive.

In this case, these studies were done

primarily for pediatric exclusivity. As was pointed out earlier, there was no requirement that they get positive studies to get exclusivity. Either way, if they did the trial according to the terms of the written requests, they would get exclusivity.

I am not suggesting in any way that companies set out to do inadequate studies, but having that somewhat unusual mind-set could operate against a trial in subtle ways, in terms of, for example, recruitment of patients. So, it is just another thing to keep in mind in terms of interpreting these largely negative data.

Finally, at the time that the written requests for these studies were issued, we were not routinely asking for Phase II dose finding studies, as we are now in all of our written requests.

Again, to the extent that appropriate dose finding was not done, that would work against positive studies.

So, just in summary on the efficacy side, I think there are several plausible explanations for failure to find efficacy in these trials other than the obvious possibility that maybe the drugs have no benefits in pediatric major depression.

In any case, the failure to meet FDA's fairly high standard of having 2 positive trials, in most of these programs, we do not consider proof of the lack of benefit. So, it is true they didn't meet the standard, but that is not quite the same thing as saying that it has now been proven that the drugs have no benefit. That is a very different conclusion.

On the other hand, the failure to show a benefit in major depression in most of these trials, obviously heightens the concern about any adverse events, in particular, in this case, the possibility of the induction of suicidality. Clearly, the burden is on those who believe that these drugs do have benefits to show it, to design and conduct studies that show this.

Again, one of the questions that I have for the committee is what your thoughts are about how to go about this, in particular, the possibility of using a very different kind of study design, for example, using the randomized withdrawal design, which has been fairly successful in showing longer term benefits in adult studies.

I will stop there. Thank you.

Open Committee Discussion

DR. RUDORFER: I think we will now open this up for questions and discussion by the committee.

DR. SANTANA: Can you clarify something for me, so under the exclusivity rule, if the results are positive, those studies can then be used by the sponsors to make a supplemental claim, and that could then become part of a new indication in pediatrics, is that correct?

DR. LAUGHREN: I am sorry?

DR. MURPHY: Yes.

DR. LAUGHREN: The answer is yes.

DR. MURPHY: Yes.

DR. SANTANA: I was trying to answer this issue of whether there was some bias in these studies because they were requested under the exclusivity rule. I have never interpreted it that way.

DR. MURPHY: I think what has been a concern from the very beginning with exclusivity, we think the intent of Congress was that they want more information. If studies are going to be conducted, they want that information to be known, and therefore, they want to say to companies we want you to go out and get this information. It

doesn't mean you have to reach the bar of having an approval, because a negative study can be just as important as a positive study.

But the other concern here is that you -- and no one is saying this, so, please, I don't want this quoted out of context -- but there is the concern that it is easy to design a sloppy study, fail, and still get your exclusivity. That is always a concern, and it is our job to try to not allow that to happen.

DR. RUDORFER: Dr. Temple.

DR. TEMPLE: I just was going to emphasize the same thing. Tom isn't suggesting that anybody was totally indifferent to the outcome, but the sense of urgency that comes when you have launched a very expensive program to develop a drug, you really must win or it's all toast, and that's not true here. You can win anyway, different incentives.

DR. RUDORFER: Dr. Fink, you had a question.

DR. FINK: This is sort of an overriding question, not to a specific speaker. In looking at the questions that are being asked of the committee, we have heard very little about the data

set that is being used.

Are the inclusion and exclusion criteria for these various studies appropriate in terms of drug history, history of substance abuse, family history of psychiatric diagnoses? Because these were placebo-controlled trials, they probably enrolled less severe disease as evidenced by the lack of completed suicides, and finally, as has been mentioned, there was no need of efficacy.

I am concerned that no amount of analyses of a possibly flawed or suboptimal data set will answer the question. If there is shown to be a relationship to suicidality, we may take away drugs that are useful in pediatric depression with different trial designs.

If the studies come out negative, we may be falsely reassured. So, I am not sure that these re-analyses are going to answer the question that has been brought forward to the committee by particularly the audience and that maybe we need to start with designing what are the optimal pediatric trials to answer this important issue.

DR. RUDORFER: Does someone from the FDA want to respond?

DR. TEMPLE: Well, Tom sort of opened that

question to a degree. One of the things that no one will let you do probably is treat somebody very severely ill in a placebo-controlled trial, they would be uncomfortable, although since it is not clear what works, maybe they shouldn't be that uncomfortable.

Nonetheless, an alternative design which in pediatric studies has been proven very attractive is to take people who appear in one way or another to be doing well on a particular therapy, and in this case it really won't be as critical how severe they were before, and do a randomized withdrawal study in which people are very, very closely observed for the first recurrence of any symptom that is worrisome.

The Pediatric Committee has discussed this at considerable length, and there is more comfort in pediatric trials in using that design where you do need a placebo to interpret the trial. So, that is one of the questions Tom raised, and I am sure we would be interested in some discussion on that.

DR. GOODMAN: I am also sharing the concern about the ability to get the answer to the suicidal risk associated with these drugs based upon the existing data set. I think the signal is

not going to be strong enough although we are clearly most interested in suicide or suicide attempts as the outcome.

I wondered if one could look at these data sets for other possible evidence of behavioral toxicity that might be antecedents of suicidality. I think there was some allusion to that earlier, but there wasn't much detail on it. I wonder specifically if one could look at some of the items, like of the HAM-D or the CDRS, looking for agitation or irritability.

If those are being induced by the medications particularly early in the treatment trial, perhaps those are creating a behavioral state that places that individual at risk for suicidal behavior.

One could, of course, validate that by first looking at those subjects in whom there was evidence of suicidality to see if it was correlated or associated with other symptoms, but if it is, then go on to look at those variables, which would allow you to maybe get a more sensitive measure of the effect of the drugs.

DR. RUDORFER: Dr. Nelson and then Dr. Katz.

DR. NELSON: Two questions. The first is about the data set. At the end of the day, when you receive the data that you are asking for, will you be looking at the same data set that were reviewed by the MHRA? I mean are we going to be drawing conclusions on similar data sets?

The second question goes to the issue of the interpretation of Appendix 1 and Appendix 2A. I am struck, if you remove fluoxetine, that you have got 1 out of 13 trials for effectiveness positive and 5 out of 13 for increased risk of suicidality positive, and does assay sensitivity apply to risks as well and why would we not interpret that as a pretty strong signal if, in fact, we accept that on the efficacy side?

DR. LAUGHREN: Regarding the question about the UK data, I can't be certain that they have the same data, however, if we look at the numbers that are presented on the UK web site, they are very familiar numbers. They appear to be coming from the same summary data that we had access to in looking at this data.

So, I am reasonably confident that we are dealing with the identical data sets. The only difference is that we have gone beyond accepting

the data at face value. It appears that the UK simply accepted the summary data analyses done by the various companies, and on the basis of a suggestion of a signal, and the admitted lack of efficacy for most of these programs, have decided to contraindicate these drugs.

We have chosen on the safety side to look more closely at what that signal is, and that is really the question. The question is -- and this gets in reference to your second question about Appendices 2 and 2A -- I agree with you that if you look across these trials, even though the signal is not consistent from study to study within programs, on balance, it appears like there is an excess of something for drug relative to placebo.

The question is what is that. You have this very broad term, "possibly suicide related," but when you dig deeper and look at what those events are, they range all the way from something that everyone would agree does not represent anything close to a suicide attempt to very serious suicide attempts.

So, that is why we think it is important to go back and reclassify those events, so we can figure out, first of all, if there is a signal, and

secondly, a signal for what. But I believe that the UK had the very same data that we have, and it doesn't appear to me as if they did any analysis of those data other than to just accept what the companies have done already.

DR. RUDORFER: Dr. Katz, did you have a comment?

DR. KATZ: Just to say that the suggestion about looking at other behavioral symptoms that might be premonitory to suicidal behavior, we are very interested here whether or not there are specific events we should be looking at that we haven't looked at yet along the lines of how we intend to look at the suicidal behavior data.

That might involve going back and asking sponsors to resubmit data sets, but we are very interested to hear that. Of course, the question of the link between those symptoms and suicidal behavior is also still an outstanding question, it's not straightforward.

DR. RUDORFER: Dr. Chesney.

DR. CHESNEY: I also felt that perhaps just looking at suicide attempts, basically what you just said and what Dr. Goodman said, may not be all the answer. I am most impressed from what we

heard in the public hearing this morning about the stimulant syndrome and the number of individuals who had demonstrated psychoses, akathisia, mania, agitation, and so on.

I was also impressed at one young lady who said that she wouldn't disclose that she had had suicidal ideation, and then particularly impressed with the three people we heard from whose children at autopsy had very elevated levels of the drug, which leads to my second question.

That is, what do we know about pharmacokinetic data in children and in individuals who develop this stimulant syndrome. I suspect someday that we will have pharmacogenomics to tell us maybe who to predict might have that, but do we have any information about pharmacokinetics in children, number one, and number two, in these individuals who develop these stimulant syndromes, is there any relationship at all?

DR. KATZ: Well, in the written requests, as a general matter, we ask sponsors to obtain pharmacokinetic information in the relevant pediatric population, so I believe we have probably asked for that information.

I don't believe we know or have had

submitted to us in any event data linking plasma levels in any individual patient and particular adverse events. That might be available somewhere, but I don't think we have it.

DR. LAUGHREN: Could I ask Daniel Pine to comment on this construct stimulation syndrome and whether or not that has been reasonably well defined in some way that is agreed to by different individuals?

DR. PINE: Sure, and then actually I have a couple other comments. I don't know if you want me to wait until after this issue.

But I would say across a range of pediatric mental syndromes, it has been fairly frequently described that a strong minority of children will get activated with SSRI medications, and not just children with major depression, and that in most studies, if it is not statistically greater than it is in placebo, that it is a fairly consistent observation across most studies, that it is higher on SSRIs than it is on placebo.

DR. LAUGHREN: Are we talking about something other than the anxiety and agitation which is well known as a drug-related risk with all of these drugs? That is something that we see in

most of these trials, but it is not quite the same thing as saying that someone has a stimulant syndrome.

DR. PINE: I think if you look across the trials and you look at the range of terms that people have used to describe this so-called stimulant syndrome, you see that the problem that you were talking about with the relatively narrow set of behaviors, self-harm behaviors or suicidal behaviors, becomes even worse because across different trials or trials for the same medication done by different individuals, really a broad range of behaviors have been kind of linked together.

It remains unclear the degree to which different investigators are talking about the same phenomenon or different medications are producing similar phenomenon. The one thing that is clear is that there is an array of what some people have called, and Dr. Goodman referred to, as behavioral toxicities that are not that infrequently observed with SSRIs, and it might extend beyond suicidal ideation, and it also needs to be better categorized.

I would also add that when one looks at those events in most of the efficacy trials, they

tend to be uniformly mild. I am most familiar with the anxiety trials where, while they are more prevalent, they tend to not cause sometimes even discontinuation of the medication.

DR. LAUGHREN: If I could just follow up on this. If we were, Daniel, to look for this, I guess the question would be how would one define it in a way that we could hope to find examples of it?

DR. PINE: I think if you look at most of the publications for most of the SSRI trials, you can see relatively broad categories that describe something that people would call activation, so, you know, in the original sertraline trial, I think it was called hyperactivity. In the fluvoxamine trial, it was called activation.

In the recent sertraline trial, I think it was called impulsivity. So, there is a whole range of terms that I think you would have to canvass the field in terms of thinking about what are the most appropriate terms to include, much the way that you have done with suicidal ideation.

That is not to say that this is necessarily related to suicidal ideation, though.

DR. RUDORFER: Dr. Goodman, did you have a follow-up comment?

DR. GOODMAN: Yes. In at least adults, I think as clinicians as well as clinical researchers, we have a good sense of kind of the array you were talking about of activation-like problems that can occur with the administration of SSRIs.

Even in the labeling, we have seen that there are warnings that you can induce bipolarity, mania. In fact, it has often been said that an antidepressant is probably not effective unless it can induce bipolarity in some patients.

We also know about psychosis and anxiety induction particularly in panic disorder patients. So, I think in adults, we have it a little better characterized. What I am concerned about with the children is, one, their characterization probably is somewhat overlapping, and also because of what is special about children is maybe that they are more likely to manifest these problems in a less differentiated fashion, which includes suicidal behavior.

DR. PERRIN: To follow up on two of these issues, one is we hear about serious adverse events being beyond suicide, but potentially also murder and other such events.

I think maybe Dr. Pine is talking about strategies that might help to elicit those sorts of ideas in the data set, but it seems to me that is a critical issue to go beyond suicidality as a potential serious adverse event.

I want to get back to the pediatric rule question for a moment, too, if I could, and just ask -- I show my naivete and ignorance here -- but what purview, what surveillance does FDA have of pharmaceutical companies carrying out their trials?

The little I know about them is that these are often multi-site trials, fairly complicated data collection among a variety of providers.

Do you have any surveillance as to how well this is carried out, or do you sort of rely on the pharmaceutical companies to say we did it reasonably well, and might that be a source for variation between pediatric rule trials compared to the sort of getting the drug on the market trials?

DR. TEMPLE: Others may want to comment. Usual rules apply. We can inspect any of the studies. As you can imagine, inspecting a study after the fact gives you only limited insight into how well those things went on.

The companies are expected to provide

oversight, the rules require that they do so, but our ability to know whether it is perfect or not is difficult at best. What I can't tell you is how often we have inspected these sites. We do sometimes, I don't know if we have on these.

DR. MURPHY: I would like to say that this is an issue at the level of the Office of Commissioner, that there is an Office of Good Clinical Practices, that they are addressing to make sure that we do have adequate surveillance and criteria. I don't think we can provide you a lot of information right now, but it is an issue that they are looking at.

DR. TEMPLE: It would be relatively unusual for us unless we had a concern about whether they picked up adverse reactions, which we might in this case, first, to inspect a study that the company agrees is negative. On the whole, that is not where you go to look.

DR. RUDORFER: Dr. Gorman, you have been waiting.

DR. GORMAN: One of the themes that struck me through the morning was the interruption or potential interruption of information flow through the system.

I would like to continue on the thread of the study and then go to the information flow question I have.

On the study, I think going back and looking at that 109 out of 3,000 patients that were being studied for efficacy and looking for them for suicidal ideation or attempts will be trying to make a silk purse out of a sow's ear. I think that would be an adventure in futility.

I don't think it's an unreasonable thing to do if it's the data that you have available, but I think the example used this morning was the needle in the haystack.

I think we have stepped on the needle and we have either got to see if it's really there or if it is really not there, and design studies prospectively either using randomized, controlled clinical trial crossover designs or withdrawal of effective therapy designs.

One of those three designs could be designed looking specifically at the questionnaires that our psychiatric and psychology colleagues tell us look for suicidal ideation.

To look for suicides as a rare event I think is going to be again a futile search, but

looking for suicidal ideation induced by these medications, I think should be relatively straightforward, and I would not use the set of mildly or majorly depressed people.

I would look at groups of individuals on these medications who are not depressed, so that we could separate that issue out, is it the disease or is it the medicine.

So, take the ODDs and take the post-distress syndromes and study them for suicidal ideation being initiated on these medications.

Now, back to the pediatric rule, which I think I understand, and the Best Pharmaceuticals for Children Act, I thought there was a provision in there, I thought, that when we fixed it after 1997, that if you went for pediatric exclusivity, when you finish the trial, whether the results were positive or negative, you got exclusivity.

But I also think there was a requirement for the pharmaceutical companies to make those data available in a public place. Is my understanding confused?

DR. MURPHY: No, that was a slide this morning. The BPCA does say that within 180 days of the submission of the application, that the study

results, clinical trial and a summary of the clinical aspects and the pharmacology report will be posted on the web by FDA.

DR. GORMAN: Is there a dissemination issue then that it comes as a surprise to me and other people in this room that 12 out of 15 studies -- and I am sorry if I got that number wrong -- were negative in their scope, or is that just something that hasn't quite made its way to the web site yet?

DR. MURPHY: No, there was an issue in that there was a window after BPCA was enacted in which the sponsors had to be informed that they now -- because they had been issued the written requests earlier -- that they now were under the new legislation. They had been issued their written requests under prior legislation.

In that window, a number of these studies came in.

DR. RUDORFER: Dr. Leon.

DR. LEON: After hearing the speakers today, I think there is at least three avenues to pursue simultaneously for being informed about this topic, and all three will provide important information about the public health risk and

benefits.

First, is looking at the existing clinical trial data, or using the experts from Columbia University, that is a good start. I think what is very important in looking at those data is we haven't yet heard what percentage of people who were screened to be in those clinical trials actually were enrolled. Was it 5 percent, 10 percent, 80 percent? We have no idea. That certainly affects the generalizability of those results.

The people we heard from this morning might have been those who these data don't apply to, who would be excluded from trials, and we need to learn about those, and I will comment on that in just a minute.

Also, in re-analyzing those data, I would really discourage the last speaker from dropping data in which there were no suicide attempts. It provides a false sense of risk actually. It inadequately characterizes exposure to the medication.

The second avenue to pursue would be new clinical trials, which were alluded to by a few people today, and those should be designed with

very comprehensive assessments of suicidality, agitation, hostility, akathisia, and assessments that are sanctioned by the FDA, maybe with expert advice again from Columbia and other universities, other academic centers with expertise in assessing those constructs.

They should carefully consider the comparison group. That is probably the hardest part of designing those studies, whether it's a withdrawal study, as Dr. Laughren alluded to, or suggested, or maybe psychotherapy versus active med versus combination, I am not quite sure, but that certainly deserves discussion, and in those trials, much broader inclusion criteria should be used than have been used in the clinical trials to date.

The third avenue I would encourage is the use of existing observational data sets. Now, observational data sets, at the expense of internal validity, at the expense of the association between treatment and outcome provide wider generalizability, and a much broader inclusion criteria.

Dr. Pfeffer, her slides referred to at least three different ongoing longitudinal observational studies of children, depressed

children, and if those observational studies are used, appropriate methods for adjustment and stratification should be used.

They could consider some of the methods used in the Division of Devices that are used to adjust for observational differences.

I will stop there.

DR. RUDORFER: Dr. Katz and Dr. Temple.

DR. KATZ: I just want to comment on the notion of how to better design trials in the future to look at this question. It is a very important question, it is one of the questions actually that Tom has drawn up, that we would like you to discuss, and a number of people have already mentioned it.

We think it's a good idea, too. The problem is I am not sure how to get those trials done. As you have seen, pretty much most of the drugs in this class have been studied already, their trials have been done under the pediatric exclusivity provisions, and I am not sure we have the authority to require sponsors to go ahead and redesign trials of the same treatments to have a better look at trying to capture these events.

I would be very interested to know if

people have an idea about that, whether or not there should be an NIMH-sponsored trial perhaps of most of the drugs in this class, because I don't think we can require the sponsors to do these studies other than for the ones that might not yet have studied them under the pediatric exclusivity provisions, whichever ones those are, and there aren't many.

DR. MURPHY: The one possibility would be that these products would be put on the list of products that need to be studied. We have an off-patent list, but we can also reissue a written request to a sponsor for a product which is on patent, and if they refuse to do it, we could send that request to the foundation at NIH.

Remember, I described earlier this morning there is a collaboration between NIH and FDA to develop products for the off-patent including the list of products that need to be studied. Some of these products have come off patent, some will be, and even if they haven't, there is another mechanism which FDA can issue a written request and then if the sponsor doesn't want to do it, even if it's still on patent, and it has a high enough rating, it can be sent to NIH foundation.

I have to tell you, though, that the problem is that funding for that foundation to do studies is very small, so it would be getting in line for a number of studies for which the funding is very limited at the moment, but those are the possibilities I am aware of at this point.

DR. RUDORFER: Also, I wanted to mention that there is, in fact, an NIMH study that is nearing completion, the treatment of adolescent depression study, or TADS, that includes a controlled trial of fluoxetine and placebo, as well as cognitive behavior therapy alone or with drug. That is a 36-week acute trial followed by a 1-week follow-up study in a total of 400 adolescents coordinated at Duke.

I understand that the results should be available by the beginning of June, so hopefully, in time to inform the FDA analysis.

Dr. Ebert has been waiting patiently.

DR. EBERT: It appears in some ways that many of these clinical trials may not reflect the typical use for these agents. We saw some data that showed that many of these agents are used other than for major depressive disorders, are prescribed by physicians other than psychiatrists,

and I am wondering if there is some way that we can measure the adverse effects that we are seeing in the typical use.

We currently have the AERS system, which I think admittedly is somewhat limited because of the voluntary reporting that is necessary, but I am wondering if the Agency could comment about some other type of a postmarketing program that could be set up that might focus on this more rigorously.

DR. TEMPLE: The people from the Office of Drug Safety need to comment, too. I just wanted to make the observation that the most difficult epidemiological situation you can identify probably is where the events you are looking for, both the product of the disease and the potential product of the drug you are worried about, it is hard to think of anything more difficult, but some epidemiologists ought to comment further on that.

I wanted to make one observation about randomized withdrawal studies, which I like very much. They are not a good way to discover whether these drugs cause suicidal thinking, because, by definition, the people on those drugs are people who are doing well on them.

It is a possible way to show that the

drugs work in a situation that is somewhat different from the high-intensity, high-support setting of the acute trial, but I don't think that is going to get us the answer on suicidal thinking. These are all bona-fide do-gooders or do-wellers if you like, so I don't think it is going to help on that.

DR. RUDORFER: Dr. Pfeffer.

DR. PFEFFER: I wanted to comment on something that struck me, and that is the placebo response rate seems to be relatively high in these populations in these studies, and I wondered how they did compare to placebo rates in adults.

My sense is they are high and I would assume maybe higher, and I wonder if that leads to us needing to think about other covariates, for example, as will be done in the analyses, such as the environmental circumstances in which the children are living, and to see what that feature may impact on not only the suicidal state, but the potential for recovery.

I wonder certainly with the placebo rate being a narrow range between the treated state, if our concerns about efficacy need to be rethought in terms of developmental issue.

DR. RUDORFER: Does someone from the FDA want to comment on the placebo response rate in the pediatric studies versus these same drugs in adults?

DR. LAUGHREN: I don't have the data in front of me. My general sense is yes, that the placebo response rate in fact is an issue for both adult and pediatric studies, perhaps even more of an issue in pediatric studies, and that may get at the issue I was raising earlier about heterogeneity that you see when you try and capture a population using the MDD criteria, but yes, it is definitely a problem in both areas, but perhaps even more so in pediatrics.

DR. RUDORFER: Dr. Laughren, is there a standard way of assessing diagnosis in these MDD trials? I mean as a matter of just the sponsor will say these subjects met DSM-IV criteria, do we know if they used any kind of structured interview?

DR. LAUGHREN: They almost always use some kind of structured interview.

DR. RUDORFER: So, presumably, if there were comorbidities, those would be captured?

DR. LAUGHREN: Yes, and there often is comorbidity.

DR. PINE: Related to that question, could I make one comment about it. When one looks particularly across the recent studies, while every study will say that they used a standardized assessment, there is really a quite marked variability across studies in terms of the way in which they documented the rigor of that approach.

So, if you read the recent letter in JAMA from Wagner, that talks about the process of establishing the diagnosis and the reliability study, that reads very differently from some of the other studies that maybe had a lower placebo response rate or smaller samples.

So, I was wondering if it might be possible to in some way evaluate or rate the rigor with which both the diagnosis and the outcome variables were assessed across the studies, paying particular attention to issues of training and the demonstration of reliability by those investigators conducting the trial and using the instrument.

DR. LAUGHREN: It would be very difficult to do that after the fact. If they claim to have done it in a particular way, to document whether or not it had been done in that way, involve an enormous amount of work, and given the time at

which these studies were done, you know, going back four, five years, it would be hard to imagine how that would be helpful.

DR. RUDORFER: Dr. Wang.

DR. WANG: I think in addition to considering what the optimal design would be, if we all had our choosing, we should keep in mind that at the best, it will take a long time to do them even sorting out all the other logistics, so I think in the meantime, it is important to consider how to enhance the use of this existing data set, which will be arriving soon enough, to study this question.

One thing I am particularly concerned about is you may lose an effect in the overall data set that you would otherwise be able to see in a high-risk population.

I think in that list of covariates that you are asking the sponsors to all submit, to also add variables that will allow you to identify high-risk populations, such as people -- some that come to mind, kids that have insomnia at baseline or high anxieties, severity symptoms, or family histories of bipolar illness, things that allow you to sort of concentrate on a group that is likely to

potentially show an effect.

DR. RUDORFER: Dr. Gorman.

DR. GORMAN: Again back to the theme of information flow, I was wondering if someone from the FDA could explain what bars we would have to meet for changing the labeling on these substances today. The labels get made when a new product is approved, but then are modified through many mechanisms, I have no idea.

What do we need to do to put a precaution, warning, or black box, or side effect or adverse event that lists these as potential -- what bar do we have to meet to potentially include these in the label?

DR. KATZ: As you heard from one of the speakers in the open session, it isn't required, for example, when we are contemplating putting something in the Warning section that we have absolute proof that the drug causes a particular adverse event, but reasonable suspicion. I forget exactly what the words are.

On the other hand, of course, two points, one, it is obviously a judgment as to whether or not there is reasonable evidence that a drug is linked to a particular adverse event. So, if you

ask what the bar is, it is hard to say. It is highly case-dependent.

On the other hand, even though the law permits us to include things in the Warning section that we have not yet proven to be associated with the drug, there is always the risk of including such events when we aren't really sure or almost sure that the drug did it, because, number one, it is distracting, but beyond that, you might be giving false information.

So, as a general matter, we tend to put adverse events in the Warning section when we are pretty sure, when we think we have pretty good evidence that the drug actually does it as opposed to its just being associated with it.

A boxed warning again is a judgment, but I would say, as a general matter, as well, we don't put a description of adverse events in a boxed warning, which is sort of the most stringent warning you can apply in a labeling unless we really believe that the drug is causally related to the adverse event.

Then, of course, we don't put all causally related adverse events in boxed warnings, only those which we think are particularly serious, not

to say that suicidal behavior would not be one of those events, but really boxed warning and pretty much warning, we like to have pretty good evidence that the drug actually did it.

Of course, the type of evidence that is brought to bear on the question of whether or not the drug is causally related varies. We like to have controlled data. It isn't always controlled data.

Sometimes for rare events, as you heard earlier, events not associated with the condition that you are looking at, postmarketing data, comparing reporting rates to what we know about background rates usually suffices. I am not sure we can apply that sort of reasoning to this case.

DR. TEMPLE: We are particularly interested in telling people of things they can do to avoid problems, if there is such a thing, that seems reasonably likely to do it. Current labeling already does tell you that early after treatment starts is the time to watch out.

It doesn't attribute that to the drug, but it doesn't seem out of the question that wording like that could be enhanced and made clearer. Everyone seems to agree that that is a dangerous

time whether you agree on why it is a dangerous time or not.

So, there are things like that that can be done. Another option that we have not used for most of these drugs is to provide information as best we can for patient or caregiver use. Those are all possibilities.

DR. MURPHY: Could I put a pragmatic response to that answer? That is, that I think one of the other things that we need to consider -- it's in your questions -- is that to get a change in label, let's just assume for some reason that people walked out of here today and wanted to change the label.

It takes a while to get all that done and by the time you came back this summer, you might want to change the label again.

So, I think what we are going to be asking you or in one of the set of questions is what are your recommendations about what FDA may or could possibly do in the interim, because I think that everyone is very interested in what additional information we can get, and we would like to make it the most efficient way of transmitting information, which would be together instead of

trying to change things maybe two times.

So, I think the pragmatics of it are what can we do to help better inform people before the late summer meeting in which we hope to have a more definitive response.

DR. RUDORFER: Dr. Nelson.

DR. NELSON: I think I will continue this conversation about labeling rather than what I was originally going to say.

I have two suggestions. What struck me in your remarks about the timing was the delay it appeared to take for you to actually get the data you were asking the sponsors to provide. That could be inadvertent or it could be, in fact, duplicitous.

So, I would suggest that you tell them that, in fact, if they don't provide the data you want, that you will label it based on just the British decision, with a warning, would be the first suggestion.

But the second is, to answer Dianne's question about a notice, I think you could honestly take Appendix 2A and put that in the letter to both health care professionals and to patients on the medication saying the FDA is really worried about

this signal and we want to look at this data, and if you are worried, too, you ought to talk to your clinician that prescribed it and discuss those concerns and name the drugs.

It is unclear to me why someone couldn't have the opportunity to see that signal and to make their own evaluation as to whether or not they would want to be slowly tapered and put on the one drug that seems to be so far a winner in all of this, which is fluoxetine.

DR. LAUGHREN: Let me just clarify one thing. We have the data from the companies, the ball is now in our court, so we are not waiting for anything at this point from companies unless the committee feels that there is some deficiencies here in terms of case finding, but we are satisfied that we have what we need.

It is now a question of working on a reclassification and designing an analysis. We have what we need.

Regarding the second issue of disseminating Appendix 2 to prescribers, I am not sure what purpose would be served in doing that. I mean we have already issued a health advisory in October saying that we are concerned, that we can't

rule out an increased risk of suicidality.

If we are not comfortable with what is in the numerators for these risks that are displayed in that table, I am not really sure what purpose is served in disseminating that.

DR. NELSON: One brief response to that and then I will be done. What bothered me in listening to the testimony this morning is the amount of off-label use, and the amount of times that people mentioned that they were given samples. I would even go so far as to wonder if the handing out of samples is marketing outside of an indication where you could even come after a company.

So, part of my desire to inform clinicians is to try to scare them away from off-label use frankly. That bothers me, the amount of off-label use that appears to be going on in this particular market.

DR. RUDORFER: Dr. Griffith.

MS. GRIFFITH: I need to clarify, I am not a doctor, I am a consumer, I am a parent, and as a lay person, the most troubling outcome I think of this morning's and this afternoon's presentations was the urgency with which this needs to be

resolved.

After the presentation by Dr. Hammed, I was really struck by, in covering the analysis plan, the last statement it remains to be seen that if we have enough statistical power, whether or not there is enough statistical power.

My question is what happens then, if there is not enough evidence to make a conclusion, how does the FDA inform the public, because as you say, you put out an advisory on October 27th, which I, as a parent and as a consumer, read, found it terribly confusing.

It was reported on very contradictorily, and what I am suggesting is I think the FDA is going to have a credibility problem if it does not get out ahead of this with some very public statements about where it is going with these studies and with the data.

DR. RUDORFER: Dr. Goodman, did you want to respond?

DR. GOODMAN: I think it is going to be some time until at least I am comfortable that we have enough data and analyze it properly to be sure of the connection with suicidality, however, I think that myself -- and my guess is there are

other people around the table -- are more comfortable with the assumption or, to use these other terms, have a reasonable suspicion that there is a subgroup of children who develop an idiosyncratic reaction to SSRIs, that include symptoms like insomnia, agitation, maybe suspiciousness, hostility, and could possibly lead to violent behavior including self-harm.

I think a lot of clinicians are aware of this already. I think that my colleagues in child psychiatry and pediatricians who are informed on this issue are very attentive when they are starting medication, if they are seeing any of these signs, they adjust the dosage, they may stop the medication, they certainly don't increase the dosage.

So, there are measures that can be taken now by clinicians as long as they are aware of it, and by parents who are made aware of it, to take steps that may reduce the development of this syndrome, whatever we want to call it, in a susceptible group of kids that may or may not increase risk for more serious adverse events that include suicide.

MS. GRIFFITH: Just to follow up, I don't

disagree and I feel that I have always been well informed by clinicians, but I think that there is a group of people who have not been able to either look at the data or not had access to good therapeutic care, and I think that it is going to become a public relations problem very quickly.

If the data comes back, if you are unable to use it when it comes back prior to this meeting in the summer, you are extending some sort of reasonable period by which you can reasonably inform the families, and it will snowball and get completely out of control.

DR. RUDORFER: Dr. Katz.

DR. KATZ: One of the questions we have of the committee is what, if anything, should we do in the interim while we are waiting to get the final analyses. Of course, as a number of people have suggested, it is possible that come this summer when we do the analyses based on these resubmissions of the data, that we won't be able to say anything definitive.

What we really want to know from you folks, first of all, in the interim, what, if anything, we should say, and it sounds like at least some people think we should do something

although I am not yet sure if and what other people think should be done.

But it is possible that come this summer, we really won't be in a position to say anything more definitive.

What we really want from you folks is, in part, whether or not there is anything else you think we can get from the data or whether or not there are any other additional analyses that we should do, so that we get as much as we possibly can out of the data, so that if we do come back in the summer and say, look, we can't give you a definitive answer, at least we can know that we have done everything that we possibly could with the data that we have in front of us at the moment.

So, those are things we definitely want to hear from you about.

DR. RUDORFER: Dr. Temple.

DR. TEMPLE: I just want to sort of remind everybody that what provoked the most recent interest in this subject was those data, the 127 cases. If those prove to be uninterpretable, we are back where we were.

What we then have is very impressive individual reports of bad outcomes. Those have

always been impressive when people have tried to look at those in controlled trial environments and things like that, and pooling our study data, they haven't turned up at least so far.

There have been some criticisms of the way that was done, but leaving that aside, they haven't turned up. The difficult question always is what to do with reports that have considerable cogency to them. I mean it sort of looks like something happened when the person started the drug, it does, that you can't really confirm in controlled trials, and that is always a problem with the postmarketing data we get.

Sometimes the events aren't the very thing that you are worried about happening in people with that diagnosis. In this case, as I said before, it is particularly difficult because people who are depressed are the very people who have some of those events.

Now, whether it looks like they were accelerated or not are the kinds of things we have to think about, so as Russ said, we are very interested in views as to what we can say that would be useful now, apart from waiting for the results of the trials, if there is such a thing.

DR. RUDORFER: We have several speakers lined up to continue the discussion on Question 1 regarding capturing all events of potential interest, and I will ask everyone else to hold your questions, and then we will move on to Question 2. There is a lot of overlap, and I have been asked to try to keep these separate and distinct.

If we could turn to Dr. Maldonado, followed by Dr. O'Fallon, please.

DR. MALDONADO: I am sorry to bring you back to the BPCA and rule. I want to clarify the point, the failed trials that the FDA is seeing right now has been an issue of cost of doing business for the pharmaceutical industry for generations, is that when those so-called negative trials happen, the pharmaceutical industry doesn't even bother to come into the FDA with those trials because they know they are not going to get anything out of that.

Now, you are seeing it in the context of the BPCA because it is necessary to disclose, and because there is incentive to disclose it. So, this is not a new phenomenon and I think that the comment that the pharmaceutical industry is not making the efforts that they should make is

unfounded.

A lot of these trials -- that is why they are called trials -- a lot of these drugs failed, failed repeatedly, and those failures actually had to do more with the ignorance of the people developing the compound than with the drug itself.

It is a process of learning until the researchers fine-tune what they want to find. Not only that, if there is a doubt that these studies are being done according to GCPs, the FDA has the authority to have that oversight.

Not only that, the FDA has a very historical authority now given by the government to issue the written request. So, those studies are in response to written requests issued by the FDA.

So, if those responses are not accurate and are not fulfilling the demands, then, there has to be a corrective that should happen there, just for clarification.

DR. RUDORFER: Dr. O'Fallon.

DR. O'FALLON: We are talking about three major topics here, and we keep flipping around among them. One of them is the potential that we can get out of this re-analysis. The second is suggestions, advice as to what to do for future

studies. The third is the labeling issues.

The questions that we are getting are primarily focused on this re-analysis, at least the ones that I saw. I want to say as a statistician that I don't have a whole lot of hope for your being able to get good information out of the planned re-analysis. I think it should be done, but I don't think it is going to be because you are going to get the information.

As a statistician again, I have learned a long time ago that if you don't get your data right the first time, that it is very, very difficult to go back and get the information after the fact, and I am afraid that you are going to find that is a problem.

If the data were not collected very well, for whatever reason, in those original studies, you are going to have a hard time finding it, and there is no such thing as being able to go back.

For example, if something is a genetic defect, if there is really a genetic defect that is underlying the ones that flip out, the kids that go crazy, no one will ever know because we don't have the information, we didn't ask about it, and there is no way to go back and get it.

I am afraid that is what is going to happen with this study. Nonetheless, I think it is worth going forward because I think you are going to learn a whole lot about methodologic issues when you struggle to analyze it, and I think that will be valuable information for writing future written requests for evaluating future studies, so I think there is a lot to be learned about it.

I don't even want to go on the labeling, but I have got a whole list of stuff there.

DR. RUDORFER: We will come back to that.

Dr. Chesney.

DR. CHESNEY: Two issues with respect to Question 1. The first one, I think we have already gone over several times, but I would really strongly encourage, if it is possible to go back and look at every patient, to look at this stimulant syndrome issue, this mania, this irritability, and so on, which I must say I was not fully apprised of at all until we came today, and I am most impressed when I hear from, again in the open session, about how some of these events occurred very quickly.

I know the potential explanation of being stimulated out of lethargy, but this sounds like

something different to me, which brings me to my second question.

I wondered of any of the psychiatrists could tell us if there is any association with drug levels, because certainly in my field, which is infectious diseases, drug levels are imperative or you wouldn't know what you were treating or how well you were treating it or whatnot, but certainly we heard levels at autopsy referred to as being three times I guess what was expected, and then Dr. Goodman made the comment about adjusting dosage.

Do we have any idea of what the dosages were in these studies and how they correlated with body weight or levels? For those of us not in the field, I just don't know anything about the value of pharmacokinetic studies in these drugs.

DR. LAUGHREN: Just to comment on a couple of your questions. For the most part, blood levels were not obtained in these trials. Any pharmacokinetic data for these pediatric programs were done in other smaller studies. For the most part, I don't think we are going to have much luck in getting PK data here.

In terms of dosages, these were mostly, virtually all flexible dose studies, so patients

were dosed within a range, usually the recommended range for that drug. They were not fixed dose studies. We have dose information, but without something to link it to, it probably is not going to be very productive.

But I wanted to come back to your first point because now several people have raised this question about some kind of a stimulation syndrome and linking that in some way with mania. If we are to look for that, we have to know what it is that we are looking for.

I mean there has to be some kind of definition. Are we talking about something that is linked specifically to suicidal behavior or something that occurs independent of suicidal behavior. I am not sure if this entity can be well enough defined for us to search for it.

We have over 4,000 patients involved in these trials. To head off looking for a syndrome, we have to know what it is that we are looking for.

DR. CHESNEY: Can I just respond to one comment. I think on several occasions we heard that it was actually homicidal behavior that seemed to arise from mania, and if we just look at suicide, maybe that is not all we want to know

about.

DR. RUDORFER: Tom, I wonder if I could interject a question for you. I think the concept of akathisia, which again has come up repeatedly, captures a lot of what various speakers are talking about, and I wonder if the Agency's experience with antipsychotic drugs would be helpful in that regard in terms of definition.

DR. LAUGHREN: We could certainly search for akathisia. That term is reasonably well understood I think clinically and would very likely appear in the electronic database, or one I suppose could come up with related terms that might get at akathisia if it wasn't specifically named.

But again, my question is are we looking for that symptom by itself or are we looking for that in association with some other behavior. Again, there is a very widespread belief that akathisia is linked to suicidal behavior, but I am not sure how strong the data are supporting that belief, that is really the question.

But again, if we are going to search this database for something other than what it has already been searched for, we have to have some fairly specific guidance about how to do that.

MS. BRONSTEIN: My comments are about labeling and if you want me to wait, I will, or I would like to get them off my chest now if I could.

If I heard nothing from this morning's testimony, I heard repeatedly that people feel the need for patients and family to have more information than they have currently.

I think that is really our responsibility to do something about it whether it is after this meeting or after the summer meeting. I think we need to get something out there that describes akathisia in a way that patients can embrace it and understand it, and family members can watch for this radical change in behavior.

I am seeing it as an apparent link to either homicidal or suicidal behavior from the testimony this morning and from what I have read, as well.

DR. RUDORFER: Dr. Ebert.

DR. EBERT: Most of my comments also had to do with labelings. I just briefly wanted to react to what was stated earlier, though, again about the issues of going beyond just the suicidal behavior and whether it's akathisia or whether there may be some other characteristics which

clearly indicate that -- and I am not in the area of psychiatry, so you will have to indulge me for a second -- but just the whole issue of kind of a concept of self versus others, whether it's through homicide or it's hostile behavior or aggressiveness.

To me, these things all seem to be a constellation of the same types of syndrome that we would be looking at.

DR. RUDORFER: Dr. Fink.

DR. FINK: Another sort of global concern -- and I think it may be particularly apropos to this class of drugs -- is that when these clinical trials are performed, they are usually performed by experts in the field, yet much of the usage today, particularly in the managed care environment, is prescription of these drugs by non-mental health trained professionals.

The results of a clinical trial performed by mental health professionals where you are already using a highly select audience and highly select practices may bear little relationship to what you see with the drug in use in the real world.

From a labeling standpoint, it would make

sense potentially to say that at least off-label use of these drugs really should be highly restricted to mental health professionals or make some kind of wording that would imply that, because I think that off-label use of these drugs by non-mental health trained professionals seems to be problematic, and it may well be that much of the placebo effect that we are seeing in the clinical trials is because they are receiving counseling about mental health.

I am more familiar with asthma trials. When we do asthma trials, we see a tremendous placebo effect which is asthma education. My guess is in mental health trials, there is a tremendous placebo effect because you are seeing a mental health professional.

DR. RUDORFER: Dr. Leon.

DR. LEON: It would be interesting to know what items were captured in the severity ratings, because if we knew the items that were there, then, we could see which ones correspond to the symptoms we heard of this morning, and look at treatment emergent symptoms, symptoms that weren't there at baseline, on the severity rating, that were exacerbated during the course of this trial, so

looking at changed scores on a handful of a priori-defined symptoms from the rating scales would be very helpful.

DR. GOODMAN: Along those lines, as I mentioned earlier, the Hamilton has an item on agitation, the CDRS has an item on irritability, so that could be a first quick look, and you wouldn't have to look at treatment emergent, you can look at rating scale items.

I agree that one needs to give careful thought into what symptoms or how we are describing this constellation of symptoms, because it could be very problematic.

For one reason, a number of symptoms you would expect to get better with the SSRIs, and what we are really looking for is a minority of patients in whom you see a paradoxical increase in those symptoms.

So, I think we need to take a very careful approach to this analysis.

DR. RUDORFER: We have four more questions on this topic.

I am sorry. Dr. Laughren.

DR. LAUGHREN: Just one follow up on a suggestion that has come up from several committee

members now about looking at items from the rating scales. That was actually done here, and it turned out not to be very helpful.

Now, this was a similar analysis that had been done with the adult data years ago, for example, looking at patients who move from looking at the suicide item on the HAM-D and looking at patients who move from zero to 1 to a 3 or 4.

That did not detect a signal in these trials, and part of the problem may have been that these events often did not occur at a time when the HAM-D would be done, because the HAM-D is done at regular intervals.

If the event occurs between visits, which it almost always does, and then the patient is discontinued at that point, you never get a HAM-D or whatever other instrument is being used.

So, companies did try that approach, and it was not particularly productive.

DR. RUDORFER: We are now going to turn to Drs. Malone, McGough, Pfeffer, and Ortiz, and then move on to Question 2 more specifically.

DR. MALONE: I am sorry, I just stepped out, so I may have missed things that were just discussed, but I was thinking that looking at

agitation would be an important thing if you think about the way we use the recent meetings on antipsychotics and agitation.

Agitation often leads to harming of self or others, and it might be a proxy for looking at suicidal behavior. So, searching the electronic database for agitation, violence, and trying to construct an agitation -- I don't know what to call it -- but try to construct agitation and see if it does differ in those who are having suicidal ideation or having other such problems.

The other thing, I end up currently treating children with autism, and I think this whole activation syndrome is something that anyone who treats children with autism worries about if they are going to consider giving an SSRI.

There is some sense in which I think you could look at fairly quickly in a controlled trial whether populations other than depressive populations get agitation or get activated, and then get some information whether these drugs in children, in fact, cause this activation syndrome.

DR. RUDORFER: Dr. McGough.

DR. McGOUGH: This is really a segue I think to the labeling issue which keeps coming up

again and again. First, as far as off-label use goes, child psychiatrists could not treat severely ill kids without off-label prescriptions, there is no doubt about that.

Secondly, even in the absence of scientific clinical trial evidence, a physician needs to be free in specific instances to choose to take the risk of using a medicine even in the lack of a controlled study. Again, there is no way to meet the needs of these really severe kids without this.

To your point, unfortunately, there aren't enough child psychiatrists trained and available to do this, so it is left to other practitioners, and what I was really struck with, hearing the stories this morning, is many of the cases we heard were kids just naively given adult titration regimens at adult doses with no consideration to slow metabolizing, in Caucasian kids particularly, with no concern about the need to monitor for akathisia and early onset activation, so I see we can't restrict non-psychiatrist prescribing, we now have pediatricians, family docs, nurses, psychologists, all of whom will be prescribing these medicines.

There has to be some way to really notify

people or put people on notice that at least in the absence of efficacy data, you have to be very concerned about safety, and if there is any labeling tweaking to be done, that is what I would want to see put in.

DR. RUDORFER: Dr. Pfeffer.

DR. PFEFFER: I have a number of questions that have to do with the analysis issues and perhaps my concern is having heard the families and the sense of their urgency, if while the Columbia group is evaluating the suicidality question, if one might look at the data in a variety of other ways that might inform us about, for example, who improved and who didn't improve.

Who improved within the placebo group and who improved within the treated group, and what are the predictors of that or vice versa, what are the predictors of a poor outcome, and we might find that that might give us some very important clues as to the way that this population are responding to the drugs.

The question also that I have, and I assume it must have been done, but I am not sure, and that is whether or not randomization really worked, and especially did randomization work, for

example, in the suicidality issue.

I don't know if that has been looked at, and certainly once Columbia group looks at the definition of suicidal behavior, it will be looked at again, but that would be an important question to also look at.

Then, if I might contribute some information, for example, I know in the venlafaxine studies, they were doing blood levels of venlafaxine because they were looking at the question of slow metabolizers or not, so I wonder if that data might be able to be looked at to, to give us some clues about issues of metabolism.

DR. RUDORFER: Thank you.

Dr. Ortiz.

DR. ORTIZ: My comments, I think are in response to a couple of things that Dr. Chesney brought up. As far as levels in psychiatry, what we certainly know is that the Sinemet kinds of medicines, which are dopaminergic, can cause psychosis, and it is at different doses for different individuals, the same thing with amphetamines, they also can cause psychosis. Again, it is not predictable in each individual.

I would also like to follow up on your

suggestion to specify the adverse effects and the descriptions of them a little better.

As a psychiatrist, when I am watching someone that I am concerned about, that may be developing hypomania or mania, I am watching how their speech patterns change, I am watching their activity levels, I am monitoring their sleep, and I think a little more precision in those kind of descriptions might be helpful.

DR. RUDORFER: Dr. Andrews will ask the final question related to Question 1.

DR. ANDREWS: I have some concerns about the exploration of this activation syndrome in the context of the existing clinical trial data.

First of all, as has been said, we may not know what the elements of that syndrome are, but in addition to that, do we know whether the elements of that potential syndrome were collected diligently, frequently, and similarly across all of the studies, and I think that needs to be addressed before going into that expedition.

If not, I would encourage the FDA and the analysts to look at more objective endpoints, which I think are the ones that were established for suicide events.

I have a bit of concern that the study may not answer all of the questions because of the issue that was raised earlier regarding generalizability. These patients may not resemble the patients who are treated with these drugs.

They are probably treated in a different way in terms of dose titration in the context of a clinical trial, and in the context of a clinical trial, patients tend to be monitored more carefully, so that perhaps those at highest risk of suicide or suicidal ideation might have been identified earlier with other symptoms and withdrawn from drug or had drug titrated down.

DR. RUDORFER: Thank you.

I think we will come back to some of these issues. The sense I have from the committee is that while people have reservations about the limitations of the existing database, the sense seems to be that we would endorse going ahead with the Columbia reclassification, but with some additional measures.

Dr. Laughren had also specifically asked us about the appropriate categories in terms of the definition of "possibly suicide related" and "suicide attempt," and I wonder if anyone has any

feedback for the FDA on those questions.

Dr. McGough.

DR. McGOUGH: I was just speaking from experience and also the work Dr. Shaffer showed. You know, my view about cutting is that it is not a suicidal behavior, and others might disagree, but that would be my approach to that. It would be not to classify cutting or superficial cutting certainly as a suicidal behavior.

DR. RUDORFER: Dr. Chesney.

DR. CHESNEY: I was interested again this morning to hear in a number of instances that people took a drug, took a dose and then found themselves in jail and did not know what had happened in the interim.

How is that described in psychiatric terms, is that confusion of thought or absence of presence, or is that something that you could pull out? That seems a fairly profound confusion to just absent oneself from the situation and yet do some fairly striking things.

DR. LAUGHREN: It is phenomenologically an amnestic syndrome of some sort. I did not see that in these trials. At least it was not described as such.

DR. GOODMAN: Also, phenomenologically, it would be a dissociative or fugue state.

DR. CHESNEY: Was that asked for in the trials? Was that a question that was on the --

DR. LAUGHREN: No, I am sure it was not.

DR. LESLIE: I wanted to add two comments. One is on the Question No. 1, which is I think part of this is a process question of where we go from now. When I look at Dr. Hammad's variables that he has listed, I think there are some that are missing and it would be good to redistribute that list to the committee for review.

For example, I only see after discontinuation. I don't see on an increase of dose or decrease of dose. The issue of family history has come up.

I think all of us or there is a good majority here that are concerned about aggressive instances, and some of the family stories this morning were not of kids who were feeling down. They were of kids who acted suicidally because of impulsivity, and not because of a suicidal symptomatology that had been ongoing.

So, I think those things are important and I also worry about what is hidden in some of the

other neurological, et cetera, categories that are listed.

So, again, I don't know the process here and how you all feel about doing this, but I think redistributing this list for some suggestions of some of the risk factors and things that might be important to be looking at, as several of the speakers have said, would be important.

I also wanted to say that I am impressed that the American Academy of Child and Adolescent Psychiatry has been here and other groups, but there is no one here from the American Academy of Pediatrics, representing the American Academy of Pediatrics, although several of us are pediatricians and on that committee, and there is no one from the National Association of Nurse Practitioners, and there is no one from the American Academy of Family Practice Doctors, and reaching out to those organizations on an official level, since so many of us are the ones that are giving those medications, would be an important step to be taking.

DR. LAUGHREN: In terms of the lists of variables, all committee members have that. It is attached to a memo that I wrote. We would be happy

to accept suggestions at any point, it wouldn't have to be at today's meeting, of additional covariates that you think might be important to add to this database, so please free to do that.

DR. RUDORFER: Dr. Gorman.

DR. GORMAN: If all of these 15 studies that we are going to re-review were not intent to treats, analysis based on intent to treat, we would not be able to answer Dr. Chesney's questions.

DR. RUDORFER: Dr. O'Fallon.

DR. O'FALLON: One process question. Do you have data for all the patients in all of those studies? Do you have the detailed data for all of the patients in all of the studies?

DR. LAUGHREN: What we have right now are in terms of data sets. We have the data sets for the variables that we specifically asked for. Again, those are listed in an appendix to my review. So, that is what we have in terms of an electronic data set for all patients, but it is limited to those variables that we asked for.

DR. TEMPLE: Just with respect to intent to treat, we expect to see all patients randomized who at least got some treatment. It is typical in symptomatic treatments not to include people who

don't get a treatment. You can debate that, but it is usually not a big loss, but anybody who was treated should be in those analyses.

DR. PERRIN: It does seem, having read that list of variables on the way down this morning, that there are some important gaps. They do include again some of the factors Dr. Pfeffer mentioned before which are really in the social environmental phenomena that might influence rates of responsive treatment or might influence rates of suicidal behaviors.

It does seem like you don't have a lot of sort of data over time. It is almost like an adverse event reporting system, if I am reading the data set right. In other words, you don't have a lot of information on other response to treatment.

We have heard, for example, a lot of discussion without a lot of evidence that the first week or two or three of treatment is really critical, so one would wonder a lot about what kind of things happened during that time that you do have data on, and you talked about the notion that maybe the next clinical trials might be a withdrawal trial.

Again, there is a moderate amount of more

anecdotal than good evidence base that withdrawal is a very high-risk time, as well, for kids on SSRIs, and again there, having some sense of what happens relatively immediately in that two or three-week time would be extremely helpful, but I have a feeling you don't have those data for even the start-up time.

DR. LAUGHREN: Could you say a little bit more about how you would characterize that early response? Are you talking about looking at formal assessments, HAM-D, and so forth? I mean clearly, we have that. What we might not have is more anecdotal information about particular ways in which a patient didn't do well.

DR. PERRIN: Well, then, maybe you do have it, but on what periodicity do you have things like the HAM-D?

DR. LAUGHREN: Every week, you know, early on certainly.

DR. PERRIN: Then, you may have the information, okay.

DR. RUDORFER: As I understand the situation, Dr. Laughren's Question 3 on patient level data analysis, I think we have been discussing essentially on important covariates that

should be considered in the re-analysis.

Dr. Laughren, would you want us to address anything else specifically on that before we turn to future directions?

DR. LAUGHREN: No, but again let me just reiterate if committee members, as you continue to look at this list, if you have additional ideas, please feel free even after this meeting to submit them, because we want this to be as comprehensive as it can be. So, if there are important covariates we have left out, let us know.

DR. RUDORFER: Dr. O'Fallon.

DR. O'FALLON: Looking at that list again with fresh eyes after this morning, you don't have any data that will help you to get at the temporality of the various things.

For example, I look at that dose, and you are looking at the max of the mods, and things like that, but you don't have -- you know, there is no way in your data set then to get at whether the incidents occurred when the dose was raised, lowered, or discontinued.

So, one of the key questions is not going to be able to be assessed.

DR. LAUGHREN: That is something that we

clearly have that information. We don't have it now, but we could get that information and add it to the model.

DR. RUDORFER: Dr. Katz.

DR. KATZ: I have a question of clarification on Question 1, I guess it is, which a lot of people have been talking about, trying to look at these other behavioral symptoms that are not explicitly suicide related, like the stimulation syndrome, so called, or an activation syndrome.

Again, you have seen what we have done to try and capture the explicitly suicide related events. You know, we had these text strings, I think we had 15, we had to go back and forth with the sponsors and ask them to look at their verbatim terms, you know, that took some time. But we spent a lot of time trying to figure out exactly how to ascertain those cases.

Is it the committee's desire for us to attempt to recreate that process with regard to this sort of stimulation syndrome, in other words, look for multiple different sorts of terms that might be subsumed reasonably under this syndrome, in other words, try to cast as broad a net as

possible?

DR. RUDORFER: Yes.

DR. KATZ: Is that a general sense of the committee?

DR. RUDORFER: Yes, the sense of the committee is affirmative.

Dr. Laughren.

DR. LAUGHREN: Bearing in mind that going back to search the database involves a fair amount of additional time, now, we could proceed with our analysis based on the data that we have now, and in parallel, go back and ask for additional searches for other kinds of events like this activation syndrome if it can be better defined. That is something we clearly could do.

I wouldn't want to hold up the suicidality analysis waiting for that additional searching because that does introduce a lot of additional time to go back to companies and ask them to search again.

DR. RUDORFER: Dr. Temple.

DR. TEMPLE: I just want to be sure I understand. I think everyone's expectation is that there will be evidence of an activation syndrome or hyperactivity or those things because the drugs are

labeled to do that.

What use would one make out of that if it wasn't linked to some or one of the suicidal terms? I mean I guess it is more information and that is never bad, but is it more than that, would it help us understand things?

DR. RUDORFER: I think if I may speak for the committee, as I understand the discussion and the concerns, there are two issues.

One is that the activation or agitation or akathisia may be what is actually more accessible both to the patient and to the family and to the clinician in terms of it seems, again going back to some of the cases we heard this morning, it sounded as if we heard more instances of an individual complaining of akathisia-like symptoms as opposed to volunteering suicidal ideation.

I think that there is concern that the akathisia may be what is driving self-destructive behavior at least in some cases, and that might actually be more informative for the clinician to be watching for than actual more overt suicidality.

I also wonder if, in fact, don't we need that information to see if in this database there is a link.

DR. TEMPLE: So, you think it would be useful. I mean obviously if it sort of went along with suicidal thinking and behavior, that would be certainly of interest as a possible early signal of that consequence.

Suppose there isn't any link to suicidal thinking and all you found was a reasonable estimate of the rate of that in a pediatric population, do you think that would be useful all by itself? You could then say how likely it is and you would know that.

DR. GOODMAN: I think the way I would approach it, as you described, as two parallel processes where you continue the work, looking for the signal and suicidality. You then develop some criteria that help describe this activation syndrome which may occur in a subset of individuals, and then you would test the validity or clinical meaningfulness of it by then plugging it back into seeing whether it is those individuals that are more likely to go on to suicide as defined by the first part of your study.

So, I would agree -- one way of saying that -- I agree that for the purposes of our discussion, it would be more of an academic

exercise and not worthwhile unless we could then find that that subgroup in which there is an activation syndrome are also more likely to go on to be the ones that were identified as exhibiting suicidal behavior.

DR. RUDORFER: Dr. Hudak and then Dr. Gorman.

DR. HUDAK: I have a question and a few comments.

The question involves the quality of the data that you currently have for analysis. Basically, the 15 studies that are presented here involved 7 drugs, and I am not knowledgeable about these drugs and pharmacological companies, I presume at least 7 drug companies are doing these things. They are using different protocols, they have different outcome measures, and they have different data acquisition tools, and all those differences, and so forth.

The question I have specifically, the information that was presented in Appendix 2, looking at the difference between the "possibly suicide related" versus the "suicide attempts," as I understand it, that in this population of kids who might be sick, you are going to have more

suicide-related type reporting, because that is thoughts and behaviors in excess of suicide attempts, which is just behavior, I mean the data that was presented.

Looking at the information here, there are a number of these studies that basically, within both the drug group and the placebo group, the suicide related thought and behavior is exactly equal to the suicide attempt, which I find inconsistent.

Is this the final plumbing of the data, or is this before the word strings were done on the other data?

DR. LAUGHREN: This is one of the problems that I was alluding to earlier. When we sent out this request in July of last year, we asked companies to follow basically the same algorithm that Glaxo had used in looking at the Paxil data, which included, first of all, a general search for any term suggestive of possibly suicide related, and then an attempt to subgroup patients from that larger set who had any indication of self-harm. I mean that is how it was defined.

What we found is that companies, in carving out that subset of suicide attempt, in some

cases appeared to count every case as a suicide attempt even though, if you looked at the individual cases, there was not any clear indication of self-harm, and that was one of the reasons why we felt it was very important to have these data completely reclassified by an outside group.

Basically, our position is that neither one of these categories, either possibly suicide related or suicide attempt, as it has been carved out and defined by the companies, is particularly meaningful, and that is specifically the reason why we want to have an outside group look at this broad group of events that were captured as possibly suicide related and help us figure out what kinds of bins to put those into.

As you saw from Dr. Posner's presentation, we will very likely end up with different categories and different data than what we have here. I mean this table is really a very preliminary table and we have very little confidence in what these numbers mean because we are not confident in what the numerators are.

DR. HUDAK: I understand, but even within the Paxil studies, there are three studies, and two

of them show no difference, and one would think that the studies were constructed in somewhat the same way and the query was done in somewhat the same way, and therefore at the end, even going back and having Columbia group look at this, you may have very imperfect data to look at.

DR. LAUGHREN: That is undoubtedly true, and that is a problem that we can't fix with these studies. You know, if ascertainment was poor, there is no way to fix it at this point.

DR. HUDAK: I have two additional comments. One is with respect to this general issue here. I think the big picture that I take away from this is the really unexplained doubling or tripling of suicide rates in particularly vulnerable populations that occurred over the past 15, 20 years, which is really quite impressive.

So, whatever socioenvironmental type etiology there is to this is a very significant public health issue. To put this sort of into context, this is a doubling or tripling. When we have a one-point difference in infant mortality, we have major committees sort of looking at why this occurs.

Infant mortality over the past 20 years

has gone down very substantially, but differences in infant mortality on the order of 1 in 1,000, which is about 10 percent of the entire infant mortality rate, are treated very significantly. And this is a huge problem, and I guess with one teenager and one incipient teenager is something that is dear to my concern.

The other comment I have is in relation to looking at treatment and the amount of prescriptions that are written, and so forth. I am struck by the fact that we have so much drug prescription done in a population that the efficacy is not established.

I fight that every day in the nursery, to come around and see patients on 10 drugs, of which maybe 2 have been shown to be effective and trying to withdraw therapy, but it must be -- I have no problem with they are children who are clearly very ill and anything that can be done should be done, and I agree with that, but on the other hand, there must be a large population of children -- a lot of the people who spoke this morning, the picture that was presented of their child or someone they knew was not someone who was very, very ill.

It was someone who had relatively minor

type findings, who were put on these drugs with terrible consequences, and I agree with every speaker who said that something needs to be done to educate practitioners and the public that these things may not at all be benign.

The fact that we don't find these things that are reported among the audience and the controlled trials is not surprising. It may be a very, low incidence phenomena that you are not going to find unless you have got randomized controlled trials, you know, 10,000 or more.

But each of these events, each of these anecdotes, and I have heard enough of them to think that, you know, you hear enough of these anecdotes, there must be some truth in it. I mean I am willing to believe that there is an idiosyncratic reaction that some patients have with these drugs, and I think that warning needs to go out in the very strongest terms from the Agency as soon as possible.

DR. RUDORFER: If we can hear from Dr. Gorman and Dr. Chesney, please.

DR. GORMAN: I would like to pick up on the thread of where we are data mining. One of the things that struck me in one of the slides that was

put up was that in August, there was the request from the pharmaceutical companies to relook at their data and present it to the FDA.

Within a month, one of the pharmaceutical companies, I am not sure they looked at their data, but they decided to change their labeling and withdraw it from the market.

I would ask the FDA to investigate what signal that pharmaceutical company found in their data that made them want to change their label without going through the FDA, and ask other pharmaceutical companies to look in their data in the same way.

DR. RUDORFER: Dr. Laughren.

DR. LAUGHREN: Yes, can I just respond to that. That company was Wyeth and the drug is Effexor and Effexor XR. Having gotten our request in July, they did go back and look for suicidality, and they also looked for hostility, and they found a signal, and on their own, as I explained, they are allowed to do that on their own if it strengthens labeling under changes being effected.

What they did is to add mention of that signal in the Pediatric Use section of their label. They did not contraindicate the drug. They did

send a letter out along with that label change recommending that clinicians not use the drug in pediatrics, but the labeling does not in any way contraindicate it. It simply mentions the signal, and it is the same signal that we have seen and are currently evaluating.

You know, we have their analysis, I showed it to you, in fact. The question is if you go back and do the kinds of work that we are now proposing to do in terms of looking at the actual events that got included under those broad categories, what signal will you see.

That is really the question, and that is why we have not acted independently to approve that label change, but it is basically the same data. I mean there is nothing we haven't seen. Again, it is not as if the drug has been pulled from the market. They have simply added mention of that signal in one sentence in their label.

DR. RUDORFER: Dr. Chesney, please.

DR. CHESNEY: This is in response to the question from the FDA about why look at activation syndrome if it is not known whether it is directly related to suicidality.

But what I heard this morning or the way I

interpreted what I heard this morning is that the activation syndrome is associated or can be associated with very violent and very hostile behavior. Whether that results in anybody's death or not, several of the families said that that became an extremely difficult issue to live with.

Where we are dealing with a drug with no apparent benefit, it seems to me that any risk becomes incredibly important, so that is one additional reason that I would say it is important to look at this activation syndrome that some of us have just learned more about this morning.

DR. LAUGHREN: Can I just respond to that? Again, we are very happy to do that. It would be extremely helpful if the committee could come up with a little bit more definition of what that is to help us in searching for it.

But independent of finding it in this database, if there is a view that this syndrome is so well described and does exist, put together the case. Send us literature, whatever else, and it is possible to make labeling changes about clear events that are idiosyncratic in some way.

Again, the problem here has been that the events we are looking at are part and parcel of the

disease. If there is an activation syndrome that is unusual in its nature, and is not part of the disease that is being treated, it could be described in some way in labeling if there is enough even non-controlled data to support the existence of that syndrome, especially if it can be linked to, as you suggest, hostility and violence and suicidality.

DR. RUDORFER: Dr. Trontell.

DR. TRONTELL: Thank you. I have a question for Dr. Posner and perhaps other members of the committee because of looking at your proposed reclassification of the cases.

I have a concern, as we have all been discussing, that a very large number of cases may well fall into the indeterminate category using the very clear definitions you laid out for us.

Is there any mechanism you can suggest in that category that there might be some classification broadly, you know, low, medium, or high, that might allow some sensitivity analysis?

I am a little concerned that data that have been volunteered, you know, since this wasn't a structured inquiry into potential suicidal behavior, might otherwise be lost.

DR. POSNER: I think it was suggested before that we do a level of certainty variability and analysis, and I think that that is a very good point and something that we will take into account when we are doing those classifications.

DR. RUDORFER: Dr. Maldonado is next, please.

DR. MALDONADO: This is a quick question. I am not trying to generate more work for the people who are doing this work, but I also have the concern that Dr. O'Fallon had, that these data may not yield what you are looking for.

Actually after hearing the comments in the morning of some of the testimonies, it appears that some of these reactions were very similar in adults also, not only in children.

I understand that the signal is much less evident and that is probably why adults have been excluded, but since the database in adults, I assume it is much larger and the disease appears to be less heterogeneous, I don't know if there will be a value in looking systematically into that data to see if there is a signal.

But again not knowing the data, it may not be warranted, but that is something that might

actually help to understand. I am not talking about only suicides and suicide attempts, I am talking about all the other signals, the wide net that has been proposed here that appears to happen also in adults.

DR. RUDORFER: We are going to hear from Drs. Wang, Leon, and Fost, and then look towards the future.

DR. WANG: I just wanted to follow up in terms of the utility of studying this akathisia-like symptom. I think there is actually a lot of utility particularly if you focus on sort of the synchrony of change, not just whether there is a link, but also if there is, you know, presumably this akathisia-like syndrome or activation is just more frequent, so you should have some power to study it, but see if there is a time relationship, because there are so many questions raised about, you know, these potentially abrupt onsets of suicidality after developing some kind of activation-like symptom.

Anyway, I would argue that there is some utility in studying it.

DR. RUDORFER: Dr. Leon.

DR. LEON: A point of clarification. Dr.

Laughren said the HAM-Ds or whatever severity rating is available from the trials. Are those available for each week of the trial or just for endpoint, and are those available at the item level?

DR. LAUGHREN: They are available by week, and they are available by item level. What I was pointing out earlier is that companies did try to do a similar analysis with the suicidality item from the HAM-D, Item 3, similar to what has been done with adults, and it did not generate a signal in general.

DR. LEON: But do they look at the agitation item? I wouldn't expect the suicide item to be very sensitive, and I expect it to be even less sensitive in kids who are probably less inclined to disclose their ideation.

DR. LAUGHREN: I think we probably already know that there is an excess of anxiety and agitation both in adults and children with SSRIs.

The question is what is it linked to, and that is why we need help in trying to define the syndrome that everyone is talking about and may well be a real thing, but we already know about agitation by itself.

DR. LESLIE: I think part of what you may be raising, though, is using it as an independent variable, and not as an outcome variable. I mean one thing would be is this is a sign of increased aggression on the item, on the HAM-D or increased irritability linked then later as an independent variable or a predictor variable, so not as an outcome variable, but as an independent variable.

DR. LAUGHREN: We already have agitation in the model. That is one of the variables, agitation on drug as opposed to a baseline variable. We have already included that in the model. So, we should be able to look at that.

The question is are there other things like that, that might be combined in some way to look at as some sort of a stimulation syndrome or activation syndrome other than just agitation by itself.

DR. MALONE: Do you have hyperactivity in the model?

DR. LAUGHREN: I am not sure that hyperactivity is a term that was even coded for. I would have to go back and look at the dictionaries and see what preferred terms were used.

Are you thinking of hyperactivity as a

term for subsuming other investigator terms or as a descriptive term in itself? I am not sure what you mean by "hyperactivity."

DR. MALONE: Increased motor activity. In addition to them just being described as agitated, they may be described as having increased motor activity, sleeplessness, all as part of a syndrome.

DR. LAUGHREN: Or restlessness?

DR. MALONE: Restlessness, yes.

DR. LAUGHREN: Again, to the extent that committee members can put these thoughts together and help us identify something to look for, it would be very helpful.

It doesn't have to be now. Again, you can think about this, and if you want to send us your thoughts about this, we will be happy to entertain them. This is the time to do it, because now is the time, if we are going to ask for additional variables, now is the time to do it.

Dr. Fost and then Dr. Pfeffer.

DR. FOST: Thank you. I have some comments that have to do with Questions 5, 6, and 7, and I think they cover all three issues.

There have been some comments both in the public session and among the committee and the FDA

people that there are two problems here.

One is the possibility of causing harm to children by prescribing these drugs that may induce suicide, and the other problem is that we may be scaring people away from prescribing them and there may be inadequate prescribing.

That is presented as if they are sort of commensurate or symmetrical, but I think that is not quite right. There is a reason for the first principle of first do no harm. It is almost the whole raison d'etre of the FDA.

The reason for that is that it is widely thought that it is more important not to harm people than to fail to help people. There is an infinite number of people we maybe can help, and we can't do all of it. It is unclear whether we can do it, but we know we shouldn't harm people. That is our first responsibility.

What is odd about this situation is that we may be doing both. That is, there is not just concern about causing harm to children, but there is tremendous ambiguity about whether anyone is being helped.

So, as several people have said, if there is any risk of harm, even if it is a very small

risk, it is not worth it if there is nothing on the benefit side of the scale.

So, it seems to me equally urgent to try to get some better information about the benefit issue, as well as the harm issue.

Now, Bob Temple said that withdrawal studies can't tell us anything about harm, which I agree with, but they can tell us a lot about benefit. In fact, they may be more powerful than prospective trials in showing benefit.

So, it seems to me encouraging, however you can get it done, getting some withdrawal trials to occur might take us a long way towards assessing the benefit issue. That can be done and it is not all that expensive to do.

That seems to me equally urgent as whatever can be done mining the database to find out about the harm. So, that is the first point. I think both of those are important.

Second, in terms of what to do while we are waiting for these things to happen, while it is correct that this long-standing section of the label that says be especially careful when you start people on treatment can be interpreted to mean they might get worse.

I don't think an ordinary person, it is all counterintuitive, but I don't think it occurs to most parents and maybe not even to doctors who aren't really highly informed about this, that that may happen, that an antidepressant can make you more depressed or at least more suicidal.

I think that word needs to get out as soon as possible, first, that that is a real possibility, that the British FDA thinks it is a very real possibility, that the FDA, the American FDA is very concerned about it, seriously concerned Dr. Laughren has said several times, that the level of concern that exists among everybody in this room, public and committee members and FDA, is not adequately out there.

For doctors, maybe psychiatrists, I can't speak for them, but I doubt that pediatricians are aware, or family practitioners, the level of concern about this potential problem.

So, it seems to me while we are waiting, it would be very important to get that word out through the AAP and the AAFP, through national meetings, through pediatric news, through newsletters, through panel discussions, presentations at national meetings, and so on, and

second, to parents, so that when they make what are ideally collaborative decisions with their doctors about whether to put their children on these drugs, they understand completely that there is at least serious concern and that while it is not a settled issue and FDA is looking into it, and you may withdraw the serious concern by the summer, or you may enhance it, but I don't think that is so terrible to say we are looking at it, it may take us another 6 or 12 months to figure it out, but while we are waiting, you should be very alert to the risk of these drugs, you should be very alert to this activation syndrome in your children, here are some signs of it.

We don't know for sure whether it leads to suicide or not, but there is a lot of smart people who think it may very well, so you need to be hypervigilant about it.

Oh, and a last point. Just to pick up on something Skip Nelson said a couple of hours ago, there is only one drug that has really been shown to be effective in children, and while you haven't disproven efficacy, it hasn't been really well established either for all the other drugs, so it seems to me at least part of the education campaign

to physicians is if they are going to prescribe anything, why not prescribe the one that we know the most about and have the most confidence about.

That is not to say they may not also cause the suicidal problem, but at least we have efficacy data for fluoxetine that is stronger than for the other, so why mess around with these other drugs for which there is less encouraging data on the efficacy side.

DR. RUDORFER: Drs. Nelson, O'Fallon, and Pine, please.

DR. NELSON: I want to just make the observation that that point about fluoxetine complicates how you might then design a trial going forward to look at the efficacy of the other drugs, because you need to evaluate the alternatives that the child would not be on.

So, if you are proposing to start off with an open-label, non-randomized treatment of a drug that has already been shown to not be effective in your short-term trials, and not put that child on fluoxetine, unless that child is a non-responder or has had an adverse effect to where you think the profile of the drug you are going to put them on would have some advantage, it is not clear to me

that that would be a trial that would get through 5052 on your IRB in evaluating whether it ought to go forward.

DR. O'FALLON: I recall that Dr. Murphy told us this morning that FDAMA was needed in order to basically motivate the drug industry to do the studies of these in the children.

When I first went on the subcommittee, I was appalled to realize that a great many of the doctors feel they pretty much have to prescribe off label because there isn't anything on the label for an awful lot of different things.

So, I think that harm, being able to identify harm in children may actually be more important than being able to identify benefit, simply because the physicians are often having to -- are often having to work off, you know, just try to figure it out on the fly.

So, given that fact, one of the things that really bothers me is the fact that the exclusion criteria are trying to get rid of kids who are taking more than one drug for whatever reason, but the kids out in the community who are getting it are generally on more than one drug.

I think that your future studies have to

include children who are on other medications, as well. They probably would have to be stratified and treated carefully, but you should be getting the data on adverse events in those populations, as well, because the physicians need to know what bad things can happen.

I think placebos are needed because you aren't going to be able to sort out the stuff that is coming off of the disease from the stuff that is coming off of the treatment if you don't have a placebo for at least some part of the time.

So, the forward studies, I mean there are a lot of things that you have got to do for future studies, but it seems to me you must be looking at these things in multi-polypharmacy, or whatever you call that, group of patients, as well.

DR. RUDORFER: Dr. Pine.

DR. PINE: I have a couple of comments in light of a couple of things that have been said over the last few minutes.

The first thing is in discussing the data on efficacy, I think it is important to point out two things, the first of which is that a number of people have noted that the data are quite discrepant for fluoxetine relative to the other

SSRIs in pediatric major depression.

Non-psychiatrists might not be aware that that is highly unusual. The data in adults, to the extent that SSRIs have been compared, really do not find that, and I think that one possibility is that kids are very different, and fluoxetine works, and the other SSRIs don't.

Another possibility is that maybe there are systematic differences in terms of how the studies were done, and I think it is important, particularly from a labeling perspective, not to jump too quickly to say, well, fluoxetine is okay and nothing else is, number one.

Number two, we spent a lot of time talking about the efficacy data for major depression. As was said in a number of presentations throughout the morning, that particularly in young children, major depression is not the leading condition for which medications are prescribed, it's anxiety disorders.

When one looks at the efficacy data for the anxiety disorders, for the SSRIs, one gets a very different picture, at least to the extent that those data have been made public and have been published, that the efficacy data really looks much

stronger there.

So, I think again it is very important to not rush to judgment in terms of saying that SSRIs have no benefits for children who present with various types of psychiatric disorders, because the fact of the matter is that a high proportion of individuals who present with major depression will also have anxiety, and I think it is very important to look at that issue.

Two other quick points. You know, I think that there are problems with the withdrawal design, and the FDA mentioned them. Probably the biggest one is it doesn't do much for clinicians, for patients, or for parents to answer the specific question if my child is depressed right now, and they need treatment, is it better to give them an SSRI or not. That is really the question that we need to answer.

The last brief comment, you know, I know you guys are asking a lot about could we better define what this activation syndrome is. Something that we need to consider very carefully is not only is it known at least among psychiatrists that this syndrome occurs, but usually it is mild. So, usually, at least to the extent that it has been

studied in trials, the activation syndrome that occurs is relatively mild.

So, to the extent that you are going to look at it, it will be very important to not only assess the type of behaviors that are manifest, but to all say, well, what is the difference between a mild syndrome which might be relatively common and a severe syndrome which might be relatively rare.

DR. RUDORFER: Dr. Temple, would you like to respond to that?

DR. TEMPLE: Partly respond to a number of things that have come up. Actually, I wanted to ask Dr. Fost something first.

The proposed addition to labeling about the possibility of an immediate deterioration, would that, in your view, be based on the results of the controlled trials that we have heard about, or on the observation from various personal experiences that this seems to occur?

I ask that because, as you have heard, the first of them were a little uncertain what it says, and the second is confounded by the difficulty that some of the consequences that have been described are potential consequences of the underlying disease, as well.

That doesn't mean we couldn't say watch out without necessarily acclaiming the state of the evidence for it. As you pointed out, we already do say this is a time to be careful when you start therapy, but I am just interested in what you think the basis for expanding that would be.

DR. FOST: Yes, I think there are multiple reasons why the FDA called this difficult meeting today, which is very challenging to put together and very stressful for a lot of people, but there are several streams of data that I am guessing triggered it.

First, there are the data from the trials themselves and the reexamination of it that is going on, and the British conclusions from it, so, first, it is that.

Second, it's, as Dr. Hudak pointed out, this epidemic of suicide and what is causing it, and maybe -- it happens to be concurrent with the rise of SSRIs -- maybe that has got something to do with it.

DR. TEMPLE: Wait, you must have seen different data than what I saw. What I saw was that in recent years, approximately coinciding with the SSRIs, the rate of suicide is going down. I am

not saying that proves anything, but I don't see it -- you didn't show it going up.

DR. FOST: So be it. The public concern, I mean the increasing number of anecdotes, I mean obviously, you think that is important or you wouldn't have spent so much time on it listening to it today.

I mean I think there are several things that trigger it, but if nothing else, the data alone, I mean the original trials themselves have stimulated concern among scientific people.

DR. TEMPLE: As you heard, we have considerable reservations about what the state of the trials themselves mean at the moment. I am not saying this is a bad idea, I am just trying to figure out the basis of it, because if we propose something, we will certainly be asked.

DR. FOST: I accept that you are uncertain about it and that is why you are going to a lot of trouble to look at it much more carefully and in much more detail, but while you are looking, I think sharing this concern, given the seriousness of it if it turns out that way, is a relatively low cost thing to do.

DR. TEMPLE: I just wanted to also say

something about randomized withdrawal studies. They are not the whole nine yards obviously.

I don't think most people would say that it is a good state to have only one possible drug. Prozac is a fine drug and everything, but it stays with you more or less permanently, when you stop it, it is very hard to get off, has a very long half-life with active metabolites.

If there were other drugs that were effective, it would be useful to know that. Now, at the moment, you can't say that there are any other effective drugs.

The interest in a randomized withdrawal study is that you take people who, in one way or another, through off-label use, are on a drug already, and you put people into a trial because they seem to be doing well, not because they seem to be doing badly, and because the current standard of therapy isn't to keep kids on therapy forever, at some point you take them off and see how they do.

Therefore, a randomized withdrawal study approximates or may approximate clinical practice, and that would be the case for saying that it's an ethically designed trial. Obviously, people are

going to look closely at all this and see if they agree with everything I said.

But it can tell you that a drug -- again, you taper the drug slowly, you don't do an abrupt withdrawal or anything silly like that -- it can tell you I think that the drug was having a favorable effect. It confirms the clinical observation that led people to keep the patient on the drug in the first place. So, I wouldn't rule it out.

DR. RUDORFER: I wonder if I could interject a comment on the labeling. We have, under Question 5, a quotation from the usual labeling about watching out for the risk of suicide early in treatment.

I am thinking, in that small paragraph, the second sentence reads, "Prescriptions for Drug X should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose."

I am wondering if that space could be better served. I think that is a legacy from the tricyclic era and I don't think clinicians today really worry so much about their patients committing suicide by antidepressant overdose.

I am wondering if instead we had a statement that encompassed two thoughts, one, that patients should be monitored frequently early in treatment, and, two, that any change in behavior, particularly early in treatment, should be reported to the clinician promptly, to avoid getting into issues of causality, which we have not settled since we don't have all the data yet, but I think -- correct me if I am wrong, committees -- but I think what we are saying is we want to put a speed bump in the road, that, in fact, the sense of the committee is that clinician should take these medications more seriously, and not dispense them overly liberally with inadequate monitoring.

I think our state of knowledge is such that we don't have the data we want in terms of showing efficacy and in terms of some of the adverse effects, notably suicidality, obviously, that the analysis is very much underway and we are saying maybe there are other kinds of data to look at, but I think the concern that many of us felt today was that the way SSRIs and other newer antidepressants are being used now is such that the warnings, as they exist in the current labeling, are not adequate and/or not being taken seriously.

My final thought is I wonder if it's time to reconsider the bolded warning about avoiding combinations with MAO inhibitors, which again I think that is a very important interaction to avoid, but I am not sure how relevant that is to practice today.

Dr. Fost.

DR. FOST: I just want to add I think that last sentence adds to the confusion about that paragraph, because the way I read it, frankly, is your patient is depressed, may be suicidal, you have just started him or her on treatment, be careful how many pills you give him because it may take a while for the treatment to kick in and during that time he may take too many of them.

It makes it look as if the message is don't give your patient too many pills until he is over the hump, he or she. So, I agree completely with your sentiment. I mean maybe that is important, too, but these are not major causes of death, overdose of these pills we have heard.

So, it seems to me the more important issue is watch for this other thing where the patient may kill himself in some other way.

DR. NELSON: To continue on the labeling,

looking through most of the labels, it says simply that efficacy has not been established. Even though that is a true statement, I think most general physicians and pediatricians have been socialized into thinking that means that the studies have not been done, where the reality here is they were done and did not show efficacy.

So, I would say you need to actually say that, in fact, the studies were done and didn't show efficacy, not that it has not been established, because that is often read as the studies weren't done.

DR. RUDORFER: We have time for Dr. Malone, Dr. Glode, and Dr. Irwin, and if we stay longer than that, we will have to pass the hat for rent, so we may have to wrap up.

DR. MALONE: I will just try to be brief. I wanted to reiterate what Dr. Pine had said, that a lot of this discussion is about efficacy in depression, but there is a lot of data about efficacy in anxiety disorders. In fact, three of the drugs are labeled I think for OCD, which is an anxiety disorder in children.

The second thing is if you are doing a discontinuation study, if the problem is that you

have such a high placebo response rate that it is hard to separate drug from placebo, and you have a lot of placebo responders in your study group and then you do the discontinuation, might it be difficult to find an effect.

DR. TEMPLE: Can I comment on our experience. That is not our experience. As Tom said, at least half of all conventional depression trials in adults fail to distinguish drug from placebo. This includes only drugs we believe are effective because they are successful in other trials.

When you do the other, when you do a randomized withdrawal trial, I am aware of only one drug that has ever failed to be successful in that setting. The reasons are fairly obvious. One, you are only putting in people who do well. It is an enriched population for people who are likely to do well. It is almost -- you know, okay, that's one.

The second is that the support system that probably helps the placebo response in the acute episode isn't there here. These are just people out in the community, they aren't seeing anybody or chatting with anybody. I mean they might be, but they are generally not.

So, the history is that those trials are much more successful, much more at showing effectiveness. Tom can I am sure elaborate, but I think we have seen only one fail out of a lot.

DR. MALONE: I am not sure, though, that the placebo response rates are the same in adults as they are in children. That would be my only concern.

DR. RUDORFER: Dr. Glode.

DR. GLODE: I just wanted to add my support to the recommendations, if I understood them correctly, by Ms. Bronstein and Dr. Fost.

I am impressed, if again I have these numbers right, that there were 8 million prescriptions in adolescents for these drugs in 2002, so between now and June, let's say another 4 or 5 million prescriptions may be written, and these may or may not be for children who were the same as the 3- to 4,000 children with major depression who were studied, again without knowing the exclusions for all of those studies, if suicidal children were excluded.

Then, one comes to the risk of overinforming people because I am going to support additional information to be provided to parents,

patients, and providers, so that what is the risk of informing versus the benefit of informing.

So, the risk of informing, as mentioned, is that parents or patients could refuse to take the medicine that might possibly help them, although again we have the limited efficacy data.

The benefit of informing them is that then if you gave them the right information, they would re-present to their provider when they develop these symptoms and be re-evaluated as opposed to here is your two weeks of samples, you know, I hope you do well.

So, it seems to me that the benefits of informing them probably outweighs the risks of informing them, and my own advice to the FDA would be to immediately request that information be provided to parents and patients at the time the drug is prescribed. You know, that just gives them more information about this and ask them to re-present --.

DR. RUDORFER: Dr. Irwin.

DR. IRWIN: I would argue that the patients may be ahead of the curve than the clinicians are, and I am a person who specializes in caring for adolescents, I run a large adolescent

medicine program at the University of California/San Francisco.

I would argue that most of the pediatricians who prescribe these agents are not as familiar as the psychiatrists are about the side effects. I think in the way that pediatricians -- when I was in training, you know, you treated everybody that walked through the door who had a red ear -- now, we don't do that. We basically do a lot of watchful waiting.

What I heard today from patients and parents, as they stood up and talked about issues, that many of them went to primary care physicians, and there was not any watchful waiting, in fact, there was immediate response, and the immediate response was based upon I think inadequate information that is going to clinicians who are acting in good faith and really committed to improving the lives of young people, of which, known in an adolescent medicine clinic, a primary care clinic, about 1 in 5 kids that walk through the door have a behavioral disorder, so you are really confronted with a big problem.

So, I think it is imperative I would say that the FDA get something out to clinicians as

quickly as possible, and it can be done through a variety of ways that have been mentioned here, because I think those are the individuals that are really acting in ways that we need to really try to encourage them to be acting in a more responsible manner when we are coming up with what really the issues are.

Thanks.

DR. RUDORFER: Dr. Leslie, do you have a word, and the we will wrap up.

DR. LESLIE: I wanted to echo what Dr. Irwin was saying as a fellow pediatrician, and also comment that one of the large pressures that many of us in primary care are under is that we cannot access other types of mental health services. There aren't mental health providers to see kids or they are not able to get services through managed care.

So, many primary care providers are trying to do what they can to help families and children by giving these medications. So, the other thing we need to do -- and I am not sure what the role of the FDA in this is -- demand parity for mental health services.

DR. RUDORFER: Thank you. I think we have

been identifying some very crucial issues. As Dr. Laughren pointed out in his handout, the FDA does not control the practice of medicine, so that we here have under the FDA's jurisdiction a limited part of the overall scheme.

Nonetheless, I think the sense of the committee is that the FDA has a very important role to play, and this challenge is an opportunity to further protect the health of young people with depression while the further studies we discussed proceed.

If I can sum up the sense of the committee, I think I have 18 seconds, I can distil this to two major bullets.

First, we concur with the plan to have the expert group at Columbia re-analyze the data from the efficacy trials that were presented and some ideas were offered.

We could do this in a more formal way in terms of other covariates, issues, such as family history, the activation or overstimulation, restlessness, akathisia spectrum, we discussed as useful information to have.

It will be particularly helpful if it is linked with the suicidality measures, but we think

nonetheless that is important to have established.

Correct me if I am wrong, committees, but I think our sense is that we would like in the interim the FDA to go ahead and issue stronger warning indications to clinicians regarding possible risks of these medications, which we don't see as contraindicating their use, but we think such warnings are required to elevate the level of concern and attention that practitioners use in prescribing them.

I think, as a group, we were recognizing the limitations of uncontrolled data. We were all concerned about the stories we heard of the actual use of these very powerful, potentially very effective medications, but in many instances, being used without adequate monitoring.

DR. TEMPLE: I would just add to your summary, information to physicians and to parents.

DR. RUDORFER: Thank you. I would now like to turn the mike over to Dr. Chesney representing the Pediatric Drug Subcommittee.

DR. CHESNEY: I just wanted to thank the FDA for bringing this issue to all of us and for being so open and listening and for asking us to continue to provide them with additional

information.

I think it really brings home to all of us the importance of looking at all drugs very carefully in children. I also, again on behalf of the Pediatric Committee want to thank all the parents and children and individuals who came to share their experiences with us today.

DR. RUDORFER: Dr. Katz.

DR. KATZ: I would like to thank very much the committee. I think this is a very complicated and important issue and through all of that, I think ultimately, your recommendations have been very clear, and I think we have a very good understanding of what you think we should do and how we should proceed at this point.

I also would like to thank the families for coming forward and telling us your stories. That was courageous and we know it was painful, but I believe we heard you, I believe the committee heard you, and we appreciate it very, very much.

DR. RUDORFER: In closing, I would like to thank the members of the two committees, I would like to thank the FDA staff. It is obvious what time, effort, and hard work has gone into this important issue, we appreciate that, and I want to

thank everyone in the audience who came, particularly people who told us their painful stories.

The FDA staff can attest to the fact I kept arguing about the time limit. I am sorry, but we would probably still be in the open public hearing if we didn't have that red light.

Thanks all for coming and obviously, this discussion is to be continued.

Get home safely.

[Whereupon, at 6:05 p.m., the meeting was adjourned.]

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