commit robberies. Dipsomania, an uncontrollable urge to drink alcohol. Nymphomania and erotomania, sexual compulsion, a pathological preoccupation with sexual fantasies and activities.

Child sex abuse has increased dramatically, with even female teachers going manic on these drugs and seducing students.

The head of the Sex Abuse Treatment Program for Utah estimated 80 percent of the sex crime perpetrators were on antidepressants at the time of the crime while Karl von Kleist, an ex-LAPD officer and leading polygraph expert estimated 90 percent strong evidence of manic sexual compulsions that demand attention.

Diabetes has skyrocketed and has been linked to antidepressants. Blood sugar imbalances have long been suspected as the cause of mania or bipolar.

0249

(Applause.)

DR. PINE: Thank you.

The next speaker is Eric Caine.

DR. CAINE: Thank you for the opportunity to address you today. My name is Eric Caine. I am the John Romano Professor of Psychiatry and chair at the Department of Psychiatry at the University of Rochester Medical Center and co-director of the Department's Center for the Study and Prevention of Suicide.

Today, I am here in my role as chair of the National Scientific Advisory Committee of the Suicide Prevention Action Network U.S.A., which is also known as "SPAN," which is an organization of survivors of suicide, themselves having attempted suicide or family members.

I have worked with SPAN now for several years because of the dedication and drive and commitment of these individuals. I want to say at the outset that SPAN has received funds from the pharmaceutical industry.

In the past, I have served as a

0250

consultant for the treatment of agitation to the pharmaceutical industry. However, I have never served in any capacity in any forum on topics related to suicide or the issues before this Committee.

Indeed, at this point in time I spend 50 percent of my time either doing suicide research or training of young researchers on public health approaches to suicide prevention. I also come with a background of more than 30 years of work as an active clinician and administrator of clinical services.

I want to really focus on several points. You already have my comments, so I'm not going to pay a lot of attention to what I have written.

Put simply, 30,000 people or more year after year kill themselves from suicide. Most of these people, when we look at psychological autopsy studies where we go back and examine the circumstances of their lives, where we gather comprehensive samples from communities, most have either never been treated with medication or have

0251

been inadequately treated with any form of psychiatric or psychological treatment.

It is very clear that the key signal in the suicide field, not in the psychopharmacology field which you are talking about today but in the suicide field, is the absence of effective care for people who need treatment.

It is essential that you look at the entire universe of experience, even as you consider this piece of a much larger pie. I would say to you as you think about this literature, which I see as very equivocal, there are some studies that people would like to say suggest decreases in suicide rates because of concurrent increases in prescription rates. There are other studies which suggest idiosyncratic and problematic responses. This is tentative literature.

At this time SPAN and I agree that a black box warning is not warranted and would scare families and potential patients away from care.

Thank you very much.

DR. PINE: Thank you.

0252

The next speaker is Rosemary Dorsett.

MS. DORSETT: My name is Rosemary Dorsett and I am here to speak to you about my son Noie Crossco. This is my son. He was 26 years old. This is happier days. This is one of his many hiking trips.

(Showing photograph.)

MS. DORSETT; On July 15, 2004, my 26-year-old son went for a complete physical. During his visit, he mentioned to his doctor that he was going through a tough time. A friend of his had recently passed, and he was experiencing financial difficulties.

His general practitioner gave him a prescription for fluoxetine, commonly called "Prozac," a thirty-day supply plus two refills. The doctor's orders were to take the Prozac and allow three weeks before feeling better.

Within days of beginning the medication, Noie had problems sleeping, eating, and complained of not feeling right. I became alarmed and suggested he stop taking the pills, but Noie

0253

decided to give it a chance and allow for the three weeks.

Noie's symptoms continued to worsen and

he became withdrawn, nervous, and again complained of not feeling normal. He told me he found it difficult to approach customers at work and had trouble staying still. My son was losing weight rapidly.

One morning he told me that the night before he heard someone calling out to him from our living room, yet when he answered no one was there.

On Friday morning, August 20, 2004, just four and a half weeks after beginning the Prozac, my son showered, dressed in his favorite Dodger jersey, he kissed his sister, drove over to a friend's garage one block away from home, and he shot himself in the chest.

This tragedy has left those of us that knew and loved Noie completely shocked as this senseless act was completely out of character for my son.

Noie was a kind, loving, thoughtful,

0254

respectable, and peaceful person. He loved his family, his cat, his friends, his motorcycle, and even his job.

Noie enjoyed life and looked forward to the future. My son had no prior history of any diagnosed mental illness or disorder, nor did he have a history of violence. I and those who knew Noie have no doubt that this dangerous drug is to blame for his suicide.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Mary Ellen Winter.

MS. WINTER: My name is Mary Ellen Winter, and I am here with my family. There is a before and after Paxil entered our lives.

Our daughter Beth's life began December 29, 1980. She was the fourth of our seven children. She loved milk and ate lots of macaroni and cheese. On May Day, she left flowers on the neighbors' doorsteps.

She was the angel in the church Christmas

0255

pageant. She loved dressing up in Halloween costumes. Beth never missed a day of work. Beth always danced. If she cried, she always ended with laughter. Beth loved to talk to the elderly and listen to their stories.

On birthdays, she would make crowns of flowers for people's special day. Beth loved jogging and taking long walks with friends. She studied abroad at Oxford and backpacked through Europe.

Beth was the godmother for her nephew, James. Beth was always happy, smiling, and she loved life. Everyone wanted to be Beth's best friend.

She graduated from the University of Rhode Island cum laude. A few months after Beth graduated, she began to experience insomnia which caused her to become anxious.

Beth never had a history of anxiety or depression. She went to our family doctor, and after a brief visit Beth was prescribed Paxil and told she would feel better.

Within a few days of taking Paxil, Beth couldn't ice a cupcake, couldn't jog to the corner, couldn't go to work, and still couldn't sleep. Beth felt out of her skin but didn't know why. She was told she would feel better in two weeks.

Beth never had two weeks. On the seventh day after taking Paxil, I arrived home from work and walked up my stairs. I saw my beautiful daughter hanging from the staircase. This was not a conscious act but a drug-induced suicide caused by Paxil.

Our family now lives in the after, a life without Beth, all that she was and all that she could have been. What if Beth's GP could not prescribe her SSRIs? What if GlaxoSmithKline, the makers of Paxil, did not tell their sales rep to downplay the serious side-effects of its billion-dollar antidepressant market?

What if the FDA had listened to their own scientists who proved that antidepressants raise the risk of suicide? What if we had an FDA we could trust, that did not falsely claim there is no evidence? What if the FDA had the integrity to come out and say "A drug we approved can kill you"?

Then, Beth would be jogging. She would be leaving flowers on people's doorsteps, spending time with the elderly. Beth could have been working hard on her communication career.

Beth could be married and have a family of her own and we, her family, would not be visiting her gravesite to spend a moment with her, like so many of us here. You can't bring back our before, but you can prevent another family from living our after.

(Applause.)

DR. PINE: Thank you.

The next speaker is Nada Stotland.

DR. STOTLAND: My name is Nada Stotland. I am a physician practicing psychiatry in Chicago, Illinois, and I have a master's degree in public health. I am a member of the board of directors of Mental Health America, which has supported my travel to this meeting.

The recognition of depression and its treatment is not limited to psychiatry. They are

listed in every comprehensive list of medical disorders and medical textbooks and taught in every medical school.

My patients and I choose their treatment, psychotherapy and medication, together on the basis of their past experiences, their symptoms, and their personal preferences.

Medication should be prescribed only after a careful evaluation and depressed patients have to be carefully followed. When I began medical practice, we had only one type of medication for depression, and that medication has to be taken several times a day. It causes significant side-effects. In fact, an overdose of that medication can be fatal.

Because of these side-effects, patients with heart or other general medical disorders or those taking other medications could not be treated. Because people with depression are at risk for suicide, we had to dole that medication

0259

out practically pill by pill.

We had to ask patients' relatives to lock up the medication or force patients to travel to the pharmacy every few days for a new prescription.

When the SSRI antidepressants became available offering fewer side-effects, once-a-day dosing, and very little risk of serious complications much less death from overdose, it was a tremendous relief for doctors and families.

I also speak as a parent. My husband and I have a daughter who has come to tell her own story at these hearings. When she got ill, we shared many parents' concerns about giving medication to a child, but with psychotherapy alone she grew so ill that we feared every day for her life.

Antidepressants gave her life back to us, so I am here to tell you that I know as a doctor and as a parent that the important risk for the FDA to consider is the risk of frightening the many people suffering and dying from depression about

0260

medication that could save their lives.

It is inexcusable to confuse having a thought or making a gesture with killing yourself. People who have lost loved ones to suicide are very clear about that difference. It is untreated depression that deserves a black box label.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Roger Peele.

DR. PEELE: Dr. Pine and distinguished panelists, I come before you as the chief psychiatrist, Montgomery County Government. I come

before you as someone who has been responsible for the care and treatment of people with psychiatric illnesses in public and academic settings in Washington, Virginia and Maryland over the last 46 years. Also, I come before you as someone who has had four uncles, one aunt, and three cousins kill themselves before there were SSRIs.

In thinking about preventing suicides, are we interested in blocking patients willingness

0261

to talk about suicidal thoughts? We are not.

None of my relatives who killed themselves talked about suicidal thoughts. Many of us have had patients who are alive today because they had a willingness to talk about their suicidal thoughts.

In thinking about suicide prevention, are we interested in blocking patients' self-injurious behavior? None of my eight relatives who killed themselves had self-injurious behavior.

We certainly don't want patients injuring themselves, but it remains that many a clinician has had patients who cut themselves as a way of reducing anxiety, and in reducing their anxiety they took an action that was less drastic.

We need to remember that the emotion just prior to committing suicide is often not sadness but excruciating anxiety in which the individual's only escape seems to be to end his or her life.

In thinking about preventing suicides, are we interested in preventing plea-for-help gestures? None of my relatives who killed

0262

themselves had a history of plea-for-help gestures.

We certainly don't want patients to have to resort to such gestures, but it remains that for many a patient such a gesture is not suicidal but an alternative to suicide.

Using a term like "suicidal" for a willingness to talk about suicidal thoughts, for cutting one's self or for plea-for-help gestures, then basing a black box on the word "suicidal," would lead the FDA to make a promulgation that the experienced clinician know is based on a fallacious understanding of the word "suicidal."

DR. PINE: Thank you.

The next speaker is Eric Swan.

MR. SWAN: Members of the Committee, my name is Eric Swan. I am from Minneapolis, Minnesota. Three and a half years ago, my brother-in-law died of suicide, five weeks after being prescribed Zoloft by his family physician for insomnia.

He was not depressed and had no history of depression. The story of his life and his

0263

struggles with the side-effects being discussed

today can be found on a website that we have built for our advocacy at Woodmatters.com.

For over three years, my sister-in-law, Kim Witczak, and I have made it our mission to be a voice for the small but important group of people that have experienced the suicidal side-effects of antidepressants.

Our website has had over 500,000 hits with many people from all ages relating to Woody's story and telling their own. The stories are from people of all ages and from all backgrounds. The one theme that comes through time and time again is, "I just wish that I knew then what I know now."

This is what this meeting is and should be about, warning all people so families like ours have a chance. Our website is not a scientific instrument. I guess some call it anecdotal.

We do rely, however, on the FDA, its advisors, and many other independent experts to debate the ins and outs of clinical trials, theory,

0264

and research.

We appreciate all that have given an honest and unbiased look at the issue. It is, however, time to consider what is best for Americans and all who depend on our FDA to lead.

In 1991, families like ours stood before a similar meeting talking about random, out-of-character suicidal activity. FDA did not take action at that time and asked for more data from manufacturers. This was a missed opportunity to warn 15 years ago.

In 2004, FDA accepted that there was a risk and did the right thing for ages 18 and under. This was a positive and needed step but a missed opportunity again for all ages. In my opinion, it created confusion for patients 18 and older.

You now have before you today an opportunity to warn all ages of the existence of a rare but life-threatening side-effect. Please do not confuse the American public again with some age-based warning that leaves some asking questions.

0265

I hope that all in this room will agree that we are talking about a side-effect that has been established by the science in people, and that despite that age may matter in the frequency of events, there still is a population in all age groups that are at risk.

This is about a warning. It is not about taking the drugs away or interfering with the doctor-patient relationship. Depression is a very serious issue. It is about making the treatment process safer for all.

There are many families in this room who

may not be here if they only knew. Please end the confusion and put a black box warning on all antidepressants for all ages.

You have shown me today that these side-effects happens in people. If I take my kids to the doctor, I want to be warned. If I take my mother to the doctor, I want to be warned. I wish you would have warned Woody. Statistics are people, people like Woody and those behind me.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Dawn Jeronowitz.

MS. JERONOWITZ: I would like to thank myself for the miracle of my being here today. In 2001, healthy, thirty-one and with no troubled history, I went to a doctor concerned about pain in my finger.

Finding nothing broken, his diagnosis was anxiety. He prescribed an SSRI for one year. Upon intake, I became high, high developed into euphoria, euphoria intensified to grandiose, until mania overtook me.

I lived delusions, paranoia, insomnia; endured radical, obsessive, irrational antics; fly-on crazy. Oblivious, other people noticed.

Within weeks, having lost 22 pounds, I was taken into police custody after running and screaming through the neighborhood. I kicked out the police car window barefoot, then dove through the shattered glass.

The emergency room described, "Impaired, disheveled, impulsive, combative, threatening, depersonalization, derealization, acute psychosis."

Held in four-point restraints, I was committed to a mental crisis facility. Days after my release, law enforcement came again when I myself called 911 twelve times repeatedly. Police arrived to find me locked in the house, razor in hand, screaming to kill myself while begging police to do it for me.

I was forced into total appendage restraint position. Again, I was committed to a mental crisis facility for suicidal ideation. My words on an antidepressant, "I will sacrifice my living breath and return to the sea of my Mother Earth, drown, car off bridge. Drugs? Death."

"Prescription suicide" is simple: A delusion manifested to actualize an escape from madness. Optimum because induced insanity is so horrific that living as such is more petrifying than death itself -- comparatively, a relief.

Make no medicinal mistake, SSRIs are hardcore, mind-altering legal drugs -- overprescribed, addictive, and deadly.

Unlike illegal drugs, however, prescription high does not subside, rather it swells higher to toxic levels masking itself in diagnosis while deflecting culpability. To end it: withdrawal, suicide.

Victimized, I filed a lawsuit against a pharmaceutical manufacturer mass marketing such a treatment knowingly, criminally failing to warn doctors, patients and the FDA of lethal consequence and poor efficacy.

Offered a settlement and gag order, I am able to speak today because I rejected that proposal. My case continues onward. I stand before you the powers that be giving you my experience. Now alerted and informed, I trust the policies you produce will be epic.

I appreciate your time. Thank you.

(Applause.)

DR. PINE: Thank you.

0269

The next speaker is Allen Routhier.

MR. ROUTHIER: This is a circus sideshow. The FDA has known all about antidepressant-induced suicidality at least as far back as the hearings in `91. This is the third time I'm doing this. And for what? I don't expect the FDA to do the right thing. They have had plenty of chances, and their record is abysmal.

My beautiful 40-year-old wife of 18 years was murdered. She was sick with undiagnosed gallbladder attack and the doctor she sought help from poisoned her with an unmarked, free sample of Wellbutrin.

After a week of severe adverse effects, she took her own life in a toxic psychosis. I blame Glaxo and the FDA. You invaded my home insidiously. These twisted mercenaries have been hiding suicides and homicides for years.

The FDA's own head of Drug Safety, Dr. David Graham says it seems the FDA has declared war on the American people and has now become the number one threat to their health and safety.

0270

Black boxes only cover financial liability and attempt at preemption. How do you put a price tag on someone's life? This can't be covered up any longer. Too many lives have been and are still being destroyed.

We all know antidepressants cause suicides by their terrible side-effects. It's all there in the "PDR." The same dubious benefits that can be achieved with crack can never outweigh the risk of killing innocence.

The time for secrets is over. The word

is out. Any idiot advocating the use of poison is part of the problem. The young, sick, old, or simply genetically unsuited can be especially vulnerable to the toxic effects.

We are told these toxic chemicals may balance something, although there is no measure, yet they admit they don't even know how antidepressants work. People who think they are being helped by staying high are facing serious health ramifications.

We are being lied to by killers.

0271

Clinical trials are riddled with suicides even though suicidal people are excluded from participating. We all know people hurt by these drugs. This is huge.

We need to shine light on this unspeakable darkness to reveal it for what it is. Drug company cheerleaders are being paid to perpetuate this nightmare. Pushers keep spewing that it is dangerous not to drug people. It's all about the billions in profit.

The FDA is bought out. Prove me wrong. Do something now. Sorry if you can't handle the truth, but the poisoning of my wife has left me bereft and bitter.

This should not be a civil matter; this is criminal. We need new Nuremberg trials. This is all old news and just the price of doing business.

Why are we here? What kind of b.s. do you have for us victims this time? What kind of black box to cover your liable asses this time? What kind of obfuscations for the media? How

0272

manipulated is this entire proceeding when we have a lottery to be allowed to speak with a few weeks notice to deliver our three minutes less than two weeks before Christmas?

(Cheers and applause.)

MR. ROUTHIER: Kill one person, you're a murderer. Redeem yourselves. Get the warnings out. Let the media report it. If you think we're going away, you are on drugs.

(Applause.)

DR. PINE: Thank you.

The next speaker is Anne Sheffield.

MS. SHEFFIELD: My name is Anne Sheffield. I have written three books about the negative impact of depression on families and on relationships.

The story that I am going to tell you is very undramatic compared to the tragic experiences that you have heard related this morning, but I still think that my story is shared by millions and millions of people.

When I was 17, this was well before

0273
Prozac, my mother attempted suicide. My stepfather got her to the hospital in time to save her life.

He and my aunt and I were all standing around her bed when she regained consciousness and said, "I did it because Anne doesn't love me." After a few days, she came home and we never had a word about what had happened.

Years later, a guy in my office who had depression told me that he thought that I did, too. He was right. I was actually so grateful to have a name put to the way I felt and a reason for feeling that way.

When the antidepressants had done their job, I finally realized why my mother had tried to kill herself and why all three of her husbands had left her and why she was such an unhappy woman all of her life.

My daughter and I have always been very close. It is a relationship entirely different from mine with my mother. Chatting on the phone with her one day, I realized she really didn't sound like herself at all.

0274
I called her a few days later, and it was the same thing. A few days after that, when I asked her what the matter, she said nothing. She had no energy, no life in her voice, no enthusiasm, just monosyllabic.

I was pretty sure that she had depression and I told her so. It took me calling every day. It took maybe three weeks to get her to see a doctor. When she got a prescription for an antidepressant, it took another two weeks to coax her to the drugstore to have it filled.

Then, one day the phone rang and she said, "Hey, I'm back. It's me. I'm me again." That was a very good story. Thanks to medication and self-discipline we have both been leading happy and productive lives.

I have always known that I would be dead if it weren't for antidepressants. It has been perfectly obvious to me. My daughter and I don't talk about our depressions. But it just happened the other day that we were with a group of people, who were talking about a friend of theirs who was

0275
depressed and refused to take any medication, and my daughter said, "Well, he's just nuts. I'd be dead without mine." This is a story, too, about suicide but it is suicide avoided.

DR. PINE: Thank you.

The next speaker is Laurie Yorke.

MS. YORKE: My name is Laurie Yorke. I'm a registered nurse of 22 years. I am here at my own expense. While I don't represent any official organization, I do represent 4,000 members of

Paxilprogress.org.

This is a website created by a Canadian man that I have taken over in the last two years. We have over 200,000 visitors, guests, per month on the site, and we are now exceeding 3.1 million hits per month. This is a peer-support website for those going through withdrawal from an SSRI.

You have also written testimony from some who couldn't get a spot to speak today or those who would be violating a gag order instituted as the result of a class action lawsuit. I am here to speak for them.

0276

This hearing is about suicidality, but you cannot address that without addressing withdrawal. The sudden violent acts seen at the start of SSRI use are only part of the story. Suicide, homicide, and other violent acts are seen in withdrawal from this category of drugs every day.

I have personally sat at my computer begging a poster to give me their phone number when they came to the website massively suicidal in an attempt to prevent that suicide.

I have talked to those who have had no idea that the possibility existed, yet they sit with a knife in their hand begging on the Internet for help.

There are people who are put on antidepressants for a multitude of reasons: depression, anxiety, freshman jitters, irritable bowel, school phobia, gallstones, et cetera. Some of these people were given a prescription instead of a CAT scan. Some have died as a result of misdiagnosis and drug reactions.

0277

These are not isolated cases. We see this reaction every single day in people from all over the world. It amazes me that we, as the general public, have seen these stunningly similar patterns of withdrawal, yet the doctors have not.

The FDA consistently refers to all 12-week trials, and you hang your decision on the fact that there were no completed suicides. Well, gentlemen and ladies, look beyond the 12-week use and you will see hundreds of completed suicides and thousands of lives devastated by Paxil withdrawal.

This is a post by a recent visitor to the site regarding FDA warnings:

"Do doctors actually receive this stuff to read? Because my doctor told me last February that suicidal risks don't happen with adults, just children. She said this after I told her that every time I try a new antidepressant I get thoughts of wanting to die. So basically she didn't believe a word I said. She said I felt that way because I was reading the wrong warning

labels," that it didn't apply to her.

This is what the public is dealing with. Talk about the stigma of depression, trying to get a doctor to take you seriously when you are in withdrawal, you have now become a nonperson.

Denying suicidality does not make it go away. We hear psychiatrists report, "I never had a patient become suicidal on an SSRI," when the bottom line is if withdrawal is denied the patient leaves and goes through withdrawal on their own, with the help of the Internet, and never comes back.

I will continue my vigilance on the Internet until I feel that the FDA is meeting its legislative mandate.

(Applause.)

DR. PINE: Thank you.

The next speaker is Hanna Stotland.

MS. STOTLAND: My name is Hanna Stotland. I am a lawyer in Chicago and I am thirty-one years old. I was crippled by panic disorder and depression starting at the age of seven. Eleven years in psychotherapy did nothing to alleviate my symptoms.

I was absent from school for months at a time. I missed out on everything from birthday parties to family vacations because it was such a struggle for me to leave the house. I flunked out of high school. I had to get a GED because I was unable to function in school.

I had no hope that I would ever be able to move out of my parents' house or support myself. I believed that I had no future outside of mental illness, and I considered suicide many, many times.

I began taking antidepressants at the age of 17 in 1993. Over the next several months, clouds lifted. My panic attacks drifted away. I began to feel hope.

Within two years, I was able to go away to college in Pennsylvania. I became a straight A student and transferred to Harvard College. I graduated Phi Beta Kappa, moved on to Harvard Law School, clerkships for two federal judges, and now a career practicing law at a major firm.

There is no question that my medication enabled me to get where I am today. I spent a decade wishing I had never been born, but I haven't had a suicidal thought in over 13 years.

I had multiple, severe panic attacks every day for years, but now I have a mild one at most once a year. I went from being unable to cope with seventh grade math to graduating from Harvard twice.

At best I thought I would end up in my

parents' basement, but now I own a home of my own; I am in a happy, long-term relationship; and I am succeeding in a demanding career.

I am here today because I am concerned that others will be frightened away from trying medication that could save their lives. I know that there are other young people who, like me, could build extraordinary lives for themselves once they are free from the burden of depression. Fear of being stigmatized already discourages so many suffering people from getting the help they need.

I hope that the FDA takes advantage of this opportunity to counter those fears rather than

0281

adding additional unfounded fears about the safety of these crucial medications. Untreated depression is the danger we need to fear most.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Charles Reynolds.

DR. REYNOLDS: Thank you very much. I am here to represent the American Association for Geriatric Psychiatry and to speak with you about the public health challenge of suicide in old age.

The Institute of Medicine's report has emphasized the grave public health significance of suicide in our country and the importance of reducing suicide.

This is particularly the case among the nation's elderly people where rates of completed suicide are five- to six-fold greater than in the general population, and particularly among men. Most elderly suicides have seen a primary care physician shortly before their deaths. Most suffer from major depression.

0282

In this context, my colleagues and I recently published a prospect study in "JAMA." This was a randomized-controlled trial utilizing citalopram and depression-care management for 598 primary care patients with major depression living in Pittsburgh, Philadelphia, and New York.

We reported that rates of suicidal ideation declined faster in patients who had depression-care management as compared with usual-care patients.

We also reported on observation that it was a much higher percentage resolution of suicidal ideation among patients in the depression-care management arm of the study, 71 percent as compared to those in usual care, 44 percent.

Sticking with acute pharmacotherapy of major depression in old age, I cite here data from Craig Nelson and Lon Nelson, soon to be in press at "The American Journal of Geriatric Psychiatry."

This was a placebo-controlled study of

sertraline treatment for elderly living with major depressive episodes and lasted eight weeks and was

a double-blind, randomized trial. It included 752 participants.

The authors reported a faster resolution of suicidal ideation among sertraline-randomized elderly as compared to those who were randomly assigned to placebo with supportive care.

Of particular relevance to today's hearing is the fact that of the 248 patients who denied suicidal ideation at the start of treatment, the number of participants with any incident for a new suicidal ideation did not differ between the sertraline and placebo-randomized participants.

Finally, I would like to emphasize what the Committee has already discussed earlier today, and that is the importance of taking a long-term view of depression care management in old age. Depression is a recurring illness.

DR. PINE: Thank you.

The next speaker is Peter Breggin.

MR. BREGGIN: Hi. I am Peter Breggin. Fifteen years ago, I warned the FDA and I warned the country and toxic psychiatry that

antidepressants were causing a stimulant, amphetamine-like, syndrome that was resulting in violence and murder.

In 1994, in talking back to Prozac, I warned the country and the FDA, again this time with tons now of scientific data, on the same issues.

During that period of time, I was asked to be, and this is very relevant to your deliberations, the scientific investigator for all of the combined Prozac suits, almost 200 of them. I got to look at all the sealed data that Eli Lilly didn't want anybody else to see.

About 20 books later now and a few dozen scientific studies and innumerable, innumerable product liability suits where I've looked at sealed data, I have come to tell you that you are evaluating junk. You are evaluating carefully edited expurgated data that I have seen and you haven't.

This is a most remarkable circumstance that you have resources, people who have been

inside the drug companies who can tell you what is happening inside the drug company. Of course, you have avoided it.

All the documents I am going to discuss now are on my website, www.Breggin.com. They have all been given to you or sent to you via the Committee.

In 1985, the Germans asked Eli Lilly to

review all of its controlled clinical trials, Phase II/Phase III for suicidality. The company came up with twelve suicide attempts on Prozac, one on alternative antidepressant, and one on placebo. This was a raging signal which the company did not report to the Germans, did not report to the FDA, and did not report at the 1991 hearings.

In addition, the company hid suicidal data. When it would get an incoming suicide from the field, it would reclassify it as depression. It would reclassify it as no drug effect.

Claude Bouchy, who was in Germany working for Eli Lilly, wrote an ashamed memo to the Central Office saying, "How would I explain this to `my

0286

family' or to `a judge?'" But he said he would of course go along with what the company said.

As for akathisia, the company was very clever. It didn't code akathisia, so none were reported. It wasn't an available term. I found innumerable cases of akathisia combing through the company files that were never reported. GSK, "GlaxoSmithKline," on Paxil, combing through their files I have found suicide attempts.

(Applause.)

DR. PINE: Thank you.

The next speaker is Robert Gibbons.

DR. GIBBONS: Hi. My name is Robert Gibbons. I am director for the Center for Health Statistics at the University of Illinois.

(Slide presentation in progress.)

DR. GIBBONS: As a member of the Institute of Medicine's study on suicide, also the Institute of Medicine's study of U.S. drug safety, and a member of this Committee in 2004, many of us during that time were concerned that the black box warning would lead to a reduction in the treatment

0287

of childhood depression, which ultimately might lead to an increase in the completed suicide rates. I will present new data to the Committee and allow you to reach your own conclusions.

These are the data for the United States from 2003 through 2005. The bottom two lines that you see are for young children. You can see there has been approximately 20 percent reduction in the prescription rates of SSRIs and NSSRIs and even TCAs.

Another important feature, that except for the oldest patients, those over 60, there have been reductions in adults as well as a function of the black box warning.

The data just released by the CDC for 2004 indicate a 14 percent increase in completed suicides in children under 15 and also 15 percent, if you consider all youth under 19.

Those data through 2005 are currently not

available in the United States, so my colleagues and I went to work with the PHARMO Institute in the Netherlands where those data were available.

What we found was from 1998 through 2005 there was a significant inverse association between SSRI prescriptions and youth suicide, which was strongest for boys under 15.

From 2003 to 2005, prior to and after public health advisories in the U.K. Europe and the United States and the black box warning, there was a 22 percent decrease in youth SSRI prescriptions, exactly what we see here in the United States, and it accompanied a 49 percent increase in youth suicide and a much higher increase in the suicide rate, completed suicide rate, for young boys.

These are the data over time. The blue line indicates the SSRIs, and the red line indicates the suicides. As you can see, as the SSRI rates increased in the late 1990s, the suicide rate went down. As they have decreased, the suicide rate has gone up.

Based on our analyses, we predicted that 27 additional suicides would have occurred with a 10 percent decrease that we saw in 2004. We actually saw 35 additional suicides. If there was a 30 percent reduction in SSRIs, we would predict to see an additional 5,000 completed suicides per year, 81 completed suicides per year in young children.

Thank you.

DR. PINE: Thank you.

The next speaker is Carl Salzman.

DR. SALZMAN: My name is Carl Salzman. I am a professor of psychiatry at Harvard Medical School in Boston. I traveled here to represent the American College of Neuropsychopharmacology at their expense.

ACNP is the leading scientific organization in the United States for research on medicines that act on the brain and behavior including psychiatric and neurological disorders.

ACNP members and many other medical colleagues are greatly concerned about unintended, serious consequences of recent warnings made by FDA concerning a possible association of some antidepressant medications with rare increases in suicidal risk.

These warnings in children, adolescents, and now proposed for young adults are based on data of adverse event reports, which are of questionable reliability and which have not yet been made available to non-Agency experts for independent assessment.

The ACNP has published its own analysis

of randomized clinical trials. This analysis found no evidence of increased completed suicides in any age group. The report concluded that the primary cause of suicide in children, adolescents, and young adults was due to untreated depression.

The ACNP report confirmed a higher rate of suicide ideation and nonfatal attempts with active drug compared with placebo, but pointed out that there was no such effect using reliable suicide items on depression rating scales.

Moreover, since there were no actual suicides, the risk of suicide could only be indirectly estimated from rates of ideation and nonfatal attempts.

This method of estimating is not reliable

0291

in youth and young adults where the ratio of nonfatal attempts to completed suicide is 30 to 1, many times higher than in older age groups, 4 to 1.

New research documents significant decreases in diagnosis and antidepressant treatment of new cases of depression in children and adults in the past two years, since the FDA warning was instituted.

Fewer diagnoses and treatment of depression may lead to the unintended consequence of an upswing in rates of suicide and life-threatening attempts.

In conclusion, the ACNP does not find the available evidence that antidepressant treatment increases the risk of life-threatening suicidal behavior or of completed suicides sufficient to support public policy.

The ACNP is deeply concerned that FDA actions are already having potentially disastrous, unintended consequences of discouraging or limiting treatment for those with serious mental illnesses at high risk of suicide.

0292

Thank you.

DR. PINE: Thank you.

The next speaker is Derek Braslow.

MR. BRASLOW: Thank you.

I am apparently one of the last speakers here today. I am a lawyer. My entire practice involves representing victims of antidepressant drugs.

You have had an opportunity today to meet some of my clients. You haven't had the opportunity to meet hundreds and hundreds of more people who claim that they attempted suicide or their family members attempted suicide as a result of taking an antidepressant drug.

I would like to, just before I begin, debunk a couple of myths that are out there. One, the first myth is that these antidepressant drugs are effective and help the majority of people.

We all know and from the FDA results that have come out that the studies, the majority of studies, show that they have no effect at all. In fact, only one out of every ten people who takes an

antidepressant has a beneficial effect from taking that drug.

Secondly, the suicide rate that has gone down over the past number of years being attributed to the increase in the prescription of antidepressant drugs, this is not science. In fact, I saw a presentation yesterday regarding the fact that the number of actual autopsies that have been conducted have decreased from 50 percent from the mid-eighties to about 5 percent today.

Finally, the myth that we shouldn't warn doctors because we might discourage treatment, that's the point of warning. The point of warning doctors is for doctors to weigh risks against the benefits to give the doctors all the information to decide what is the proper treatment, not to keep the risks quiet in the fear that doctors might misinterpret the warnings.

The idea is to give the doctors the information. Your jobs here are not to promote treatment, but to warn doctors of the risks and the benefits.

If you remember only two things today, remember two points. One, the data relied upon by the FDA in its meta-analysis is not reliable. Data has been excluded. Data has been falsified. They have never done the studies. They have never done the specific studies that this Committee asked for 15 years ago to find out whether or not these drugs specifically cause suicide.

They never did these suicidality studies. The data they are relying on is wrong, and it is worthless. The science is here. Here is the science: the people's stories, the case reports of people with no history of depression.

Tell one of my clients who wasn't able to come here at the last second, Joe Colachico, whose wife a practicing psychologist who used to advise her patients that suicide was a long-term answer to a short-term problem, tell him that these drugs don't cause suicide. Tell him that it only affects people up to 24 years of age.

Thank you.

(Applause.)

DR. PINE: Thank you.

The next speaker is Robert Valuck.

DR. VALUCK: Thank you. Thank you, Dr. Pine and the rest of the Advisory Committee for the chance to come and share some research with you today.

(Slide presentation in progress.)

DR. VALUCK: I am Rob Valuck from the University of Colorado. I focus on studying the effects of drugs in large populations after they have been marketed, Phase IV studies largely using managed-care administrative claims databases, so a very different source of data than clinical trial data.

To address these questions, we have done two recent studies, one on SSRI antidepressant use and rates of suicide attempts among adults with MDD, the other an evaluation of the FDA warnings on antidepressants and suicidality on patterns of care for MDD.

By way of disclosure, the first study I'm disclosing who my co-authors and collaborators are.

0296

The first study is unfunded and investigator-initiated work. We did this on our own time and our own coin on breaks basically about a year ago.

The second study, again coauthors are disclosed. Funding was by an unrestricted investigator-initiator grant from Eli Lilly and Company. I went to them for the money, not the other way around.

The first study, I give the details here of the methods of the study. Time precludes me from going into any great detail. Suffice it to say, it is a retrospective, new user cohort of newly diagnosed major depressive disorder subjects, about 371,000 subjects over 19, approximately 36,500 of those were 19 to 24. Our primary outcome endpoint was suicide attempt.

Basically, the gist of this was the overall result at the bottom. The relative risk for suicide attempt among all adults taking SSRI antidepressants was 0.86. It was not statistically significant.

You can see the age groupings broken down

0297

by the similar age bands the FDA used for the meta-analysis, which shows similar effects, none of them statistically significant other than the .77 relative risk, which was slightly lower for adults 25 to 64. We had extremely high power with over 320,000 subjects in that group.

Our bottom line is our data, a much different source, came to a very similar conclusion and a very similar 0.86 finding on the risk ratio.

The second study, we looked at PharMetrics data, again similar managed-care data, to establish patterns of care for major depressive disorder from 1998 through 2005, seven years of data, five years before these warnings and advisories started and two years after. We looked at a variety of things: diagnosis, prescribing, and possible substitution effects.

Our primary findings, in the pediatric population, the rate of MDD diagnosing went down. There was a decrease in antidepressant prescribing and a shift towards no therapy. The emergency medicine physicians prescribed more and PCPs and pediatricians less with no major substitution effect that we found towards other drugs and psychotherapy. The other finding was that all of these findings spilled over into the adult population.

(Applause.)

DR. PINE: Thank you.

The next speaker is Steven Daviss.

DR. DAVISS: Good afternoon, ladies and gentlemen. My name is Steven Daviss. I am the chairman of the Department of Psychiatry at Baltimore-Washington Medical Center, past president of the Maryland Psychiatric Society.

I am also a family member with several relatives who have major mental illness and a cousin who killed himself, tragically, this past summer.

I don't have stock in any of these pharmaceutical companies, and I paid my own way down here.

I guess I am the wrap-up speaker here. It looks like you've got a challenging task ahead of you, lots of data to review, opinions to consider, and recommendations to make.

All of the points I am going to make have been made before. You need to weigh the risks and the benefits of putting a black box warning on these medications or not.

The majority of these medications, of course, are prescribed by primary care doctors. I don't have answers, but I have questions. How many patients will no longer be able to find a primary care physician who will prescribe an antidepressant for their depression? How many primary care doctors will be afraid to use the drugs because of the liability associated with a black box?

The risk of increased suicidal ideation and suicidal attempts is inherent in the treatment of depression, with or without medication.

A recent state review in Maryland of HMOs found that many people being treated for depression did not have adequate followup. These patients need to be seen more often, more closely, more carefully.

As Nada Stotland said earlier, maybe we don't need a black box on antidepressants; maybe we need a black box about depression.

Any assessment of the risks and benefits of adding a black box warning should be balanced by

an assessment of the estimated number of increased suicide attempts and completed suicides and the increased amount of morbidity and lost productivity that will occur in all of these people who are not being treated.

You need those numbers, I think, to be able to make a good decision. This information needs to be included in the labeling, too, so that when patients read it, they don't just see the risk, but they also see the benefits so they can weigh, "What are my chances?"

I guess the bottom line for me is will a black box result in more suicides than it prevents? How many people will die with the black box and how many people will die without a black box? I don't know the answer to these questions.

Some possibly more effective solutions,

0301

listening to some of the comments earlier today: number one, make consumer education about mental disorders, medications, and potential side-effects more prevalent.

Number two, balance the magnitude of the risk with the magnitude of the benefits.

Three, a previous speaker, Sheila Matthews suggested MedWatch information be included prominently in all advertising. That makes a lot of sense.

Then, finally, provide best practice recommendations for monitoring mood disorders so insurance companies can stop discriminating against mental illness.

DR. PINE: Thank you.

In closing, I want to say just a few words of summary. First of all, I want to thank all of the speakers for your honest, frankness, sincerity, and most of all for their courage.

It really takes a tremendous amount of strength to stand up in front of us and to tell the stories that you have had.

0302

Obviously, I think there is disagreement in the room about many, many issues, but I think that there is clearly strong agreement about some of the most important, and that is, what a tremendous public health problem we are faced with today.

We as a Committee are going to discuss both the problem that is presented to us by the burden of mental illness and also how to determine the best way to weigh the most appropriate treatments. As a number of speakers have said, obviously this is a problem of life and death.

In closing, I want to thank all the speakers fro really calling the Committee's attention to the seriousness of those issues, and to hold us to task in a certain sense to weigh

these issues as carefully as we will for the rest of the day.

This is going to conclude the morning/ early afternoon session. Very briefly, three or four quick announcements. I am going to remind the audience and the panel members to refrain from discussing any of the issues that were raised and to only allow the discussion to occur here rather than during the lunch break.

I will also ask the audience and the press to refrain from asking any of the committee members any questions until the end of the day. I will ask the committee members rather than leaving through the back, if you would, meet at Cicely and you will get instructions about how we're going to get lunch.

We are going to try to stay on a very tight schedule, so if you will be back in the room at 10 after 2:00, we are going to start at 2:15.

Thank you.

(At 1:39 p.m. the luncheon recess was taken, the proceedings to resume at 2:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:15 P.M.)

SUMMARY AND ISSUES FOR COMMITTEE

DR. PINE: I would like to call the afternoon session to order. Most of the time is going to be open time. I will talk a little bit about how we might structure that time.

To kind of gets us started, Dr. Laughren is going to review and summarize the data and some of the deliberations that have gone on in the FDA until now, and then he is also going to clarify for us what the FDA would like us to think about, to talk about, and to comment on in terms of their report.

Dr. Laughren?

DR. LAUGHREN: Thank you, Dr. Pine. I would like to welcome everyone back to the meeting. We have reached that point in the meeting where the Committee has an opportunity to discuss the findings from this morning and to provide us some feedback.

Before you do that, I would like to summarize what I think are a few key points for you to consider during your deliberations. Before I do that, I want to comment on some of the very personal stories that you heard in the public

session before the break.
The suicides that you heard about are all tragedies, now, and it's very difficult to listen to these stories because we know that the impacts of these deaths on the families and friends of these individuals is horrific.
These tragedies are relevant to this discussion I think in two ways. First of all, this is why we care about this issue, and this is why we have invested as much time and effort as we have into trying to understand these data.
Secondly, I think these individual stories do give us some clues about what to look for in trying to understand the finding, for example, the activation syndrome. However, I think it is also important to recognize that these individual stories do not really help us in figuring out causality.

0306

I think for that we have to look at the data. We have an enormous controlled-trials database that we think is a useful source of information, and so that's where I think we need to focus our attention.
When we brought this issue of antidepressants and suicidality in pediatric patients to the joint meeting of this Committee and the Pediatric Advisory Committee in 2004, we felt that we had a fairly clear signal with a modest increase in the risk of suicidality associated with the short-term treatments of antidepressants.
We were advised at that time to add boxed warnings to the labels of antidepressants to label for that risk, and we have done that. We also added a medication guide to alert patients and their families to this apparent risk.
Now, at that meeting and afterwards there was general interest in our extending this analysis into the adult data. We have done that. We have presented you the data. This is one slide from Dr. Levenson that I think summarizes very nicely the

0307

bottom line from this effort.
(Slide presentation in progress.)
DR. LAUGHREN: I think that what we are seeing here is an extension of the suicidality risk finding that we were seeing in pediatric patients and young adults up to age 25, but we are not seeing it beyond that.
In fact, there appears to be a beginning of a reversal of the effect in adults beyond age 30 with the suggestion of a protective affect. That affect appears to be even more clear-cut in the elderly.
As was the case for the pediatric data, we don't have information here that informs about completed suicides. There was only a total of

eight suicides in this very large database. We really can't conclude anything from that small number with regard to complete suicide.

We feel that overall our findings are consistent with the findings that were reported in the articles in the February 2005 issue of BMJ, particularly with the Gunnell paper. I think,

0308

again, we had the advantage of having access to patient and trial-level data that allowed us to look in greater detail at the data and to discover this age effect.

There are other data, however, that I think also you should feel free to consider as part of your deliberations, and I want to talk about two different types of data that seem inconsistent with the findings in younger patients.

The first type of study that I want to talk briefly about are what are referred to as ecological studies. You heard about those this morning.

These are studies that look at recent trends in absolute suicide rates in the U.S. and compare those with trends in antidepressant prescribing.

This is not an exhaustive survey. This is just focusing on some of the more recent studies, and one in particular that is of particular relevance to the younger patients.

Grunebaum, et al., in 2004 looked at a

0309

period of time from `85 to 1999, and they found an overall decrease in the suicide rate of about 13 percent at the same time that antidepressant prescribing had increased about four-fold. This was mostly SSRI prescribing.

A study by Gibbons, et al., in 2005 looked at a narrower time window. They looked at 1996 and 1998, and they focused on county-level suicide rates across the age spectrum with adjustments for age, sex, income, and race.

They found no overall relationship between antidepressant prescribing and suicide rate, but they did find significant relationships within antidepressant class.

For the SSRIs and other newer generation antidepressants, increased prescribing was associated with lower suicide rates while it was the reverse for tricyclics.

A more recent study by Gibbons, et al., in 2006, used the same methodology and looked at the same time window, but they focused on children age 5 to 14. You saw those data. Basically, they

0310

show higher SSRI prescribing was associated with lower suicide rates.

Finally, a study by Milane, et al.,

focused specifically on fluoxetine. This study looked at the years from 1988 to 2002. As others have found, they also found a decline in suicide rates since the introduction of that SSRI.

Now, all of the authors of these papers and others will note, clearly, that it is not possible to reach a causal conclusion based on this aggregate data. Nevertheless, this consistent finding is something that needs to be taken into consideration as you are deliberating on these new data.

Of course, the other finding that was reported during the meeting today is a suggestion of a reversal in that trend with a slight uptick in absolute suicides at the same time that SSRI prescribing is coming down in adolescents.

Another type of study that I want to briefly mention are the autopsy studies. These are two studies that were done looking at adolescent

0311

suicide victims, one by Gray, et al., and one by Andrew Leon and his group.

The important finding from these studies is that in both cases they failed to find evidence of antidepressant drug use in most of these victims, even in those who had been prescribed antidepressants.

Now, we published the results of the pediatric suicidality analysis in April of this year. In our discussion we suggested, as others have suggested, possible alternative explanations for the finding other than an actual increase in the risk. One suggestion has been that antidepressants may, in fact, increase communication about suicidality.

Dr. Stone in his presentation discussed the fact that the signal is even stronger for suicidal behavior than it is for ideation; it seems to be coming mostly from behavior.

That tends to argue against this explanation. However, I think it is true that a lot of suicidal behavior, particularly in younger

0312

patients, is secretive and may not be observed by others unless it is reported.

The other possible explanation is the fact that patients who are assigned a drug have other side-effects that may draw attention to those individuals and may increase the detection for suicidality. The problem with either of these explanations is that it is very hard to confirm or refute them.

In any case, this slide is sort of our bottom line at present on these new findings. We think despite the possibility of alternative explanations and despite the existence of other data that are not entirely consistent with a

finding of increased risk in younger patients, we continue to view these data as at least supportive of a modestly increased risk of antidepressant-induced suicidality both in pediatric patients and in young adults up to about the age of 25.

However, as I pointed out, we are not seeing the finding extending beyond that age. On the contrary, the drugs appear to have the expected

0313

protected effect when you get beyond age 30 and particularly beyond age 65.

What are we going to do with these findings? Our current position, and we are very anxious to get your feedback on this, is that we think that we can extend the current warning language.

As you know, there is a box warning on all antidepressant labeling, and we think that that language could be modified to extend the risk into young adults up to age 25.

However, at the same time note that the expected protected effect for suicidality with antidepressant use appears to emerge beyond age 30 and particularly beyond age 65. We could also modify the medication guides to reflect this new information.

Finally, we think that it is just good clinical sense to carefully observe any patient who is being treated with an antidepressant of any age, especially at the initiation of treatment. We would intend to add that language, emphasize that

0314

as well, in the labeling.

What is your task for today? We would like you to have a full discussion of the findings that we have presented on antidepressants and suicidality in adult patients.

We would like your comments on these findings and on our proposed plans for modifying labeling based on these findings. However, you should also fee free to discuss any other issues that you think are relevant.

In particular, we think that this finding of a differential risk across the age spectrum for suicidality is intriguing. We would be interested in your thoughts about how that might be explored.

Now, we have not suggested any specific votes; however, clearly this Committee is free to propose issues and vote on issues, if you think that that would be useful. I will stop there and let you get on with your deliberations.

DR. PINE. Thanks, Dr. Laughren.

COMMITTEE QUESTIONS FOR FDA
AND COMMITTEE DISCUSSION

0315

DR. PINE: Just to give the Committee a little background and maybe a little structure for

the next period of time, we have less than three hours. We are committed to ending at 5:30 sharp, and there is really a whole range of issues in front of us.

To give just a little structure to the discussions, what I thought we might do is devote the first hour to trying to stick relatively narrowly to the data that were presented in front of us this morning. I will say a little bit more about what are the pertinent issues that I think we need to discuss.

We will do that for about an hour, just talking about the data, what they say to us and again a few other details, and then I thought we would take the next two hours to talk about, given these data, what do we do. That will really address all the issues that the FDA wants us to comment on.

My sense, speaking frankly, it seems like figuring out what the data are and how they can be

0316

improved and the quality of them is relatively easy relative to the task of figuring out what to do, given that we have these data.

I am going to open up the discussion now again with that first topic, which is I would really like to hear thoughts about what are people's impression of the data.

The issues that I would like for people to comment on are the process of the data collection, data summary, and data analysis, the quality of the data in terms of potential deficiencies and the statistical approaches to data, things that might have been left off that should be looked at in more detail.

I know we've already heard about a couple of those. We heard about an issue of ascertainment. We heard about issues of withdrawal. I would like to hear people's thoughts about that.

Most importantly, I would like people to comment on the FDA kind of bottom-line slide, which was their Slide 6, Dr. Laughren's Slide 6, where it

0317

says the current FDA view of suicidality data for adult antidepressant trials.

I think we really need to either say yes, we endorse that, we agree with that, or we don't irrespective of whether we vote on it or not.

Maybe I will just open it up for any comments.

Dr. Goodman?

DR. GOODMAN: We talked about this a little bit earlier. We questioned about relationship to treatment outcome. I went back to the briefing document. If you turn to pages 31 and 32, there is a paragraph on the impact of clinical

response as well as two tables.
Although it doesn't rise to levels of statistical significance, there is a suggestion there of at least a trend for among the young population for nonresponse and suicidality to show some association.
I just wondered if any of the FDA Panel would comment on whether you would change your position as it is stated there or at least clarify

0318

it?
DR. STONE: Yes. I think that wasn't as clearly written as it could be, particularly because I think I said one thing and I tried to take it back in the next sentence.
DR. GOODMAN: That's why I brought it up.
DR. STONE: Right. What you are really seeing is a segregation effect that you're more likely to have responders in the drug group because the drugs do have efficacy. I wish I had an overhead projector to kind of show this graphically.
However, if you assume that there is no effect on suicidal events, on the people who have suicidal phenomenon, and say you have equal numbers of placebo and drug, patients in each group, you would have say 10 people on placebo with events and 10 people on drug with events, they are really absolutely equal.
You have five responders and five nonresponders within each of those ten, so there is really no difference among the responders. You

0319

have 500 or 5,000 people who did not have events.
You look at that 5,000, and in the placebo group they split 2,500/2,500, so that your ration is 5 to 2,500 in each group. However, in the treatment group, because you have some efficacy, you would get, say, 3,000 responders and 2,000 nonresponders.
It looks like 5 out of 3,000 of the responders are having event and 5 out of 2,000 of the nonresponders. It looks like that there is a negative correlation with response. That is simply an artifact of the segregation between responders and nonresponders; it is differential.
DR. GOODMAN: I'm sorry. I'm still having trouble following. But if we look at Table 20 and if you just confine your response to the less than age 25 group, if you look at the odds ratio, the odds ration for suicidality among nonresponders is 1.96 and it is 1.29 in the responders.
DR. STONE: Right.
DR. GOODMAN: That is not true for some

0320

of the other age bands.

DR. STONE: Right.
DR. GOODMAN: Well, how would what you are saying now apply?
DR. STONE: In the example I just gave, if you can, imagine that it's analogous, that you have an odds ratio or a probability of 5 and 3,000 in the responders and 5 and 2,000 in the nonresponders, and that is simply because of the segregation between the two groups due to the response rate, while in the placebo group, if you have 2,500 responders and 2,500 nonresponders, it is 5 to 2,500 in both of those groups. It creates this exact kind of effect.
DR. PINE: I know Dr. Leon had a comment and a question on this issue as well.
DR. LEON: I'm puzzled by the temporal relationship. Now, you're stratifying by the outcome but something that happened before the outcome in these odds ratios is now your outcome. It makes it difficult for me to follow the logic here.

0321

What I'm saying, to be more specific, is you are stratifying on response at the end of the study, response status at the end of the study, yet you are looking at suicidality during the course of the study.
I mean, well, as you know from these data, some of those who did have a suicide attempt maybe in the first say or week of the study went on to become responders, how does that get incorporated?
DR. STONE: I'm just showing that that kind of analysis is potentially misleading, not that things couldn't turn out to be significant, but that you could have absolutely nothing going on other than the fact that you have a shift in the proportion of people that respond among people that don't have suicidal events, and you would get results that look exactly like this.
DR. LEON: If we go back to the question I asked three hours ago, if we had those HAMD items, which I imagine you do for quite a few of these studies but not all of them, and I understand

0322

that's why you didn't present those data, but at least there you would have weekly. We could look at the concordance, the contemporaneous nature at least between the suicidality and response week to week.
DR. STONE: It would be a very interesting project to look at time series and individuals. It just would be enormously difficult.
DR. TEMPLE: Of course, even in the pediatric population where the event findings were clear, the suicide item didn't show anything. I

don't know what that means.
DR. LEON: Which is more believable? I'm not saying I have the answer to this. But which do we want to believe more? The one that was looked at with a very different grain of ascertainment versus the one that is more systematically--?
DR. TEMPLE: No, it's a fair question. One of them is really an event adverse enough to draw somebody's attention and the other is a rating. I don't know how we know. I think one of

0323

the reasons this was missed for so long is that the suicide item never showed anything -- well, one reason anyway.
DR. PINE: Let me summarize.
DR. TEMPLE: Can I ask about the other thing?
(No response.)
DR. TEMPLE: I guess what strikes me about Table 20 is that it goes in both directions or that one seems to show a little something in relation to what you might expect it to be related to, like, whether you are better, and the other data don't. I guess it strikes me as an intriguing thing to keep looking at but not quite there yet.
DR. PINE: I guess the bottom line, my interpretation of the data and the summary which I think is a little different than what you just said, is that if you just look at the point estimates of the odds ratios, it is clearly higher in the nonresponders, all right, it's 2 versus 1.3.
DR. TEMPLE: In the under 25.
DR. PINE: In the under 25. To the

0324

extent that those are unbiased estimators, it's a hint to something on the one hand. On the other hand, that difference is obviously not statistically significant.
DR. STONE: What that was describing has nothing to do with statistical significance.
DR. PINE: Correct.
DR. STONE: It has to do with a methodological bias. The methodological bias, you can see exactly this, and you will get those same kind of point estimates whether or not they are statistically significant.
It has to do with, as I said, if you have exactly the same distribution between the two groups and the only difference is in the response rate according to drug -- for example, let's say, instead of doing clinical response to improvement in depression, you have a side-effect like a rash, you're going to see more rashes in the people that take drug rather than placebo.
If you do the same thing, you're going to say rash is protective against suicidality. It

0325

would look the same way.
DR. PINE: Actually, I don't want to belabor this point too much, because I think no matter how we read it or interpret it the bottom line is that there is really not much support to say that this signal that we're starting to talk about is strongly related to whether or not you respond to the medication.
I mean, I think that's the bottom line no matter how we talk about it. Getting the details straight right now in the little, limited time that we have is something that I think is going to consume too much time.
I do want to come back to the other point that Dr. Leon just raised and maybe push him a little bit and hear some other people's thoughts about this.
The gist of your comment was that you're concerned that due to some artifact of ascertainment that you think that there might be some bias in the spontaneous reporting data relative to a handy suicide item that is asked to

0326

an individual subject every week when they come in. That's kind of the gist of your comment; right?
DR. LEON: (Moving head up and down.)
DR. PINE: I guess the counter to that that I would like to hear other people reflecting on is if we did that by calling attention to spontaneous reports and kind of weighing those, from a statistical standpoint or a methodological standpoint, we would be being cautious because we are weighing those events and we are saying they are significant even though we have these other data that suggest that there is not a signal.
I guess that's the other thought that I would like from the other members of the Committee. Again, Dr. Leon's comment is suggesting don't interpret those odds ratios of the increased signal from the spontaneous reports so quickly.
I guess my reaction is the fact that we see a signal anywhere bothers me. The fact that we see it one place and not in the other, it does not really reassure me in terms of paying attention to it. However, I would like again comments from

0327

other people about that.
DR. ARMENTEROS: Yes. I'm still stuck on the treatment issue. I won't go back to Table 2, I promise. One of the reasons that in 2004 I voted for a black box was because in addition to there being a suicidality signal that was quite clear is that in the trials that you presented at that time only 20 percent were positive showing the advantage of drug over placebo.
You may have already answered this. However, now if you look at the young adults

between the ages of 18 up to age 25, can you say anything -- and you may not be able to but at least I want to ask the question -- about the efficacy of that group either relative to the younger population or a population older than that?

I just want to get the right balance between benefit and risk. If there is a cutoff in benefit, I guess I'm wondering at age 19 is the benefit that much different than the benefit at 18?

DR. PINE: Dr. Laughren.

DR. LAUGHREN: Yes. We don't have the

0328

same level of data that we had for the pediatric studies that were focused on a narrow age range. I mean, what this would mean doing is going back and trying to stratify it by looking at these different spectra, 18 to 24 and so forth.

What we do have that I mentioned earlier is we have a fairly crude measure of response that was defined differently by different companies, and we have the odds ratios for drug to placebo for that response measure broken up by these different age bands.

As I mentioned, the odds ratios for the 18 to 24 is 1.54, it's 1.85 for 25 to 64, and 1.39 for 69 and above. All of those have confidence intervals that don't include one. If you interpret that as a crude signal for efficacy across these age bands, then we have that.

DR. PINE: Other comments from a broad perspective about people's feelings about the FDA conclusion?

Yes, Dr. Pollock?

DR. POLLOCK: Yes, just a specific

0329

question related to some of the comments we heard earlier that you failed to include akathisia as a string in the suicidality analysis. I was wondering, like, wouldn't akathisia be listed as a specific treatment-emergent side-effect if it occurred in most of these studies?

Wouldn't there be an opportunity, since you have this massive placebo-controlled database with 100,000 people, to actually state one way or the other, like, what the risk of akathisia is relative to placebo in the SSRI-treated patients, whatever the frequency of it is in placebo and active-drug groups?

DR. LAUGHREN: No, we wouldn't have that in this database because this database was created specifically for this analysis. We went back to the companies who designed the database structure and asked them to populate it.

The only events that were included were the ones that we asked for. Since we were focused on anything that related to suicidality, it may very well be that something like akathisia or

0330
activation precedes suicidality, but that is not in this database.
The companies obviously have that in their own databases, but we don't have a large, comprehensive database that includes that information.
DR. Pollock: Don't you have it in the regulatory trial database?
DR. LAUGHREN: He is asking do we have it in an electronic database that we could go back and try and search for that as a precursor to suicidality.
DR. Pollock: I'm not even asking as a precursor to suicidality. I'm just asking if the public can be told that the risk of akathisia with an SSRI treatment is two or less than five percent and in placebo it was found to be three percent?
DR. LAUGHREN: It's probably not coded that way. Akathisia may be occurring, but it all depends on how the data are coded. At the time that these databases were put together we weren't thinking in terms of akathisia being a side-effect
0331
of antidepressants, so the events that are representative of akathisia got coded as something else, and that's the problem.
DR. Pollock: Many side-effect scales that I'm familiar with at least have a category for, and maybe even in antidepressant trials, for extrapyramidal side-effects. I mean, there is a side-effect coding scheme. There has to be in every regulatory trial, doesn't there?
DR. LAUGHREN: Well, but a lot of the adverse events in these trials are basically spontaneous reports. It varies widely from trial to trial. In many trials, a patient comes in and a clinician asks, "How have you been in the past week? Have you had any problems?"
The patient reports something, it gets recorded, then those data go back to the company, and the company codes them using some preferred terminology COSTART or WHOART or a MedRA, any of a variety of coding systems to reduce those data into something that you can analyze. There isn't any easy way to do that in terms of creating a
0332
comprehensive database.
DR. TEMPLE: For the old data?
DR. LAUGHREN: For the old data.
DR. TEMPLE: Would akathisia be in MedRA for new ones?
MR. LAUGHREN: I'm sure that akathisia is in MedRA, but most of the data we have are not coded using MedRA.
DR. Pollock: I guess I would make the observation that that's probably not something you

want to use a pooled database on, because it is common enough you want the individual rate for each drug.

That doesn't mean you can go back. However, for the future, I mean, you have to pool this because you don't have enough data without pooling it, so you do your best. For something that is reasonably common, you ought to get the data for each drug separately.

DR. PINE: Dr. Armenteros.

DR. ARMENTEROS: Likewise, in the data that you have available to you, is there any

0333

provision for timing of the events during the trial? I'm not even asking after the trial is over, during the trial.

DR. STONE: We did have a field that asked when the event occurred, the most serious event occurred. We thought about doing some kind of time-to-event analysis. The problem is you also have a bias here.

Again, for example, if say someone on drug developed suicidal ideation on day 30 and commits suicide on day 60 while someone on placebo just developed suicidal ideation on 40, in the database it will show us as day 60 for the event for the person who had a completed suicide attempt and day 40 for the one who just had suicidal ideation. It would like that was in fact protective, but in fact the person on the drug did worse.

DR. PINE: Dr. Leon.

DR. LEON: When we discussed the pediatric data, the term "confounded by indication" came up quite a bit. The challenge that we are

0334

dealing with is teasing apart the illness from adverse event caused by the medication.

When you showed the incidence of suicide events for the different disorders including nonpsychiatric disorders, I would think that if the medications are doing it, are triggering suicidality, we would see more suicidality in the nonpsychiatric trials, yet we saw very little. Of course, there is a lot less exposure time there, but at one point you broke it down per 10,000 person years.

DR. STONE: Well, I've got a little brain cramp here.

DR. LEON: It was your Slide 8, by the way, from the handout that we got earlier. That's not stratified by medication?

DR. STONE: Right.

DR. TEMPLE: That does go to what you think.

DR. STONE: The issue is whether the effect you're looking for is based on an absolute

increase in risk or a multiplication of an
0335
underlying risk.
For the most part, we modeled it as a multiplication of an underlying risk. If you look at risk difference, you will get a somewhat different approach. Risk difference would be more sensitive to an absolute increase.
Given the fact that we have a two-fold difference in underlying risk within the psychiatric diagnoses and we saw the same odds ratios, that would suggest to me that we are doing more with a multiplication of risk rather than an addition of risk. If you have a two-fold increase in a population where the background rate is extremely low, you are not going to see much.
DR. PINE: I mean, I've got to say when I look at your Slide 9, Andy, you might want to look at that slide, I would be hard-pressed to say that there is any meaningful difference as a function of diagnosis. There is not much data, but I don't know that it helps us.
DR. LEON: No.
DR. PINE: It doesn't.
0336
DR. LEON: Yes. Slide 8, I would have expected more in the behavioral and other disorders. You're right, Slide 9, given the ends and the sample size, the confidence intervals are very wide.
DR. STONE: You are probably going to be following people less closely for these kinds of symptoms in these trials, smoking cessation, rather than even people with nondepression but serious psychiatric disorders. You're going to look out for those sorts of things.
DR. PINE: Dr. Temple.
DR. TEMPLE: It sort of depends on what you think is going on. I mean, there are a lot of hypotheses, but I don't know. Maybe kids are more likely to have a bipolar component, so maybe that's why the young people get worse. I mean, we don't really know.
It doesn't seem inconceivable that it's your underlying disease that has something to do with why you get this exacerbation. We don't know enough to be surprised or not surprised, I think.
0337
DR. PINE: Other comments or questions about the data or the process that was gone through? I haven't heard anybody comment on the fact that we did not look at withdrawal-related events. Any other questions or comments about that?
DR. LEON: Did you look at all at differential dropout? The reason I bring it up, I mean, was there earlier dropout among those maybe

on placebo and, therefore, a greater opportunity for risk in those on active meds?

DR. LEVENSON: We did look at drug exposure. There were small differences in treatment groups that had overall less exposure than the placebo groups but not by much.

DR. PINE: Yes. Dr. Schultz.

DR. SCHULTZ: Some of the earlier comments spoke to the importance of separating ideation from behavior. I know in your primary outcome measure you have ideation with behavior lumped together as a presumed continuum.

Now, in your secondary outcome measure,

0338

you have behavior including preparatory acts, et cetera. However, from what I understand, you included one data point per person so that persons who exhibited ideation in later behavior counted one time as a behavior, if that's correct.

Now, what that tells me is that in that secondary outcome measure there are people who exhibited the behavior both with and without previous ideation.

I'm curious, and I think it may possibly speak to the impulsivity factor, that if there are persons in the data set who have behavior with no antecedent ideation, might that be a group that is perhaps vulnerable to that activation effect, the ones that come out of the blue with no previous ideation? Did you look at that separately?

DR. STONE: Well, I think it does point to a problem with us trying to be parsimonious about the data we collected and focusing on that, because in retrospect, yes, we would have liked to have had a collection of all events.

In fact, we have a companion project

0339

where we are looking at suicidality and anticonvulsants where we have gone out and asked for all events so we can do that.

As Mark pointed out, it is a little misleading if you look at ideation alone, because if someone had ideation and behavior they would be taken out of the group.

If the drug caused you to go from ideation to behavior, it would look like it was preventing ideation, which of course it isn't. Yes, that's certainly a problem.

Then, I think you make a very good point about the pattern that this may be manifest as behavior without any previous evidence for ideation, and that would be very nice to know, yes.

DR. PINE: I wanted to know if anybody wanted to comment on the process of how events were identified and coded? I know when we considered the data for the pediatric database, it was really

a lot of time spent in terms of recoding of events. We had some discussion of why that wasn't done here and some discussion of the validity of what was done.

Are there any comments in terms of the process of finding events or the need to go into more depth or to query the databases that we have or could get beyond what we have so far?

Dr. Schultz.

DR. SCHULTZ: I know you mentioned early on that you have the HAMD information but that it is coded in various ways and it has been very difficult to detect a signal. However, rather than waiting for adverse events to be reported, the fact that you have symptom scales on a weekly basis, as confusing as it may be, it might be useful to at least look at what is there.

DR. STONE: We don't have HAMD scales on a weekly bases; we have baseline and end of study. Most of them are not item 3. Some they sent us it's just item 3 and some they sent us the entire score in various and different versions, so we don't really have that kind of data.

DR. PINE: Dr. Goodman?

DR. GOODMAN: Yes. I think we could spend more time trying to dissect some of these issues. I think there are some important methodological points, but I think the sample size trumps all those details. I mean, certainly in psychiatry I can't remember the last time we had clinical trials with an "N" of 100,000.

Moreover, that figure, which maybe we could have it up there again, showing either the odds ratio or the risk difference by age, it almost looks like it would be manufactured. I mean, it is so linear. It is too bad it's about suicide.

I mean, it's good news that there may be a protective effect, but it makes even our earlier pediatric studies more credible. It's almost like doing a dose-response study in order to verify that there was an effect there in the first place, so here instead of a dose we have age.

I think at least on my part, yes, we could spend some time talking about ascertainment and coding, and I would love to see some additional data, particularly antecedent symptoms that would help us predict. I would like to know more about timing. In terms of the credibility of the finding there, it is quite robust and credible. I agree.

I mean, the convergence of these results, I mean, the pattern there is fairly convincing and the convergence of results across methodologies also was convincing. I do have one question about that, though.

In the briefing document, we were shown the odds ratios for all ages pooled across about eight different methods of estimating odds ratios. Did you ever evaluate, do age-specific odds ratios using each of the eight methods? I am curious how that might affect particularly the youngest age group.

DR. LEVENSON: No. The only sensitivity analysis we applied by age group was the risk difference, which I showed in my presentation. I don't have reason to believe that they would differ much.

DR. PINE: Jean Bronstein.

MS. BRONSTEIN: Let me come back to it.

0343

Let me wait one minute.

DR. PINE: Dr. Pollock.

DR. Pollock: Yes. Just because I'm wondering about the other side about efficacy in those 65 and older, and my impression is that at least the placebo-controlled trials that have been conducted only involve a few SSRIs, I am just wondering is it possible, is the question, I mean, is there are any differential distribution by drugs, especially in the 65 and older? I mean, are you confining to sort of fewer trials?

Because even the label that you have, I think it's only, like, for one SSRI, which there are sort of some questions about that particular trial in the over 65. A couple of the other efficacy trials have failed. I'm just really wondering if there is a change in pattern of SSRIs that you included here?

DR. STONE: Well, first of all, we didn't just look at geriatric trials. We have a lot of trials where you have some subjects over age 65 even if the trial was specifically focused on older

0344

subjects.

Secondly, I did look at the slope of age and suicidality by drug to see if there was any indication of a difference or any heterogeneity, and there really wasn't.

If you want to say that this data was somehow cherry picked by the drug companies, they did a very good job coordinating. I mean, you can group them by class and look at the similar.

DR. PINE: Dr. Goodman.

DR. GOODMAN: I assume that you pick these age brackets a priori, and if you did, you did an amazing job of picking the inflection point there. Am I fair in that assumption, that you didn't do it after you saw the data? You picked these are the brackets? We're going to define those?

DR. PINE: How did you pick them, specifically?

DR. GOODMAN: Then, the second part of that is assuming it was a priori and it's as it was shown with that inflection point, what happens if

0345

you were to change that second one from starting at 25 to, let's split hairs, age 26? Would the data look any different?

DR. LEVENSON: We were already collecting the data before the analysis plan was finalized, but we hadn't looked at it in detail or we would have observed this.

The 25 to 30 age group was primarily chosen by the GSK report that we reviewed before we started analyzing data where they suspected there might be some signal there.

DR. PINE: Jean Bronstein.

DR. STONE: I was going to--?

DR. PINE: Go ahead.

DR. STONE: You notice in my presentation that I didn't take out the 25 to 30 as a subgroup for that reason. Also, it turns out if you include the active controls, look at behavior rather than behavior and ideation, it isn't quite as smooth.

I mean, this is nice conceptually to give you the neatest looking one. You will get some rise. It's a little higher in 30 to 40. As people

0346

love to point out, we did get a little flip in the 45 to 54 range, but that is basically statistical I think most fair observers would say.

That is again why in the review, in the briefing document, you see it broken down into small groups. You can see that it is bouncing around and not perfectly smooth. We think as an overview the under 25, 25 to 64, and 65 and older are probably the most robust and most reasonable way to look at it.

DR. PINE: This since day one, back in 2004, this outcome has always consistently been the primary outcome that I know you have been emphasizing.

DR. STONE: Well, this started out to look at adults in general. If we had just taken that very first slide of mine, we would have said there is nothing going on, let's all go home. However, because we looked at the pediatric data, we said maybe we ought to look at age.

DR. PINE: Did you have a final question, Dr. Goodman, or--?

0347

DR. GOODMAN: Well, given your answer and anticipating our discussion later, it is not a trivial point. Would you have some advice, let's assume we decide to declare that higher risk is associated with a certain cutoff on age, would you stand by under 25, given what you just said, or does it depend upon whether you are talking about

ideation or behavior or both? There is some noise as you mentioned.

MR. STONE: Well, the 25 is pretty robust, and that is one reason why we stuck with it. Again, there is nothing magical about 25. You have a phenomenon that is pretty much continuous, declining with age. It is just with diminishing frequency.

Yes, it's not like this goes away the day you turn 45. That's of course silly. However, to get a general feel for various risks among groups and the fact that the risk seems fairly flat in the 25 to 64 range and fairly steep in the 18 to 25 group, that is what we feel comfortable with.

DR. PINE: Dr. Temple.

0348

DR. TEMPLE: Well, everybody is very conscious of the fact that this is an unusual degree of subsetting. I mean, as was said, your first observation is there is nothing here. The hazard ratio is the same; the risk ratio is the same.

Having said that, you always want to look anyway. It is the consistency and persuasiveness of it and the linkage with the pediatric data that make everybody believe it. Now, those are the things that make people make mistakes, too, because it looks plausible.

However, it looked pretty good. Even though we are nervous about subsetting analyses and secondary and tertiary analyses, it looks pretty strong and sort of fits with previous data and all of those things.

DR. PINE: Jean Bronstein.

MS. BRONSTEIN: This morning I asked about the design of the study had to knock out everybody who had reactions more than one day after stopping using the drug. I know that is how it was

0349

designed. My question is, Can we glean anything from or do we have any data about those people who dropped out?

I am harkening back to the public's testimony today and the obvious to me signal that folks who stop taking the drug suddenly or have an odd reaction in the ramping up. Is there anything, even though you had to eliminate it, we can learn from that data that was eliminated from those data?

DR. STONE: Well, for the most part, we don't have the data that was eliminated because we tried to be specific about our data requests, and so that was left on the cutting room floor at the sponsors.

If you want to think about this in general, though, I think you have to think a little bit about the difference between safety and efficacy.

When you do a drug trial and you are just trying a proof of concept that the drug causes an effect and maybe not, it's going to be good for people to take or in the wider population it may not turn out to be that effective, but to show that it's not inert, that it's not snake oil, you try to concentrate on a group of people that you feel are going to be susceptible.

You are going to say if it doesn't work here, it's probably not going to work in anyone. This is how you have to look at this particular data.

We tried to get a group of people where we thought we could see in a clear and unbiased way, without too many alternative explanations, if an effect existed.

I think what this data says is there is something going on with antidepressant drugs that causes suicidality; it seems to be far more predominant in younger people than in older people; and we can't ignore it.

If this came out completely negative in all adults, no matter how we looked at it, and we say, "Oh, maybe something is crazy about the pediatric data," it's clear that that's not what happened.

It doesn't mean that you don't have similar things happening in other people outside of this group, but again, it is just to show the equivalent of efficacy in terms of the safety issue.

DR. PINE: Dr. Mehta.

DR. MEHTA: Just a question of FDA. Are these findings unusual? Because you almost never see an age effect where one age group responds one way and the other extreme group responds exactly opposite. I don't know of any drug class where you can see such an effect.

DR. STONE: Well, this isn't a treatment effect. Certainly, people do age and respond in different ways. If you looked at a drug that helped exercise performance, you would see more younger people running six-minute miles with the drug than older people. Certainly, it is an interaction with age, for whatever reason.

DR. TEMPLE: I mean, the people who like large, simple trials used to make this point all the time, that usually things go in the same direction. Quantitatively they may differ, but usually they go in the same direction.

I can't think of a whole lot of examples of things like this. However, it does seem to me we don't really know that the disease is exactly the same in all these people, and that could be an

explanation. We can't say that it is. There are a number of reasons to think it might not be. That's my leading choice anyway, because this is unusual.

DR. PINE: Well, I would also -- oh, I'm sorry. Go ahead.

DR. MEHTA: I would not have been surprised at the odds ratio getting larger and larger as patients are getting older, but it's exactly opposite and that's a concern.

DR. TEMPLE: One other thing. Somebody I guess from the audience made the point that you don't really know whether this is just something that goes in one direction or whether it's a balance, namely, that the drugs have the ability to reduce the risk in some people, we heard lots of people say it reduced their risk, and exacerbated

0353

it in others.

As Tom said, there was always this idea that some people could be empowered to do something that they couldn't do before.

That is another possibility, that you have a difference in the balance. That could explain the difference in outcome in people of various ages.

DR. PINE: I would also add, from a neuroscience perspective, in terms of what we know about the underlying systems that get perturbed in people with mood and anxiety disorders and other conditions for which SSRIs and other antidepressants are prescribed, that there is pretty clear evidence that development extends far beyond eighteen.

From that perspective, the data and the figure right there are really not all that surprising at all, which again lends a certain sense of they need to be taken seriously to them.

Yes, Dr. Robinson.

DR. ROBINSON: I might have missed this

0354

in your presentation. Dr. Levenson, when you were presenting on Slide 17 you said there is no difference between the drug and the placebo groups based on history of suicide attempts and based on suicidal ideation, I was wondering if you looked at those two variables across the different age ranges and also whether that was related to any of the suicidal events that you analyzed during the trials?

DR. LEVENSON: No. We didn't further stratify that by age. That was a trial-by-trial comparison of all the subjects.

DR. ROBINSON: Was there a reason why you didn't look at baseline suicidal ideation or attempts as a predictor of later suicide?

DR. LEVENSON: No.

DR. PINE: They would have the placebo

control, because they had a placebo control and randomization. If there were differences, as long as the randomization.

DR. ROBINSON: No, I was thinking of we have this one measure of suicidal activity before you enter the trial and even though it is distributed equally among the drugs, is that one predictor of suicidal activity within the trial?

Also, is it evenly distributed, like, are 18 to 24 year olds having the same amount of previous suicidal behavior as the 65 and up as a potential alternate explanation of the age effect?

DR. LEVENSON: No. Again, we didn't look at it stratified by age. We were mainly interested if the randomization created the correct balances.

DR. PINE: Jean Bronstein.

MS. BRONSTEIN: I have another thought about this age variation. It seems like it is very logical to me that children have very little experience feeling all sorts of symptoms and they have much less impulse control than older adults. In my experience, teenagers are well extending into their twenties.

I think you are seeing a very natural progression of life experience helping you contain whatever emotional response you are experiencing.

DR. PINE: Along those lines, it would be interesting to see the data on accident rates. Because in looking at deaths from accidents, if you look in the 15 to 25 cohort, it doesn't necessarily look all that different in terms of mortality from accidents.

Dr. Leon.

DR. LEON: Can you remind me, were most of them flexible dose studies, or were you able to look at dose response?

DR. STONE: We didn't get dosages within trials. If it was a fixed-dose study, everyone on the drug was treated the same.

DR. LEON: Were there different doses within a program across trials that you might be able to look at? I mean, it would be a surrogate for a dose response.

DR. STONE: We didn't ask for dosage. Occasionally, it was listed. The basic approach was what drugs someone was on or placebo and separate out the titration phases or deescalation phases and just look at that time period on drug.

DR. PINE: Gail Griffith.

MS. GRIFFITH: Given that we are looking at this 18- to 24-year-old and the risk variability with that, as Ms. Bronstein pointed out anyone who has raised teenagers knows that we now go up to about 24 or 25, but could we look at the method of

attempt, the adverse event?
Would it give us any ability to determine? If we were to see that there was more serious risk involved in the actual events, say, guns or accidents, would that help us determine whether or not this was something we could control for?
DR. STONE: We don't have that information. There may be something in the adjudication process. Kelly is shaking her head no, so no.
MS. GRIFFITH: Thank you.
DR. PINE: Dr. Armenteros.
DR. ARMENTEROS: It may be interesting to look at the data in relation to the background rate of suicide, provided that we know it is a pretty situation in younger people and then it goes down
0358
in middle age and then again we have some issues later on in life.
Perhaps, that may help us understand this data or maybe open a window into what is happening with this phenomenon we are seeing with age here.
DR. PINE: I am going to actually have Dr. Pollock make a comment or ask a question, and then I'm going to kind of summarize the discussion up to this point.
DR. Pollock: Yes. Just a further point of information. It's related to something I asked this morning, Dr. Stone. Just so we can compare the geriatric data with other things that have come out recently like the "Journal" study, do you have any information -- I mean, you've told us that it may be a couple of thousand patients, subjects, over the age of sixty-five. What is the mean or standard deviation around that age? I mean, is it sort of sixty-five mostly? Sixty-eight? Sort of what is the range and the mean? I mean, you must have that.
DR. STONE: We have that. We did have a
0359
subject who was 99 years old, one of them, and a fair number over 90 -- dozens, maybe hundreds.
(Perusing) Okay, it is 2,336 over age 75 compared to 7,600 overall over 65. Over age 75, there were 2,336 and over age 65, which is slightly different than the 65-plus because I was a little sloppier, there were 7,599. Roughly, a third of those over 65 were over 75.
DR. Pollock: That is very helpful. Thank you.
DR. PINE: I am going to summarize now what I hear from the discussion, and I am going to slowly start to move us off of the first topic and towards the second topic.
We are going to take about 10 more minutes on this, so if either I'm summarizing

things wrong or if there is a major thing that we haven't talked about in terms of the data that were presented today, the next 10 minutes is probably the time to talk about it. I would call everybody's attention to Dr. Laughren's Slide 6.

You can even put it up there.

(FDA Staff complies.)

DR. PINE: I think the first thing that we really want to do as a Committee is either agree with this or say why we don't. A lot of people comment on the quality of the data. At least what I'm hearing is that overall people are quite impressed with the amount of work that was done here and that the data do lend themselves to drawing reasonable conclusions.

Clearly, there are a lot of thoughts and a lot of other things that need to be done. You have heard a lot about that, but again, I think people feel satisfied is what I am hearing, number one.

Number two, there was a lot of discussion about more specific research on this question that we need to get done. Again, I'm not going to go over all of the things that were said.

Although, the one thing I will add, just to show Dr. Temple I remember this, I do think it would be important to continue to specifically encourage using the withdrawal design where everybody is treated openly and then randomized to either placebo or active treatment to get better information at the question of how does efficacy factor into the association with suicidal ideation or behavior.

That being said, again, the sense that I am getting from the Committee is that people are pretty uniform in terms of, number one, the quality of the data; number two, the kinds of studies that need to be done; and then, number three, the Committee's take on the slide that is in front of us.

At least, just speaking for myself, I would agree with the two main points that are made in the slide. The data that you have presented do seem compelling in terms of your conclusion that finding of an increased short-term risk for suicidality with antidepressant treatment in pediatric patients appears to extend into younger adults; then, number two, beyond age 30, antidepressants begin to show a protective effect; and this is most pronounced beyond 65.

That is my summary of what we talked about. I'm seeing a lot of nodding heads. I don't see any violent shaking heads on the panel anyway.

Yes, Gail.

MS. GRIFFITH: If this information is made public, as it already has been, I would suggest that could we add just the age group between 25 and 30, suggest that it's flat there

Because there will be a lot of questions. If you are putting this out, the increase in younger adults up to 25 and the decrease in adults over, people are going to want to know. The public is going to be interested in what's going on in that median group.

DR. PINE: I would second that. Yes, I would second that. You need to say something even if is "The data are such that we can't determine what happens between 25 and 30." The public needs to hear this message, and needs to hear at 25 to 30.

Other thoughts or comments?

Yes, Dr. Robinson.

0363

DR. ROBINSON: Well, I think one of the things I am concerned about is we seem to be focusing on these ages as if we really think that age is the thing that is really driving this.

(Applause.)

DR. ROBINSON: Is it that you are having differential pruning that is causing this, or is it because of comorbidities? Because we haven't talked anything about it. We don't know what the comorbidity patterns are, that sort of thing.

I think we have to be very careful about saying, well, 25 versus 26. I think we have to acknowledge that we think that this is a proxy potentially for biologic mechanisms, comorbidities, et cetera.

What we have is that the patterns are sort of different by age, but magically 24 is not really different than 26 in terms of what we think is the biologic mechanism.

DR. PINE: Well, I guess your comment really speaks to two issues. On the one hand, in terms of all the data that we have seen, the only

0364

variable that we have seen where there is any suggestion, let alone a strong suggestion that it moderates this association with suicidality, is age. At least that is the only variable I have heard about.

That is just looking at the data for the variables that we have and judging what we see in terms of the causal association based on randomized control trials. That is one issue.

The second issue is, as you say, it has to be more complicated than age, of course. Age has to be a proxy for something. You just listed a bunch of really good ideas. I think that there are going to be many more. Obviously, there is something very important in terms of development.

I do think that is a little different in terms of trying to explain why this is happening as opposed to do we believe the data that we are seeing, do we believe that there is this reliable, observable, statistically significant causal association between the use of antidepressants and suicidal thoughts or acts up to age 25.

I guess what I'm concerned about is in terms of how we present this to clinicians. It isn't that I think most of us believe that it's a direct age effect. What we have is very limited data of things we have examined, I mean, gender, race, age.

This is the one that gives us some evidence of signal in certain groups. A clinician evaluating their patient, when you are 26 you are not safe, and when you are 24 you really are not at increased risk probably because of age; this is just a proxy for something else. I think that is very important, again, with the message that everybody should be monitored for suicidal ideation.

DR. PINE: Would you agree or would you disagree, though, would you endorse the statements from the FDA, or would you not want to endorse those?

DR. ROBINSON: I think it is important to precede all of this by saying we have only looked at very limited variables and it looks like there is this pattern by age even though it is probably a proxy for something else. Then, the data sort of falls out this way, just again to get focusing on age, when we don't think that is the real mechanism.

DR. PINE: I think that is a point well taken.

Yes?

DR. TEMPLE: Are yo concerned that this might undermine the idea that you should watch these people closely? You seem to be saying, oh, well, you don't have to watch them, particularly if they are sixty-five.

That is absolutely not the intent because we don't have to know why it's important to watch them closely. Whether it is the drug, the disease or whatever, we just know that you have to. That has been in the labeling for a long time.

We don't think there is any less reason now to do it just because of these data. I wonder if that was part of what was on your mind there?

DR. ROBINSON: Well, I think there is that. The other thing is, again, for example, comorbidity or substance use or something like that. We don't know.

We just know that globally patients who have a major depression and they are under 25 seem to be at a higher risk than if you are treating somebody over 65, but we don't know what the real reason is.

I think it is important that it not just come across as sort of age. Because, one, that means that people, tragically, might not monitor somebody if they are over 65.

Then, also, we have to be very clear that we don't know what the drug disease interactions are and that you should be, again, monitoring everybody very closely and trying to understand all of their disorders, et cetera. I think just focusing on age gets people to where they might get into that sort of false sense of security, if they are 65.

DR. PINE: I am going to take two more comments, and then I'm going to really summarize.

0368

Dr. Leon.

DR. LEON: Well, moving beyond this slide, something else you said, I don't think there is consensus. We didn't reach consensus on what design should be reached, used, to study this, I mean, other than careful, prospective assessment of suicidality.

These are rare events. We need very large N's. We don't know what comparator really should be used if these are suicidal objects, or maybe they are not, so maybe a placebo might be appropriate or might not. I just wanted to qualify that statement.

Dr. Goodman.

DR. GOODMAN: Yes. If I understand Dr. Pine's question correctly, I am ready to endorse that statement. I think it is a different matter about how you translate that into labeling.

I agree with all the points that you made, Dr. Robinson. I am willing to endorse it with one caveat, talk about splitting hairs, up to around or about age 25 rather than to age 25

0369

because there was some admission that there is not a precise cutoff. Otherwise, I think I would completely agree that those conclusions are valid based upon the data that were presented.

DR. PINE: I would also say that I agree with that statement. I don't feel a particular pressing need to bring this issue to a vote just because I really have not heard anybody say that they disagree with it. The only things that I have heard are ways to qualify it.

Unless anybody either wants to disagree or say that we need to bring it to a vote, what I would say is that our recommendation to the FDA would be that we agree with the conclusions in this

slide, acknowledging the need to go beyond the conclusions both in terms of future research as well as in terms of how we interpret this for clinicians and for the public, both in terms of what we say to clinicians about monitoring and the need to monitor carefully in all ages, despite what is written here, and then also to recognize that age is probably a proxy for some other variable.

Dr. Schultz, do you have one last comment or--?

DR. SCHULTZ: I guess my one worry is some of the proceeding comments showing the effect on prescribing practices and how that may have inadvertent consequences in the younger age groups. There was already evidence to suggest that that is spilling over into adults already.

I just want to be careful that we make sure that we are following up what is happening now over the last warning, and if it is already spilling over into adults, that we are paying attention so that we just make sure we don't run into unintended consequences.

DR. PINE: I think that comment does very nicely segue into the next more major issue for us to discuss. I think, again, the data are really pretty clear to me and I think to all the committee members that we need to look at this issue very carefully, and the public needs to know more than what has already been said in terms of the association between the use of antidepressants and suicidality.

Now, there is a huge range in terms of what you, as the FDA, could do or could say. I mean, I think we have already agreed and decided that you have to do something because we have all agreed with this statement that is written up there.

Dr. Schultz raises the issue of concern with the data that might the change in prescribing that would follow one or another type of recommendations have an ultimate adverse effect on the public health by making it more difficult for people to get the necessary treatment.

It is now about a quarter to 4:00. What I'm going to do now is I'm going to open up the next issue. I am really just going to open it up for about the next 20 minutes. We are going to go until 4 o'clock, and we are going to just start fleshing out what to do. Again, there is a whole range of things to do. I think we are not going to move towards that until maybe 4:30 or a quarter to 5:00.

I would like to hear comments, much along the lines of the comment that Dr. Schultz just

made, about what are some of the issues that people are thinking about in light of the data that we have had, in light of the experience and the data that is accumulated following the various actions after the pediatric hearings to flesh out as many of those issues as possible.

Gail Griffith.

MS. GRIFFITH: Could I just ask for a clarification from Dr. Laughren? Are you suggesting in the planned regulatory actions in your Slide 7 that we include this language in a black box?

DR. LAUGHREN: Yes. That was a suggestion that we already have black boxes and all these labels, and so the suggestion that is being made here is that we modify that language to incorporate those new findings, but it would still be a black box.

DR. PINE: That is how I read this. How I read this slide is that what the FDA wants to do,

0373

unless we tell them otherwise, is they want to effectively extend the black box up to 25.

DR. LAUGHREN: Also, include other relevant information that we have learned from this analysis.

DR. PINE: They want to extend and modify the black box.

DR. LAUGHREN: Right. There is new information on adults beyond age 30.

DR. PINE: All right.

MS. GRIFFITH: That would go in the black box?

DR. LAUGHREN: That is the suggestion, that that language would basically go in the black box.

DR. PINE: Basically, the language that we have on the slide is what you want it to be, unless we tell you otherwise?

DR. LAUGHREN: It is an opening suggestion.

DR. PINE: Got it, got it.

Dr. Goodman.

0374

DR. GOODMAN: I wanted to say something about black box or not that struck me ever since 2004 and again today hearing the different public testimony.

I actually feel that undue emphasis is placed on the black box sort of like if you go into an art gallery picking up the frame before you decide what painting you're going to purchase.

As long as we keep in mind that it is not so much whether it is in a black box or not but what the message is, what the content is, and what the content is.

What I was about to say I want to see is

a little bit decreased emphasis on whether there is a black box and more of what the message is inside that black box.

That having been said, I think that this is a very good starting point. I think that we have to be very clear and transparent in a way that is understandable to consumers and to the prescribers what the relative risk is.

Some of the data I saw today, I like the

0375

way it was presented in a way that I think that most individuals can understand what the probability is of an event.

One of the slides, not the odds ratio but the risk difference, you talked about, if I understand this correctly, in the pediatric population of 14 cases per 1,000; is that correct? Just take that as an example. I think most individuals, if presented with out of 1,000 cases, 14 may show increased suicidality in this population group.

DR. PINE: Medication-related.

DR. GOODMAN: Medication-related versus placebo. Let's assume we could clarify that and express it in terms I feel are easier to understand. What is still missing, and I think we have heard this a lot today in the discussion, is what is the relative risk of taking drug versus not being treated? What is the relative risk of being treated with drug versus not diagnosing and intervening in depression? That is really the missing element.

0376

I'm not sure how we can get at it today because your data doesn't directly address it, but I think it would be a mistake for those people in the audience or in the press thinking that the placebo group represents untreated depression; it does not.

These are individuals that are in a clinical trial that have been identified as having depression. There is a safety net. There is monitoring.

They are not the same as the folks that a lot of people here today were talking about they were worried about. Those people because of the black box will never be identified, will never be recruited into a treatment. What is the risk of suicidality in that group?

DR. PINE: Dr. Leon.

DR. LEON: The postmortem data provides a little piece of that puzzle, a small piece of it. I want to ask are there data from other classes of meds where you know how introducing a black box affects sales, affects use, affects the adverse

0377

events that were the concern?

DR. TEMPLE: There may be people who actually do know that, but a lot of these warnings come with a lot of other things at the same time, a risk management program, things like that. You have to separate those things out. What else has gotten the black box lately?

DR. LAUGHREN: Well, the antipsychotics, the antipsychotics has gotten a black box for the mortality in elderly patients.

DR. TEMPLE: Well, we don't have any easy way of tracking the effect of that, other than looking at overall prescribing. We do have some experiences that have been looked at and documented.

For example, when we tried to get, and this has actually been studied and written up, when we tried to get people to do liver enzyme monitoring with troglitazone, we put it on the label, put it on the label, and most people didn't do it. There was clearly a black box associated with that, that it caused fatal hepatoxicity.

0378

When we have made other kinds of warnings, and it depends probably on how you write them, it was pointed out that I guess cisapride use didn't come down right away when we put warning information about possible QT prolongation.

You have to look at exactly what we said. The first thing we said was it prolongs the QT interval. That doesn't mean you shouldn't use it. When we finally got around to saying, "You really shouldn't use this except as a last resort," then the use came down.

In this case, it is worth thinking about what it is that scared people off so much, the need for monitoring, was that beyond their perceived resources? Is that what made GPs unwilling to use it? I mean, I don't know the answer to that. You all may have better insight.

DR. PINE: When you say "that," what are you referring to?

DR. TEMPLE: Well, what is it in this black box, I mean, if use has declined, and it seems as if it has, what is it that did that? Was

0379

it the anxiety about the suicidality itself or the need for a level of monitoring that seems so burdensome they weren't willing to do it anymore?

I mean, I don't know the answer to that. You would sort of have to know to figure it out. It goes to what the alternatives and choices are. It would be hard to argue you don't want that level of monitoring. If you want it, you have to tell people about it. If that is the thing that decreases the use, I don't know what you're supposed to do.

DR. PINE: We actually did talk about

this quite a lot at the 2004 meeting. I think there was a lot of concern with the fact that the availability of clinicians who are expertly trained to use these medications in the way that they have been recommended has been a problem. I think some combination of those forces probably played a role.

Jean Bronstein.

MS. BRONSTEIN: The whole area of public education I think is what we are beginning to talk about. Certainly, I know that in our intent, or at least when I voted to support the black box in `04, the intent was to educate people, to get the word out that monitoring has to be taken a lot more seriously and involving family in doing that. That was at least for me the message that we were trying to get out.

I think today even more so or again I am hearing from the public their desire to have more information more readily at their fingertips to understand what it is we are asking them to watch for. I think we need to talk about activation syndrome as one of the things to watch for.

Education and availability, I think in this country we have a terrible problem with access to medical care. We are not going to fix that on this Committee, but it is something that we need to at least be cognizant that general practitioners have to be using this drug. Because that's who is out there serving a whole lot of the public.

I think we discussed that at length in `04, that we didn't want to hamstring people into having to see child psychiatrists, and I think the same is true with adults. We don't want to have to have that happen.

However, I think the way in which we put out information has to be so inclusive that physicians feel that they can prescribe this drug, that they can monitor this drug, that they can involve families and patients in the limitations of the drug that are available.

Thanks.

(Applause.)

DR. PINE: Gail Griffith.

MS. GRIFFITH: I recall in the `04 meetings that at midpoint on the day that we were deliberating we indeed queried the FDA to see if they had any relevant data about prescribing practices.

At some point somebody from your division went back and looked at the Medco data which suggested that from the time of the very first warning in October `03 to March `04, that the prescription writing was indeed steady or had increased 7 percent.

I had to suggest that in the aftermath of that, I think that that gave a lot of members of the committee a sense of comfort and some reassurance that we wouldn't be seeing a precipitous decline, which then we did the following January.

I guess I am very troubled by the epidemiological data which is showing some sort of correlation between the really significant drop in prescribing and the increase in suicides.

I think the black box is everything, you know, for whatever reason, whether it is litigation, whether it is a lack of expertise. The media picked up on that and ran with it. I am not surprised. It is a sexy thing. If that happens again, I think that we run a significant risk of severely undertreating.

I would like to come back to that point, because I actually remember it exactly the way that Gail Griffith remembers it and the way Jean Bronstein was talking about it.

I remember sitting around and everybody

0383

was uniform, much like they are today on the Committee, that the public needed to be notified and that we really needed to be creative and energetic in terms of what we needed to do to notify the public.

I remember hearing the data. I also, then, remember hearing and seeing other data that came out from the same time period from different data sources that suggested that the earlier warning had actually initiated a decrease in utilization even before the black box had come out which again, as Gail Griffith just said, got people quite upset both because it wasn't really clear what the data were, number one.

Number two, they felt like the message that was being sent by the Committee was that you really should not treat people, which was not the message that the Committee wanted to send.

Could you comment a little bit on that data in particular and how you view those events, how you view what you say and how it is going to affect the availability of treatment?

0384

DR. LAUGHREN: Well, these are several different issues. In terms of the use data that we were presented at the September 2004 meeting, those were preliminary data that were pulled together at the last minute covering a fairly short time span.

We have more data now that confirms almost everything that you have been hearing this morning about a decline in use. The numbers are going to vary, depending on what your source of data is and how you break up the age spectrum and so forth. However, I think everyone agrees that

there has been some decline in antidepressant prescribing, particularly in younger people.

The other issue of how you best convey this information to the community, that is a tough one. We all agreed that we should have a med guide, and we have a med guide. However, we know that those are not being uniformly distributed. It is very hard to know how to improve that other than something like unit-of-use packaging.

I mean, the thing about a black box is that it gets people attention. Sort of the sense

0385

that I'm getting from you is that perhaps it has had a negative impact. That never was FDA's intent to discourage physicians from appropriate prescribing of antidepressants. We never had that attempt.

DR. PINE: I'm actually trying to solicit opinions on that very issue.

Did you want to say something, Dr. Temple, before--?

DR. TEMPLE: Well, I did want to throw out the question of, How do we know what the right amount of prescribing is? There must be some people who are overcasual. Maybe it discourages that more than serious use. I don't practice this art, so I have no opinion on it. But how does one really know what the absolute right amount is?

DR. PINE: Yes, I think it's an open question that I'm not about to try to answer.

Dr. Slattery?

DR. SLATTERY: Yes. I would like to come back to the issue of potentially giving sort of a false security, if you will, at the age brackets

0386

that we're talking about. Specifically, as I look at the statements, and this comes from the public education piece that we were talking about, of what defines risk for the clinician and what defines a protective effect.

My concern is that when the information is disseminated, particularly regarding the age brackets that we are proposing, that potentially without having more information about what to specifically to assess for regarding risk and protective effects, that precludes some practitioners/clinicians from prescribing, because it is more of an all or none in contrast to being able to sort out potential risk factors or potential protective factors.

I think a lot of the family members we were hearing similarly from the importance and the assistance of having parameters to monitor is going to be critical in terms of contributing to the discussion as well.

DR. PINE: Dr. Mehta?

DR. MEHTA: Look at it this way, the

0387
black box is not positive for any drug. I think the promotion and advertising of the drug becomes more difficult because in the black box there is never a positive statement.

You are not going to say that "In children or people up to the age of 25 there will be some effect; however, in the elderly patient, there is a positive effect."

That just doesn't happen. When you put a statement in a black box, take it for granted that usage of the drug will go down. There is no other outcome.

DR. PINE: I think you do intend to put a positive statement in, though, so this would be the first instance of that.

Dr. Armenteros.

DR. ARMENTEROS: Yes. We keep talking about number of prescriptions, but again, number of prescriptions, it's not the same thing as people being treated. A lot of the emphasis is on how much usage you saw there and how little usage is there, which is already a problem.

0388

The message, if it goes out there in a black box, it could be polarized, meaning we are delivering a message that says that we had better be careful. There is data to support that we should be careful.

However, that message by itself without somebody actually mentioning something like this to the public, without a message saying "for the disorder by itself," is horrible.

We've got to do something about it. When we don't do it, it is polarized. That polarization is a problem. It is a serious problem.

I don't know. I don't have the answer to the question. I think we are a little bit narrow in thinking of prescription numbers and thinking about this little message. We really have to somehow deliver a message that is not polarized, that everybody actually gets some help from this.

DR. PINE: Jean Bronstein?

MS. BRONSTEIN: I am not an expert in health education, and I don't know that any of us around the table are. However, there is a whole

0389

field out there how to get messages across.

I think that's maybe a study group of those people plus some people from the FDA and maybe some people from the Advisory Committee. I'm not really making a recommendation of who should do it, but there is a whole field out there of health education that really could be brought to bear on how to package this message and run that important gamut.

I think we heard very clearly about the

importance of access to treatment. I don't think any of us want the black box warning to preclude the proper use of these medications. However, we need to warn people. It is a very tight balancing act. I think there is help out there that may not be from this Advisory Committee.

DR. PINE: I think the other message you are hearing, which again I think that there is some unanimity in the Committee about, is about how serious this need to properly inform the public is and I think to pay a lot of attention to what both the intended and potential unintended message is

0390

going to be from anything that we say and that we do.

I think we are all struggling with that a little bit because we do not have a real good feel, as Jean Bronstein just said, in terms of how to maximize the right message getting out and minimize the wrong message getting out.

Dr. Mehta.

DR. MEHTA: One other comment, and that is, we need to have some recommendation for an important age group, which is 25 to 30. That's missed out here.

DR. PINE: You guys, you did hear that, right, about the 25 to 30? Dr. Mehta just raised that point, that you can't leave our 25 to 30 or whatever. You've got that?

(Committee moving heads up and down.)

DR. PINE: Okay. Gail Griffith.

MS. GRIFFITH: I think that when we did this in `04 what we did was not only worthwhile but potentially life-saving. I guess our hope was that we would get rid of cavalier prescribing. I would

0391

say that the jury is still out on that.

I think that children are a protected class if citizens. It is an arbitrary number 18 and over. What we needed to do was make some strong statement about the signal that we saw as it related to the data about children, and we did.

I fear that it had perhaps negative consequences, and we are still trying to figure out what those are and what they really look like.

But when you talk about 18 and over, everybody has to do the risk-benefit analysis themselves. I am a mother of a child who attempted suicide at seventeen while on drugs.

I look at this anecdotally, but I do the risk-benefit analysis. I did it for him, and I do it for myself. I think that the public has to become educated to the point where they can do that also.

What we did by virtue of the black box warning was due diligence, protecting a class that should be protected. At this point I don't know

that I would be excited about seeing a black box around the rest of these different categories of age.

DR. PINE: Yes, Dr. Temple.

DR. TEMPLE: Tom and I both look at the proposed modification of the black box as not making it nastier, but suggesting that this is complicated. It may relate to age. It doesn't look to us like it makes it more stringent than it was before.

Now, maybe some people think it ought to be less stringent; I don't know. It provides more information, but the basic message is still the same, that you've got to watch people and there is this problem for the young people.

However, there is the additional thing -- as Dilip said, it is novel -- that would also say risk seems to go away as you get older and maybe even it goes the other way. I am curious as to what you think we could do with the labeling to convey more of what you want.

I mean, you can't say these drugs prevent suicide, even though probably a lot of people believe they do and it seems logical because there is not a lot of data on that. Maybe some of the ecological data could be used that way, but we have really rarely used that kind of data to make a claim, I mean.

DR. PINE: I would not recommend that. I think the data clearly don't support that, without question.

DR. TEMPLE: Right. Balancing it in the way that you are talking about doesn't seem entirely straightforward. We would be definitely interested in what you have in mind.

DR. PINE: Well, so I guess I have three replies to that. The first thing is, and I said this in 2004 and I will say this now, I totally appreciate that everybody and particularly you are between a real rock and a hard place in terms of wanting to weigh the risk benefit analysis as precisely as possible to meet the public good.

I totally understand that, and I believe that. I believe that that was the case in 2004. However, for whatever reasons, we are at a very precarious position.

I mean, it sounds like you would agree with the idea that the black box statement in 2004 had unanticipated consequences on practice.

DR. TEMPLE: Not totally unanticipated. I mean, all of the discussion and this meeting itself and the strong statements people make, those get reported and they have an effect. I mean, I'm not amazed by that.

DR. PINE: Or, at least as Dr. Laughren would say, it had an unintended -- I'm using the words that you said in terms of looking at the data. I don't know that we can totally predict what is going to happen based on what our recommendations are.

Given that and given the potentially major consequences of making an error on each side, I just think we need to think about this incredibly carefully.

DR. LAUGHREN: When we started off this discussion, you laid out two issues you wanted us to focus on. First of all, was sort of the black

0395

box versus not, and the other was the content.

(Cross-talk.)

DR. PINE: No, no, no, no, the two issues were what do we --

DR. LAUGHREN: Well, no, the content of the message, the content of the message.

DR. PINE: Correct.

DR. LAUGHREN: It would be very helpful to be clear on the ladder what information do you think is useful for us to convey to prescribers in the community at this point, then we can talk about how to package that. I mean, that is sort of a separate issue.

It is really important to know of all the data that you have heard what are the critical things that you need that would be helpful to clinicians in the community to educate them about it.

DR. PINE: That is actually a very helpful comment, and, hopefully, we can now talk specifically about that.

Dr. Goodman.

0396

DR. GOODMAN: Just from a procedural standpoint, it seems to me that unless we are ready to vote on our previous recommendations about whether to place the pediatric population in a black box, I don't think that we have very much choice other than to extend somehow those warnings.

I guess I'm going to pose the question, then, are there individuals around this table or does the chair feel in a position to entertain a question about reviewing that previous decision to recommend the black box?

I heard some hesitancy from Gail. I know each of us, I think, who have voted in past times have probably had years to reflect on whether we made the right decision.

I for one was actually aware of those unintended negative consequences when I made that vote. I wasn't aware that prescribing had decreased, but I was aware that there would be some

negative ramifications.
It seems to me unless we are willing to
take up that issue again, how could we just not extend it into another age range including the protective effects?
DR. PINE: I would go back to Tom's statement which was, first, tell the FDA about what is the message that we want to send to the public and then figure out how we are going to make that message. I think that is an important point, so that's number one.
Number two, I for one, but I would be interested in other thoughts, would not want us to revisit the black box in children issue. I think that would be nonproductive from many avenues, not the least of which is communicating the message to the public.
I will tell you, along the lines of what Dr. Goodman just said, I voted against the black box. If the vote came up again today, I would probably vote against it again.
I still do not think that we should reraise the issue. I think that will actually move us backwards. I'm not sure if anybody else has any
other feelings about that.
(No response.)
DR. PINE: No? Okay. I really would like us to think about what is the language, what is the message. We all agree that the data say something very clear to us. Number one, we all agree that getting the message out to the public is of the utmost importance.
I actually also think that the slide in front of us gives us a pretty good starting point in terms of really capturing the key things. I don't know if anybody wants to comment either endorsing or changing the message in the slide, leaving aside how that message is put forth.
Yes, Dr. Schultz.
DR. SCHULTZ: If I could just make a comment as a geriatric psychiatrist. I am extremely concerned about the welfare of my elderly patients.
I can tell you that that is the age group that will not seek care. Often, if they seek care at all, it is with a primary care doctor. I am not
at all surprised that they may have differential effects.
Antidepressant medications, age-related brain changes do incur in a number of unique clinical situations. Late-life depression is quite different. In fact, I can't speak to the adolescent issues very well at all.
I am just very concerned that the elderly

feel the stigma very deeply. They are deeply ashamed of seeking care, and they tend to be a very unrecognized, underrepresented population that is a very high risk for suicide. I worry very much about anything that might deter the older adult from seeking care.

DR. PINE: Dr. Schultz, do you think that the language that you see there would have that effect? Because I have to say that when I read it, Dr. Mehta's points notwithstanding, my gut is that the language there wouldn't discourage treatment.

DR. SCHULTZ: Only to the extent that I believe it's the family doctor who is going to be a little bit more likely to say, "Okay, I won't

0400

those, then."

My only concern is the increased use among the elderly of their family doctors. They are very, very leery of mental health professionals at all. That's the only link that I can make, but I leave it open.

DR. PINE: Dr. Mehta.

DR. MEHTA: Well, just one comment. I am not being facetious here, but black box usually is negative. One other way would be to take this positive information about age 65 and above and put it in a white box just next to that.

In that case, people will still look and then they get the information in the black box, and I think Dr. Schultz's comment would be taken care of.

DR. PINE: You agree with the message? You agree with the content of the message? You do?

DR. MEHTA: Oh, yes. I'm talking about how to display it.

DR. PINE: Okay.

Dr. Robinson.

0401

DR. ROBINSON: Well, one thing I was thinking is if we had the first point, which I think all of us agree on is the relationship between suicide and depression is very complex. Untreated depression, suicidality is a core feature of untreated depression.

Then, what we know is that from placebo-controlled studies that there seems to be a differential effect, drug effect, on suicide and it seems to be in pediatrics. In younger people, it may increase the risk. In middle age or older, it may go down; it may be the same or go down.

DR. PINE: Can I ask you something right there? You specifically avoided putting an age on younger people. Is that intentional?

DR. ROBINSON: Yes, intentional because in actuality, from my understanding, you didn't do analyses where you looked at the suicide rate by age and saw an inflection point at age 25;

correct?
DR. STONE: This morning when I put up my slide with the confidence intervals I tried to make
0402
that point, and that is based on a linear relationship. I tried other functional forms, and they weren't very convincing. Your confidence interval for crossing that line from an elevated risk to reduced risk runs from 20 to 65.
DR. ROBINSON: I think it is pseudospecificity at 25 versus -- I mean, it is pediatric and young adults. I think you have to be very wary about saying 25 is really -- unless you have data to show that.
DR. PINE: Of course, there are two sides to any statement like that, if you are not precise. I'm forty and I think I'm young. People could interpret that very differently, if you don't put data into that.
DR. ROBINSON: Well, if you are going to put an age, you are going to have to tell people that this is not an exact age. Because again, it is pseudospecificity. Also, it is not based on the data. With that confidence interval, all you can really say is young adults really.
DR. PINE: Dr. Armenteros.
0403
DR. ARMENTEROS: Another thought about the message here is that point number one is the age. Once again we have been talking about it plenty.
I think actually the stronger message is, Why don't we observe these patients carefully? In my mind, that is actually more robust and more important.
Yes, we could give the information. Yes, age is an issue. We are very aware of age, approximately, and so forth. However, I think what people really need to stick in their minds is that it doesn't matter.
The fact that you don't see it so often at 45, does not mean that they don't have to look. I think we've got to look and then, sure, listen, you had better look because we have an issue here with age.
However, I think it is a little bit misleading just to say, okay, these age groups show this and that, and maybe you don't have to worry. Maybe protective data, as it is, is not totally
0404
precise.
I think the message is let's be careful, in my mind, and then we have backing for that very clearly. I am not so sure about this dichotomy on this order; I don't know.
DR. PINE: Dr. Goodman.
DR. GOODMAN: Unfortunately, we're stuck

with this term "suicidality," and that is actually one of the issues I have some regrets about.

No matter how much I try to explain it, particularly to a lay audience, suicidality gets equated to suicide. We know at least from the pediatric data that is not true.

In fact, if you type out "suicidality" in Word", you always get the red underscore. It really proves that it is a term that we invented. It has been very carefully defined in a very reliable fashion, I am very confident in it, but it is a problematic term.

Again, it may be too late to change it. In hindsight, I wish we had placed more emphasis on a more generic term saying something like "serious

0405

adverse behavioral side-effects including suicidal ideation, suicidal behavior," and maybe some of the other behaviors that have been presumed to be part of this activation syndrome.

I don't know how you can soften that at all. I can just tell you countless times, no matter how you try to explain it, suicidality equals suicide. It isn't the only thing you want people worrying about. I know you explained the other symptoms, but this obviously overshadows them.

DR. PINE: Yes, Dr. Laughren.

DR. LAUGHREN: Well, the issue, however, is that we studied suicidal ideation and behavior. We didn't study all the other things. It's true that the black box asks clinicians to observe for those other behaviors, but that is more speculative. The actual endpoint was something related to suicidality.

We don't have to use the term "suicidality." We can revisit that. I mean, actually in some of the talks this morning the term

0406

wasn't used; it was suicidal ideation and behavior. That is a little bit longer.

I agree that there has been a problem in interpreting that term. For example, when you see news stories, the story is usually "suicide" not "suicidality." Personally, I prefer suicidal ideation and behavior.

Dr. Leon.

DR. LEON: I want to underscore what two of the previous speakers said. One, it would be nice if the risk of not treating depression is included in this. I have heard it several times and I want to say it one more time, because that is the biggest concern about the black box warning.

The other that we just heard, the other very important point regardless of age, is observation. Patients have to be observed after being treated.

DR. LAUGHREN: Let's just be clear about that. Again, and I don't disagree with you, but that message has been on antidepressant labeling for decades.

The big change two years ago was, well, first of all, to put this in a black box but to emphasize a particular group that was at risk, pediatric patients.

Now we have additional data suggesting that that risk may extend beyond the pediatric age group. Exactly where the inflection point is, is not clear but it does appear to be an age effect. We could convey that in a less precise way.

I guess the question is, What do you start with here? I mean, do you start with again going back to what we had for decades? Observe all patients who are being treated and then get into the message about where there might be differential risk?

DR. PINE: What I heard Dr. Leon say, and you will correct me if I get it wrong, is that if we are going to pay very much attention and be very careful in terms of what this new message is.

Because it does seem like whatever we've said beforehand there is really a tremendous amount of attention that is being paid to this new message, even if it has been said before.

What Dr. Leon is saying is that part of that new message should be that we have new data to also emphasize how important it is to recognize and identify and treat depression.

Just like it would be novel to have in a new warning some statement about protective effects, I think what you are also saying is it would be novel to have some statement calling the public's attention to the fact that you are emphasizing the need to treat. Is that a fair summary?

DR. PINE: Yes, Jean Bronstein.

MS. BRONSTEIN: Not to belabor it, but that is exactly what I was trying to say and Dr. Robinson and now Dr. Leon are very, very clear in saying what is put out about depression in the black box, that this is important. You've got to treat for depression and monitor, and then go into your specifics. We've got the specifics; we've got to use them.

DR. PINE: Dr. Goodman.

DR. GOODMAN: This statement is going to make me even more unpopular among my professional societies, but I am going to make it anyway. I am a little bit uncomfortable with using the term "protective effects" in the elderly. That is really the expected effect.

I mean, that is what everybody always expected is that if you administer antidepressants, that you are going to see less suicidality in your drug compared to your placebo group. It is only protective compared to the group in which you see a suicidality signal.

DR. PINE: Dr. Laughren and then Dr. Pollock.

DR. LAUGHREN: Yes. That is absolutely right, and that is why we wouldn't entertain adding this as a new indication, because they are after all antidepressants. That's why it says "the expected protective effect."

In other words, you are describing risks that are being seen, but then pointing out that these risks aren't necessarily uniformly

0410

distributed across the age spectrum, that other parts of that spectrum actually have the expected effect of the drug. It is a subtle difference. We hadn't intended adding this as a new claim to labeling.

DR. PINE: Dr. Pollock.

DR. Pollock: Yes. Just a comment about some of the things that have been said. As somebody that voted for the black box warning a couple of years ago, I actually feel better about that decision based on the new data that you have brought out today.

Because I think there really is evidence that there is some, to use what Dr. Goodman said, dose-response phenomena, that it really does seem that there was something that the drug is doing that in a vulnerable younger population the drug is increasing the risk. I think that certainly is the duty of the FDA to advise practitioners of that.

I think it is the job of other professionals and other professional societies to discuss risk-benefit. It doesn't seem to me that

0411

it is the mandate of the FDA beyond safety to start talking about the benefits of the drug.

I am concerned that also, again in these telegraphic messages, there are risks to the elderly that were underemphasized perhaps in earlier data such as hyponatremia from SSRIs or risk of GI bleeding, for example, or drug interactions.

You can't put all of this on a pinhead and say that you are governing medical practice. I think would really feel much better that really your job was really advanced by finding a real drug effect that seems to be age-associated.

I don't think necessarily, the other side of the coin, that it is the job of the FDA to necessarily say that it is protective in those older. I mean, it is the job of the rest of us

with other public health data and our studies to show the risk-benefit of these medications.

DR. PINE: I would like to just comment on two things that Dr. Pollock said. I do think it is significant that you make those points about the

0412

elderly population, given that is a population that you obviously have a lot of experience with, that you have some unease with aspects of the wording as it is in that it sends the wrong message, so that is number one.

Number two, I would actually like to hear from the FDA about another point that Dr. Pollock raised. I want to flesh out a little bit again, kind of looking historically over the last four to five years again, talking about the message that is being sent, which may or may not be intended, and just call your attention to this.

The message has come out that you, as the FDA, are doing more clearly than just talking about medications. When you read some of the language, you have talked a lot about diagnosis and treatment and how often people should be seen and the way that medicine should be practiced.

I have to say while I agree with the message that Dr. Leon was just spelling out, in terms of a key issue that has to come out, the public needs to know how important it is to

0413

identify and recognize and treat depression.

Again, it does feel like we are pushing you to regulate not so much the advertising of medications as much as a delivery of medical care. I mean, that would be the message in some sense.

I just wondered if you could comment on that and your take on it and what you struggle with in thinking about sending those messages.

DR. LAUGHREN: We generally don't want to get into practice of medicine issues, but the reason that we included fairly specific advice about monitoring in this warning statement came directly out of the last Advisory Committee meeting. There was a lot of testimony about concerns that patients were not being followed. Now, I know that the Committee didn't vote on that specific issue, but there was discussion about it.

Certainly, there seemed to be an awful lot of concern about the frequency with which patients were being monitored. The schedule that we ended up adopting for labeling was based directly actually on the TADs trial. That was the

0414

basis for that recommendation.

Dr. Goodman.

DR. GOODMAN: That's fine. I just want to underscore for those of you in the audience that it was not this Advisory Panel or the previously

constituted Advisory Panel in `04 that dictated or advised on the specifics of the schedule.

In fact, I think you guys did a great job in terms of the content, but that wasn't something that emanated from the Advisory Panel in terms of dictating how it should be put into practice.

DR. PINE: I do want to hear what Dr. Temple has to say, because I noticed him smiling as you were talking about how involved in talking about medical practice you want to be.

Because I do have to say that there is a bit of a disconnect in terms of what you're saying on the one hand versus the message that comes out of the Committee.

Dr. Temple.

DR. TEMPLE: Well, we like to say we don't dictate the practice of medicine, and of

0415

course we don't specifically. But if there is advice that is necessary to the safe use of a drug, we do want to put that in label and with some drugs, clozapine or something like that. We go further and we enforce certain good practices. I mean, that is what risk management plans and things do.

What is difficult is something you have touched on a little bit, and that we don't often do, which is sort of promote use. We assume that companies will, on the whole, take care of that and August societies will take care of that.

For example, the idea that depression is really bad, so you better think about treating it, is not the sort of thing that goes into labeling until you have a mortality outcome, in which case it does.

Lipid-lowering drugs all have mortality findings, so they get to claim that. We are actually close to what you're talking about a little bit. None of the antihypertensive drugs have had outcome claims up to now.

0416

We have actually been to the Advisory Committee with an intent to put outcome claims in a generic way for the treatment of lowering blood pressure because we know it would decrease strokes. We've got a lot of evidence. That is as close to sort of promoting the virtues of use as we get. We don't usually do that in the absence of a specific finding.

Whatever we may think, I mean, everything I've heard says you really should treat depression. It's sort of a so said. You should treat something, that's a so said. However, until there is a specific claim involved, it is very hard for us to communicate those things. Although, I understand what everybody is saying, that you don't want it to be unbalanced as if it is all negative.

That is hard for us.

DR. PINE: All right. What I think I'm going to do now, we have about a little more than an hour. I'm going to ask that we take a 10-minute break, then what I'm going to do is I'm going to summarize all of the discussion, and then we are

0417

really going to take about 45 to 50 more minutes to close and consider if there are any more specific recommendations we have to give. In 10 minutes sharp, we're going to start.

(Recess.)

DR. PINE: If committee members could have a seat, we will finish in the next 45 minutes.

I thought what I would do as we get started is I might summarize where I think we are in terms of what the global message from the Committee has been to the FDA. I think that there are four main points that, while we could quibble about the details, I think seem pretty uniform.

Then, there is one major last point that I would like to make sure we focus on in the remaining 45 minutes, but then also ask any of the other committee members to bring up any other major points in the next 45 minutes so that we can end promptly at 5:30.

Point number one, as I see it, is that the Committee seems in agreement that there is evidence of a causal association between the use of

0418

antidepressants and suicide thoughts or behavior, and this relationship does show a meaningful relationship with age, so that is number one.

Point number two, the Committee has raised clear concern about discouraging the treatment for depression, on the one hand, but the Committee has also clearly said that they do not want to reconsider in any way reversing the black box that current exists.

Number three, the Committee spent a fair amount of time noting the importance of paying a lot of attention to the precise message that is sent from the Committee and from the FDA and to think about some novel ways of trying to evaluate the potential effects of those messages.

Number four, there seems to be pretty good agreement on the core features of the working that you recommended; although, there was clear lack of consensus on the issues on the issue of how to discuss age, how precise and how specific to be.

I heard opinions both for and against

0419

talking about it and about how to mention exactly the nature of the effect in the elderly. Again, I heard some people recommending to emphasize the potential protective effect and other people not

mentioning that.
Also, then, there was walking the line between encouraging the appropriate treatment of depression much in the same way one would encourage the proper monitoring of a white blood count in an individual being treated with clozapine, on the one hand, but, on the other hand, not encouraging use in an inappropriate fashion.
Again, I think on those four points -- the existence of a phenomenon and its relationship with age, the concern about discouraging treatment but not wanting to reverse a black box, paying a lot of attention to the message, and basic agreement with the wording -- again, I think the message has been pretty clear.
The main issue that we really have not talked about at all, we have kind of avoided it, is what is the feeling about how this message should
0420
be packaged, specifically, the issue of what is the feeling of the Committee about simply extending the black box.
That is the main issue that I really want to spend at least a good half hour on in terms of talking about the black box issue in particular.
Dr. Goodman, will you start us off?
DR. GOODMAN: Yes. I just want to quibble with one of your summary remarks. I think in the first one you talked about the relationship between drug and suicidality as being causal. I think I know what you mean, but I just want to inject some qualification in that.
At least the way I conceptualize this phenomenon, even in those people where it ultimately produces suicidal ideation or behavior, it is not an overnight change.
I think there are intervening state changes that occur, that if we could identify them, hopefully, we would see some precursors to it.
I don't think there is a suicide gene that we have that gets expressed in certain
0421
vulnerable individuals. To use the word "causal" I think that will be picked up and seized. Some individuals may say, "Well, we believe that these pills induce people to become suicidal."
I think that what we are suggesting, and this is part of the intention of the monitoring, is that even in those individuals who might have that susceptibility, with appropriate dosing and close monitoring, we may be able to intervene before they reach the point of exhibiting suicidal ideation or behavior.
DR. PINE: Gail Griffith.
MS. GRIFFITH: I don't mean to quibble with you either, Dr. Pine, but I just would suggest that when we talk about your item number two, that

the Committee doesn't want to "reverse" the black box, I think that "revisit" is more accurate.

I think that a lot of us around the table expressed the notion that we would probably not have voted for a black box labels had we known the consequences. I would suggest that, too, it might be appropriate to revisit the black box at some

0422

future date when there is more data.

DR. PINE: Thank you. I misspoke. We do not want to revisit the black box, that's right.

Yes, Jean Bronstein.

MS. BRONSTEIN: Before we move on to your last question, I would like to just throw out there for future research maybe mandated a request from the FDA to the drug industry to look at activation syndrome and akathisia and see what kind of signal that shows in relationship to suicide.

DR. PINE: Other comments or comments specifically about the issue of a black box, extending the black box?

MS. GRIFFITH: Could I ask a question?

(No response.)

MS. GRIFFITH: Are you asking us to give the FDA advice, are you suggesting that we tell them whether or not to include this information in the black box?

DR. PINE: The way I read it, based on the presentation that the FDA gave, is that it their intention is to add some version of the

0423

language that we saw, that I think is up there, some version of the language to the current black box. In effect, what that would do is that would extend the black box.

When the FDA clarified to us that that was their intent, my impression that I got around the table is that there was a fair amount of unease.

The FDA in turn picked up on that unease and thought it was legitimate, on the one hand, but then kind of said, "So, well, what do you want us to do? Because we've also said we've got to do something." That is kind of where we are now.

It seems clear to me that there is hesitation in the Committee to simply endorse the suggestion that Dr. Laughren and Dr. Temple put on the table, which was to extend again the black box in the way that it is up there on the one hand. On the other hand, I think there is also hesitation about, well, what exactly would we do if we didn't do that, and that is really the issue that I would like to hear discussed.

0424

Dr. Goodman.

DR. GOODMAN: I for one wouldn't endorse you going ahead and modifying the current language

within the black box to extend the age range basically to add these data. As I mentioned earlier, I don't see any viable alternative to including it within the existing black box.

Again, we have already concluded that we are not about to revisit that question. Therefore, just procedurally I can't imagine how you would treat it separately. As long as we're talking about within the box, it has got to be in there.

DR. TEMPLE: At least in part because it is more information about the very thing that you are talking about in the box but with additional information about the other age groups. It sort of seems hard to leave it unmodified now that you have more information. I think that's what we thought.

DR. PINE: Dr. Laughren.

DR. LAUGHREN: We can't also take your advice about somehow modifying the overall statement to give it better balance. We have to do

0425

this very carefully, but it is something that we certainly could think about doing.

DR. PINE: Other thoughts?

Dr. Goodman.

DR. GOODMAN: Yes. In terms of the other kind of modifications, some of the things that were mentioned earlier, one, is to put the risk in perspective. I mentioned earlier I liked the way the data was presented.

I think people can understand looking at a denominator of 1000 that there is a 14 out of 1000 chance that if taking the medication compared to taking placebo, you might experience increases suicidal ideation behavior, at least in the younger group.

Now, where it gets complicated is that now you have to present whatever that next number is. What is it? Six for the next age bracket?

DR. STONE: Four.

DR. GOODMAN: Four. I understand that it could be a little bit daunting, but one of the problems that I have encountered in trying to

0426

translate the black box down to the individual patient level is really putting it in perspective. I think unless you put some numbers in there I think it is going to be very hard for the average citizen to understand what kind of risk.

DR. TEMPLE: The current one gives a number that basically says the risk goes from 2 percent to 4 percent for that. I mean, that's pretty easy to understand. These numbers are considerably lower, for whatever reason.

DR. PINE: Gail Griffith.

MS. GRIFFITH: I am terribly concerned about this particular age group, the 18 to 24 year olds, given the stats, being the second leading

cause of suicide in that age group.
Just knowing that that demographic is oftentimes on their own, they are not legally beholden to parents who are overseeing the treatment regime and they are not required by any institution to take medication, I think that they are very likely to be undertreated or just opt out on their own.

I don't know how we get around this, but I think that that is a very vulnerable age group, probably one of the most vulnerable. In my mind, the black box is a semantic, but it's a terrifying semantic.
If it is up to a 19-year-old kid to seek treatment and all of a sudden they are told, "Well, you know, there is this black box, you don't want to do that," I think it has a huge deterrent effect.
DR. PINE: Just to push you a little bit, one could interpret your comment as either encouraging an extension of a black box because we want to be particularly cautious in that age group, on the one hand, or one could interpret it as you would feel uneasy about a black box and you would discourage it because you think that it would interfere with access to treatment. Which of those two?
MS. GRIFFITH: It is the later. I fear that they don't seek that treatment. They are no longer at home and they are no longer being

supervised by family or by a caregiver. They can make decisions on their own. Given that they are at such terrible risk, I see it as a deterrent writing it in the black box.
DR. PINE: Yes, Dr. Laughren.
DR. LAUGHREN: Again, what I thought I was hearing and what we are prepared to think about doing is keeping the box but putting it in a context that gives it more balance.
I mean, I'm looking at the current box and it starts off with the sentence "Antidepressants increase the risk of suicidal thinking and behavior in short-term studies in children."
Many pediatricians and family practitioners, when they start reading the box, that would be it. They might stop at that point. If you put this in the context that is being described here, the fact that depression is a serious illness, we might be able to not soften the risk, but give the message better balance. I mean, that is sort of what I thought I was hearing.

DR. PINE: Dr. Leon.
DR. LEON: Yes. I like that. I want to

follow up on what Dr. Temple said. The 2 percent versus 4 percent, the last line in the black box right now, I think is the most interpretable.

Providing these new numbers of less than 1 percent versus even further less than 1 percent would also put it in context. It is a very small risk. That should be a part of it. We're making this a big, black box.

DR. PINE: Gail Griffith.

MS. GRIFFITH: It is still a black box, and perception is everything.

DR. LEON: Well, it is still a black box, but I still think that it is possible to modify the language so that we don't discourage appropriate use. I mean, that's what, it seems to me, everyone is concerned about not wanting to do.

I think we can certainly take your advice and struggle with this and try and make it a more balanced message without avoiding talking about what we see as risks.

0430

DR. PINE: Dr. Robinson.

DR. ROBINSON: Two points: one is I think it is more appropriate to rethink the black box, in the sense of putting the potential benefits into it, because the pediatric one was a time when the studies essentially for antidepressants in the pediatric group were all showing no efficacy and all we had was risk.

That sort of is the way the black box -- it doesn't start off saying suicide is part of depression and these medicines can help because we had no demonstration of efficacy, whereas if we are going to talk about black box for antidepressants in adults and in geriatric populations, it is much more appropriate to talk about some of the benefits. Because obviously these drugs have efficacy in these age ranges.

Also, in terms of your question about the 18- to 25-year-old, I was one of the people who voted for the black box for the pediatrics. I again come back to the thought that I had when I voted the last time, which is if there is really a

0431

risk that we think the data has shown and it's a potential risk that involves death, how can we not let people know that?

I think what we are all struggling with is that doesn't mean you shouldn't be treated. There are sort of practice guidelines in education that should be done for clinicians so that they don't automatically say that.

The problem is that is not really an FDA type activity; that is the activity of practice organizations and things like that. I think that is one of our difficulties. The professional organizations for the GPs should be teaching them

how to do this right. That is not our mandate.
DR. PINE: I do think Dr. Temple did address that with the last comment right before the break. I don't want to put words in your mouth and maybe you could say it a little bit more accurately.
However the FDA does feel compelled, if part of the appropriate prescribing of medication is to do certain things, and justified to

0432

communicate that.
There are instances where they will make statements about things that do not directly involve giving the medication to a person because they feel it is part of the delivery of the medication.
MS. GRUDER: (No microphone) Two years ago, this Committee stood and said that the risk only applied to children and adolescents. It was a lie then and it is a lie now because they apply to adults as well.
DR. PINE: I'm sorry.
DR. REESE: Ma'am, if you could please identify yourself for the record?
MS. GRUDER: (No microphone) It applies to everyone, not just children.
DR. REESE: Ma'am, we need you to identify yourself.
MS. GRUDER: My name is Deborah Gruder. My husband was 52 years old when, after 13 days, he killed himself when taking Paxil. He was not diagnosed with depression. He never tried to kill

0433

himself before.
For you to sit here and say that it only applies to a certain age group, it is a lie. It is just a complete lie. What it does is it gives other people false security that they are secure to take these drugs.
THE AUDIENCE: Yes.
(Cheers and applause.)
DR. PINE: Because this is no longer an open forum, we cannot have any further comments from the audience.
Dr. Temple.
DR. TEMPLE: Well, it's worth noting that the labeling does recognize the possibility that people who are depressed and maybe have other illness can get worse. The labeling doesn't say we know why they get worse, whether it is the drug or lack of effect.
I don't believe any individual case can reveal which those is. That is not to dismiss them as unimportant. They are obviously unbelievably important to the people they happen to, but it is

0434

not easy to know the ideology.

The only thing I was saying before is that whatever our personal beliefs about how important it is to treat depression, those things don't go in the label because they are sort of claims.

A claim, I might believe that it has something to do with suicide, but there is no documentation of the kind that would allow a claim for that, at least not that we are aware of.

It is not easy to write a balanced statement about that even though in your gut you think maybe it is a good idea to pay attention to treating people, but it is very hard to put things like that in labeling -- and we almost never do.

It is even worse than that. We very infrequently use epidemiologic data or group data like that to support a claim, and there isn't going to be any other kind of data to support that claim. It is very hard to balance it in that way.

As Tom was saying, there might be some things to point out, which is that "Depression is

0435

associated with suicidal thinking and behavior and even suicide. It is complicated. Here is some more information about it." I don't know whether we could get to something like that, maybe.

DR. PINE: Jean Bronstein.

MS. BRONSTEIN: I didn't ask to speak, but thank you. I really believe we have an obligation to warn the public, and I'm comfortable with expanding this as we have just been talking about.

I understand it is going to be a balancing act, but I think we do have two major things to balance it with about depression and suicide and monitoring. I think those things have to be pumped up as well as giving the warning.

DR. PINE: Let me make a bit of a summary statement and then a comment. What I am hearing from the Committee pretty clearly is that the strong feeling from a clear majority of the Committee is that these types of statements really should be reflected in the black box.

I have to say I have heard very little

0436

disagreement with that. Gail Griffiths, I took your statements as a disagreement. I would say that I would disagree with it, that I'm not so sure that I would at this time recommend just going forward and doing that. The problem is I am equally uncomfortable doing nothing.

I'm not sure that in the next half hour we can decide what is the right thing to do. Although I will say this, that my sense from just listening to the Committee and the feeling from the Committee is if we did take a vote, my sense is that the motion would clearly pass. The Committee

would recommend that this exact or some version of this wording be inserted into the black box.

I would say that I'm perfectly willing to do that in 15 minutes. Maybe we will do that in 15 minutes, unless anybody objects.

Other questions or comments?

DR. LEON: Well, I think extending it up to young adults, age 25 or whatever we choose, the tradeoff there is if the black box warning is extended in that way, but at the same time modified

0437

in the way that Dr. Laughren mentioned about the introduction about the need for treatment and that suicide is a symptom of depression, I would be comfortable with that.

I feel like it is a bit of a tradeoff. We are making part of it a stronger warning, but at the same time stressing the need for some form of treatment.

DR. PINE: Dr. Goodman.

DR. GOODMAN: Just one thing. I think we would have trouble saying anything about the need for treatment. We could say something about how depression is associated with a lot of bad outcomes.

DR. LEON: The risk of nontreatment.

DR. GOODMAN: It is hard to go that next step and say what you don't really have data on.

DR. PINE: What? You can say the risk of nontreatment, but you can't say the importance of treating?

DR. TEMPLE: I didn't say the risk of nontreatment; I said the risk of depression. I

0438

mean, depression is associated with the following things. You didn't hear me say anything about nontreatment.

DR. PINE: Yes. I guess Dr. Leon said the risk of nontreatment, which clearly they can't say.

DR. TEMPLE: That could be hard for us, very hard. It would be, it would be very hard.

DR. LEON: Maybe, Dr. Laughren, could you repeat your first two sentence or three sentences you are proposing?

DR. LAUGHREN: Well, all I was pointing out is that the current box starts off with a fairly strong statement about risk. What I was suggesting, and this is basically what I was hearing from the Committee, is a need to somehow balance that with more information about the illness.

Again, as Dr. Temple was suggesting, there are various ways of doing this, short of adding a claim which doesn't have any solid basis.

DR. PINE: Dr. Mehta.

0439

DR. MEHTA: I heard what Dr. Robinson said earlier that there is nothing sacrosanct about age 25. However, if it becomes very fuzzy and then one extends it up to 30, then you are going to lose a lot of patients right up to 30 years of age. I mean, the use of antidepressants will go down in that group right up to age 30.

DR. PINE: Other comments?

Okay. Gail Griffith.

MS. GRIFFITH: Yes. I would have a hard time voting on something without looking at very specific language as to what we are going to put in there. I don't know about other members of the Committee, but I am uncomfortable about taking sort of a temperature on this issue.

Is there any possibility that something could be circulated to the Advisory Committee for comment that would show the language that was intended for the labeling?

DR. LAUGHREN: If we are going to have interaction with the Committee, it has to be in an open public meeting. There isn't any other

0440

mechanism.

DR. PINE: Maybe let's do this, because I think we are pretty clear on one issue. One issue is the acknowledgment of the need to alter the labeling in some form to communicate the information again in some form that is listed on the slide.

My sense is that there is strong unanimity at that point. Maybe if we could vote on that issue as a group first, and then we can try to call the question to a more specific issue, unless anybody has an objection.

Do you want to do this first, Dr. Pollock and Dr. Mehta, or do you want to make your comment?

DR. Pollock: I didn't have a comment.

DR. PINE: Oh, you can't vote. They can't vote, okay.

So the issue to vote on is for or against whether the Committee feels that there is a need to alter the current labeling in some form to communicate the information that we heard today related to the age modification between suicidal

0441

thoughts and behavior. Why don't we start with this (pointing) end of the table?

DR. GRIFFITH: Yes, I can go along with that.

DR. GOODMAN: Yes.

DR. PINE: Yes.

DR. LEON: Yes.

DR. SLATTERY: Yes.

DR. SCHULTZ: Yes.

MS. BRONSTEIN: Yes.

DR. ROBINSON: Yes.

DR. PINE: All right. We uniformly agree, and again all the discussion has been around that, that you need to alter the label, number one.

Number two, I think we've got to decide now do we want to bring to the floor the question of voting on adding that language into the black box. I am fine, if we vote on it.

I also think that if we do vote on it, it is clearly going to be very early in the process of discussing it, but I think we need in the next five

0442

or ten minutes we need to reach consensus about whether it is time to vote on that issue or not.

MS. BRONSTEIN: I would like to ask the FDA whether they feel like they have a sense of what this Committee is already -- I think we have chewed this myself. I think we have already expressed our opinions. I wonder if you feel like you need anything further, particularly in the way of a vote?

DR. LAUGHREN: I don't feel the need for a vote on this issue. I think I have a pretty good sense of what the consensus of the Committee is.

DR. PINE: I don't feel a need for the vote. Again, I would agree I feel that I have a consensus of the Committee.

Do other people feel the need for the vote?

(No response.)

DR. PINE: So I will open it up for other issues to bring to the FDA related to this? More research? Specific things that we need research on?

0443

DR. LAUGHREN: Do we want to summarize what we think the consensus is before?

DR. PINE: My feeling of the consensus is that the Committee is divided in terms of whether or not this exact language should be added into the black box, but the majority of the opinions that have been expressed by the majority of people is that -- oh, you want to disagree with that?

DR. LAUGHREN: No, no, no.

DR. PINE: All right. The majority of the opinions that I'm hearing is that the Committee does feel, if you need a yea or a nay, that the language should be in a black box.

Now, I also am hearing from some of the people who have said that, that they don't feel that we are ready to really vote on that. But again, the feeling of the Committee is if it's either yes or not -- yes, go ahead Dr. Temple.

DR. TEMPLE: Well, there are probably some people who aren't sure whether they want to vote that there should still be black box. Leaving that aside, suppose we assume that there is a box.

0444

DR. PINE: We should assume there is a box.

DR. TEMPLE: Then, the question is shouldn't this new information, which I note is related to the thing that is already in the box, shouldn't that go in the box, too; and if not, where would you put it? What would you do with it?

DR. PINE: I guess what a lot of people are saying is they don't necessarily feel ready to vote on the box, that we very well might end up making that recommendation.

I guess we feel a little torn, with a decision really at the end of a long day of a very difficult issue, where we don't want to make an error on either side, avoid making an impulsive decision either way.

DR. TEMPLE: Well, again, let me distinguish. You may not be ready to pick the exact language. Let's ignore that question. Would you feel comfortable voting on the question of whether some version of the new information ought to go in the box with the pediatric stuff? Is that

0445

right?

DR. PINE: I'll look for comments from the Committee.

Dr. Leon.

DR. TEMPLE: Without picking the exact language yet.

DR. LEON: Well, as you said at this earlier summary, we want to extend the age in the black box and at the same time not discourage treatment. That is a tough balance.

DR. TEMPLE: I think Tom addressed that. We will certainly think, but we are not ready to propose language yet, about some way to provide context without giving a claim that isn't merited and all that.

I think the only question, and I don't think that hard on this, is whether the new information should be in the box or somewhere else? I guess I would advertise, How can it be somewhere else when it is talking about exactly the same thing?

DR. PINE: I think that is the issue,

0446

that is exactly the issue.

Dr. Goodman.

DR. GOODMAN: Given all the constraints that we have already discussed, I certainly favor including language similar to this in the existing black box extending the age range of concern.

I think that should be balanced, however, with some statement or statements that suggest the risk of not treating depression. I'm not sure exactly what you would be comfortable with.

Could you say something like the following, "These data do not address the risk of suicidality in untreated depression," and if you are really bold, you would go on and say, "which is widely believed to be significant," or something to that effect?

Even if you can't do the second part, I think for the benefit of people reading this or trying to interpret it, that it needs to be clear that the risk on placebo in these clinical trials is not the same as the risk of suicidality in untreated depression.

0447

DR. TEMPLE: Well, Tom and I were schmoozing. We think we can probably figure out something to say along those lines without, however, bending over to give a claim suggesting that we know that treatment fixes that.

DR. PINE: Maybe let me do this. I mean, it seems a little extreme, but I think I would like to call a vote on whether we want to vote on the black box. We can decide that right now. Either yea or nay whether we want to have a vote today, or whether we want to put it off for a later meeting?

DR. LAUGHREN: What you means is extending the current black box?

DR. PINE: Extending the current black box.

DR. LAUGHREN: On all labels?

DR. PINE: Yes, extending the current black box.

Jean Bronstein.

MS. BRONSTEIN: I would like to hear what we said yes to before, because I think we said yes to this.

0448

DR. PINE: No, no, we said yes that we want to change the labeling. We said yes that we wanted to modify the message that has been sent. We all agreed with that.

MS. BRONSTEIN: Did you not precede that by saying something about --

DR. PINE: No, no.

MS. BRONSTEIN: I misunderstood.

DR. PINE: We all agreed with that. Why don't we start with Dr. Robinson whether we want to call --

MS. GRIFFITHS: Dr. Pine, excuse me again. Could you just restate what it is you're asking?

DR. PINE: It's not clear to me whether people want to take a vote on extending the current black box or not. We have heard a couple of people say that they don't feel ready to vote. We have heard a couple of people saying that.

Yes, Dr. Temple.

DR. TEMPLE: Well, there is an

assumption. Assume for the present that the black box is still there.

DR. PINE: Right, correct.

DR. TEMPLE: Now we are talking about where to put the new information that the first vote said should go on the label, where to put it.

One place is to put it in the box, and the other choice is to put it somewhere else in some other part of a warning section. Those are the choices. Avoid the discussion of whether you like the box, because obviously the Committee feels various ways about that. Assumes that the box persists. Is that clear?

DR. PINE: I'm going to state for the record that the point that we are voting on right now is whether we want to call a vote to either support or not support Dr. Temple's statement. Do we want to call that vote now, or do we not want to call that vote? We will start with Dr. Robinson.

DR. ROBINSON: I think we should call the vote.

DR. PINE: Dr. Pollock.

DR. ROBINSON: He is not voting.

DR. PINE: Jean Bronstein.

MS. BRONSTEIN: Yes. Yes, that's fine.

DR. PINE: Dr. Slattery.

DR. SCHULTZ: I still want to clarify we are again talking about putting this new information, as you well described, in the black box or not in the black box?

DR. PINE: The issue now is whether we want to vote on that. Do you want to call a vote on that?

DR. SCHULTZ: Yes.

DR. PINE: Yes.

Okay. Dr. Leon.

DR. LEON: Yes.

DR. PINE: Yes.

DR. GOODMAN: Yes, I want to vote on it, and then I want to vote yes on the next question, too, just get it out of the way.

MS. GRIFFITH: Yes.

DR. PINE: All right. We have all decided that we want to change the labeling. We have all decided we want to vote on whether or not we want to extend the current black box. We have all decided that. All right, so the last thing that we are going to vote on now is whether we are in favor in some form taking all the --

DR. TEMPLE: Putting the information you agreed should be in the labeling in the first question into the box?

DR. PINE: Correct, correct. That is the last thing that we are going to vote on.

Dr. Schultz looks confused. Now do you understand?
DR. SCHULTZ: I'm chronically confused, but I think I understand, I think.
DR. PINE: Any other questions or comments before we call this issue for a vote?
(No response.)
DR. PINE: All right. Just so everybody is clear, the issue we are voting on now is whether we want to make a recommendation to the FDA that the current language that we have recommended adding, that we have unanimously agreed on needs to be added, are we in favor of that being added in the black box or are we in favor of it being added
0452
somewhere else?
In favor of the black box or not, add it into the black box or not?
You still have questions, Gail?
MS. GRIFFITH: (Moving head from side to side.)
DR. PINE: No? Okay.
DR. SCHULTZ: I don't mean to be facetious, I am chronically confused, but am I understanding correctly that we are voting on language that has yet to be determined? And we are voting on that that language will be placed within the black box?
DR. PINE: That is correct.
DR. SCHULTZ: The language is as yet indeterminate?
DR. PINE: That is correct.
DR. GOODMAN: Could I just say, that happened last time, too, so there is a precedent.
DR. PINE: That did happen last time. I think that you've heard our discussion, and you are pretty clear on what all the issues are.
0453
Dr. Robinson.
DR. ROBINSON: I think instead of saying this language is really saying that this information is data, because all of us I think have had questions about exactly how this is going to be phrased, we are really saying this information should be included in the black box.
DR. PINE: That is correct, that is what we're saying. That is what we're voting on.
Any other comments?
Jean.
MS. BRONSTEIN: (Moving head from side to side.)
DR. PINE: Okay. Where did we start last time?
DR. REESE: We started with Dr. Robinson, just start with Dr. Griffith.
DR. PINE: Okay. The question is for or against do you want to extend the current black box labeling in the way that Dr. Temple said. At the

risk of confusing everybody again I won't restate it.

Do we want to modify the current black box to include the new information that we talked about today or not?

VOTE

DR. GRIFFITH: I vote no.

DR. GOODMAN: Okay. I vote yes, with the caveat, if I'm allowed, that it also would include some information about what these data do not tell us, namely, they do not give us an estimate of the risk of suicidality with untreated depression.

DR. PINE: I vote no.

DR. LEON: I vote yes, with the same caveat that Dr. Goodman has.

DR. SLATTERY: I vote yes, also with the same caveat.

DR. SCHULTZ: I vote yes, but with the same concern about information on untreated depression.

MS. BRONSTEIN: I also vote, yes with the same caveat.

DR. ROBINSON: I vote yes, again with the same provisions.

DR. PINE: I counted six in favor and two nos. I have to say even though we might have confused everybody over the last 20 minutes, that was my sense of the Committee.

Are there other questions or issues that you would like us to address?

(No response.)

DR. LAUGHREN: I think this has been very helpful. The only other issue that I would just call everybody's attention to before we do finish is that there have been a number of other current research avenues that people have talked about, and we haven't had as much time to talk about those.

Does anybody have any other further specific issues that they want to put on the table in terms of future research?

MS. BRONSTEIN: I'm just wondering whether my request has really been heard about further research and activation syndrome?

DR. TEMPLE: Can you say more? Is this something you would like to see in all trials, that is, have a defined activation syndrome before the trial so that people would look for particular things? That just may be my ignorance, but I didn't quite understand what you were asking for.

MS. BRONSTEIN: I think both in the hearings in `04 and again today, we are hearing more than just a little anecdotal information about activation syndrome.

I would like to see, actually I think the

data is probably already there, perhaps asking the drug companies to analyze all of their data for this information.

Maybe if I could clarify because again I've heard Jean Bronstein talk about this for two or three years. The point that has been made is that there is a fair amount of feeling that part of the story that might help explain the association between SSRIs and suicidal thoughts or behaviors is a potential association with an activation syndrome.

That point has been made, but there has not been a systematic series of studies designed to look at that question, nor has there been an

0457

obvious encouragement to do that. I think that's the point she is trying to make.

Yes, Dr. Laughren.

DR. LAUGHREN: I think we are all in agreement that that is going to be a useful avenue to pursue. Whether or not we have in the existing database enough information, I'm really not optimistic that it's there. I know there are some efforts underway to prospectively look at that question.

I think it's the kind of thing where you really need to collect, very carefully collect, information if you're going to be able to go down that path. I am not optimistic that we have the kind of information that we would need to explore that in our existing data.

DR. PINE: Dr. Leon.

DR. LEON: Along the same line, when protocols are submitted to you for studies or clinical trials that are about to be conducted, are you now making sure that careful assessments of suicidal ideation and attempts are administered? I

0458

would encourage that.

DR. PINE: We are. One of the problems is exactly what method to use to assess for suicidality is not so clear-cut. There are different approaches.

Yes, I mean, the issue of exploring for suicidality is generally a part of the discussions that we have with companies at end of Phase II meetings. More research is needed along those lines as well.

Dr. Temple.

DR. TEMPLE: Well, let me ask my favorite question, which is whether there is enough uncertainty about what to do long-term with people to carry out a trial of continued long-term therapy with antidepressants versus interrupted therapy followed by watchful waiting.

It seems to me that's the only way we are ever going to get the answer on whether serious

events are prevented, but there would have to be doubt in the community sufficient to allow those two choices. I'm curious what people think about it. That is a vast undertaking, obviously.

DR. PINE: I mean, I think most people would probably agree that we know a lot more about acute treatment than we do about chronic treatment.

Whatever we can do to increase the knowledge base in terms of the long-term safety and the long-term efficacy, that would be a very good thing. Of course, the devil is in the details, which I'm not sure we have time to talk about.

DR. TEMPLE: Probably not. I mean, you have to randomize people to these two things. There would have to be uncertainty about what the best treatment is. I'm not sure, I don't have any idea whether there is that level of uncertainty. Maybe another time we will talk about that.

DR. PINE: Dr. Leon.

DR. LEON: Given the rare nature of the event, the sample size would have to be fairly substantial.

DR. PINE: I think I have heard everything from the Committee. I do want to make just a couple of closing remarks. Again, I think I want to return to some of the sentiments that we heard about towards the end of the morning and that I commented upon right before lunch.

I think it is really an extraordinary time in that we are dealing with incredibly important issues. I think the level of emotion really speaks to how important these issues are.

Again, both the issues of recognizing the importance of treating mental illnesses, on the one hand; but then, number two, effectively balancing efficacy and safety issues.

I have to say that I am very thankful for the deliberations both of the FDA and the Committee. I do think that with a very difficult, complicated issue relatively clear consensus did emerge. I appreciate everybody for their efforts on that behalf.

DR. LAUGHREN: We appreciate your efforts as well. It is a difficult topic, and I think it has been a useful discussion.

DR. PINE: Thank you. The meeting is adjourned.

(Whereupon, at 5:30 p.m., the meeting was concluded.)

* * * * *