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

Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) and the Psychopharmacologic Drugs Advisory Committee (PDAC)

Thursday, July 10, 2008

8:00 a.m.

Sheraton College Park Hotel
4095 Powder Mill Road
Beltsville, Maryland

PAPER MILL REPORTING
(301) 495-5831

C O N T E N T S

C O N T E N T S

(Continued)

P A R T I C I P A N T S

Larry B. Goldstein, M.D.,
Chair

Yvette Waples, Pharm.D.
Designated Federal Official

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Britt Anderson, M.D., Ph.D.
Lily K.F. Jung, M.D., M.M.M. (Consumer Representative)
Ying Lu, Ph.D.
Matthew Rizzo, M.D.
Stacy Ann Rudnicki, M.D.

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

Roy E. Twyman, M.D.

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jorge Armenteros, M.D.
Rochelle Caplan, M.D.
Gail Griffith, M.L.S
Susan L. Schultz, M.D.
Robert F. Woolson, Ph.D.

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

William Z. Potter, M.D., Ph.D.

TEMPORARY VOTING MEMBERS

Ruth S. Day, Ph.D.
Sid Gilman, M.D. FRCP
Wayne Goodman, M.D.
Andrew Leon, Ph.D.
Richard Malone, M.D.
Daniel S. Pine, M.D.
Delbert G. Robinson, M.D.
Andrew Winokur, M.D., Ph.D.

P A R T I C I P A N T S (CONTINUED)

DRUG SAFETY AND RISK MANAGEMENT VOTING MEMBERS

Sean Hennessy, Ph.D.

PEDIATRIC ADVISORY COMMITTEE VOTING MEMBERS

Melissa Hudson, M.D.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH PARTICIPANTS (Non-Voting)

Robert Temple, M.D.
Russell Katz, M.D.
Tom Laughren, M.D.
Alice Hughes, M.D.
Evelyn Mentari, M.D., M.S.
Mark Levenson, Ph.D.

P R O C E E D I N G S

Call to Order

DR. GOLDSTEIN: Good morning. My name is Larry Goldstein and I am the Acting Chair for this joint meeting. It should be a very interesting discussion and again just to start, for those of you who have not been at these things before, the purpose is really for the FDA to hear the Committee's views and to hear the discussion.

The voting that will take place based on questions that they ask is important to give an overall sense to the FDA, but really, the main purpose is for them to hear the discussion of our views about the questions and issues that they have asked us here for.

To begin with, we have to read into the record the Conflict of Interest Statement.

Conflict of Interest Statement

DR. WAPLES: The Food and Drug Administration, FDA, is convening today's meeting of Peripheral and Central Nervous System Advisory Committee, the Psychopharmacologic Drugs Advisory Committee, and representatives from the Pediatric Advisory Committee, and the Drug Safety and Risk Management Advisory Committee of the Center for Drug

Evaluation and Research, under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the Industry Representative, all members and temporary voting members of the Committee are special Government employees, SGEs, or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of these Committees' compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, are being provided to participants in today's meeting and to the public.

FDA has determined that all members and temporary voting members of these committees are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has

authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, the members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for the purposes of 18 U.S.C. Section 208 their employers. These interests may include investments, consulting, expert witness testimony, contract/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

For today's agenda, the Committees will discuss and make recommendations regarding the results of FDA's analysis of suicidality, both suicidal ideation and behavior, from placebo-controlled clinical trials of 11 drugs; carbamazepine (Carbatrol), Equetro, Tegretol, Tegretol XR, felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine

(Gabatril), topiramate (Topamax), valproate (Depakote, Depakote ER, Depakene, Depacon), zonisamide (Zonegran). This is a particular matter of general applicability.

Based on the agenda and all financial interests reported by the Committee members and temporary voting members, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

Additionally, we would like to disclose that Dr. Roy Twyman and Dr. William Potter are serving as non-voting industry representatives, acting on behalf of all regulated industry. Dr. Twyman is an employee of Johnson and Johnson, and Dr. Potter is an employee of Merck.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committees of any financial relationships that they may

have with any firms at issue.

Thank you.

DR. GOLDSTEIN: Thank you.

I would like the people sitting around the table, the members of the Committee and FDA staff, to introduce themselves.

Introduction of the Committee

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

DR. LAUGHREN: Tom Laughren. I am the Director of the Psychiatry Products Division.

DR. HUGHES: Alice Hughes. I am Deputy Director for Safety in the Division of Neurology.

DR. MENTARI: Evelyn Mentari, Clinical Safety Reviewer, Division of Neurology.

DR. LEVENSON: Mark Levenson, Statistical Safety Reviewer, Office of Biostatistics.

DR. DAY: Ruth Day, Director, Medical Cognition Laboratory, Duke University.

DR. ARMENTEROS: Jorge Armenteros, Child and Adolescent Psychiatrist.

DR. CAPLAN: Rochelle Caplan, pediatric

neuropsychiatrist at UCLA.

MS. GRIFFITH: I am Gail Griffith. I am the consumer representative to the Psychopharmacological Committee. I am a writer on mental health issues.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I do drug safety research at the University of Pennsylvania.

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

DR. SCHULTZ: Susan Schultz, geriatric psychiatrist at the University of Iowa.

DR. GILMAN: Sid Gilman, clinical neurologist, University of Michigan Medical Center.

DR. RUDNICKI: Stacy Rudnicki, adult neurologist, University of Arkansas.

DR. GOODMAN: Wayne Goodman, psychiatrist at the National Institute of Mental Health.

DR. GOLDSTEIN: I am Larry Goldstein. I am from Duke University.

DR. ROBINSON: I am Delbert Robinson. I am a psychiatrist at the Albert Einstein College of Medicine in New York.

DR. PINE: Danny Pine, psychiatrist from the National Institute of Mental Health, Intramural Research Program.

DR. JUNG: Lily Jung from the Swedish Neuroscience Institute. I am the consumer advocate.

DR. WOOLSON: Robert Woolson, biostatistician, Medical University of South Carolina, Charleston.

DR. LEON: Andrew Leon, biostatistician, Cornell Medical College, New York.

DR. WINOKUR: Andy Winokur, Director of Psychopharmacology, University of Connecticut Health Center.

DR. RIZZO: Matt Rizzo, University of Iowa, neurologist, member of the PNS/CNS Committee.

DR. MALONE: Richard Malone, child psychiatrist from Drexel University College of Medicine.

DR. LU: Ying Lu, statistician, University of California/San Francisco.

DR. HUDSON: Melissa Hudson, St. Jude Children's Research Hospital, Memphis. I am a member of the Pediatric Advisory Committee.

DR. ANDERSON: I am Britt Anderson. I am a neurologist and currently at the University of Waterloo in

Ontario, Canada.

DR. TWYMAN: I am Roy Twyman. I am with Johnson & Johnson. I am an industry rep.

DR. POTTER: Bill Potter. I am with Merck Research Labs. I am an industry rep.

DR. GOLDSTEIN: Thank you.

We are now going to proceed to our first presentation from the FDA. I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I think our first presentation introduction will be by Dr. Katz.

Opening Remarks

DR. KATZ: Thank you, Dr. Goldstein.

I would like to welcome members of the PCNS and Psychopharmacologic Drugs Advisory Committees. In particular, I would like to welcome the members of the Pediatric Drugs and the Drug Safety and Risk Management Advisory Committees who agreed to come and lend their particular expertise to today's deliberations.

Briefly, as you know, we have convened the meeting

to discuss the Agency's analyses of suicidality, which we defined as episodes of suicidal behavior or suicidal thinking, in controlled trials of 11 antiepileptic drugs or AEDs.

As you know, in the packages you have received we have sent you the Agency's reviews of the issue that explain in considerable detail how we got to this point, why we did these analyses, as well as of course the results of the analyses themselves.

We have also outlined our plans to ask sponsors of all marketed AEDs that are given chronically to add a boxed warning describing the risks to their product labeling, as well as to produce a Medication Guide, which is a sheet describing the risks to be given to patients each time they refill their prescriptions.

Of course, we are here today to ask for your advice and guidance with regard to our analyses, our interpretation of the results and our plans to communicate what we believe to be an increased risk of suicidality to these drugs.

Again, I know you have received the detailed reviews of our work, but I just want to very briefly recount

how we got here and the results of our work.

We got here because a number of years ago a single sponsor came to us with results of analyses that they did of their controlled trials for their particular AED, which suggested to them that particular drug had a signal for suicidality.

At that point, we decided it was prudent to ask sponsors essentially of all AEDs that had appropriate controlled trials to systematically examine those trials for any indication, not just for epilepsy, for those drugs that met certain criteria.

You will hear about what the criteria was that we applied to define the studies of interest, to look at these studies for events that would possibly be considered to represent suicidal behavior or suicidal thinking.

We had concluded that there really only were 11 drugs currently approved as AEDs that actually had controlled trials that we thought were appropriate to analyze.

So, we contacted those sponsors--there weren't exactly 11 of them--and asked them to submit appropriate data for us to analyze and, in particular, we asked these

sponsors to prepare narratives of all relevant events to be reviewed blindly and then to classify these events as representing either suicidal behavior or suicidal thinking according to a standardized scale created by experts at Columbia University.

These analyses were essentially identical and analogous to those performed over the past several years for the antidepressant drug products. Of course, you know those analyses have been presented to the Psychopharmacologic Drugs Advisory Committees on numerous occasions, and those have resulted in significant changes to labeling for those products.

So, as far as the results, you know our analyses included almost 200 trials, over 40,000 patients, and we found an overall odds ratio of 1.8, which was a statistically significant increase in episodes of suicidality for the drugs taken as a whole compared to placebo.

Eight of the 11 drugs had an odds ratio greater than 1, and of the three that didn't, two had the fewest patients of all 11. There were multiple sensitivity analyses that were performed, various groupings of the data.

The results in our hands were robust to all of those maneuvers

Based on these results, the Agency issued a public health advisory in January and decided to bring the issue before these combined committees.

These analyses have led us to several conclusions. But, of course, we are here to seek your advice and guidance on what you think about those conclusions.

First, we have concluded that the results should be considered to apply to all 11 of the drugs analyzed, and not actually just to those 11, but to all AEDs to be given chronically, including those that were not included in the analyses. And we recognized that this conclusion is arguable I suppose for at least two reasons.

First of all, not every drug that we have analyzed was seen to have a signal, and, two, and perhaps more interestingly, there is no obvious reason why there should be a similar signal for this event for drugs with such at least presumed disparate pharmacologic activities.

Regarding the first point about not all drugs having a signal, as I noted earlier, of the three that didn't have a signal, two of them, carbamazepine and

Felbatol, had very few patients. In fact, those were the two smallest cohorts of the 11 that we looked at. So, of course, that suggests that the estimates in those particular cases might not be as reliable, as precise, as for the other drugs.

The third drug, which did not have a signal, divalproex, did seem to have a reasonable number of patients in drug versus placebo, over 1,000 patients in each of the treatment groups.

So, if you consider that, in fact, there aren't necessarily 11 drugs that were capable of generating a signal, but 9 that actually had sufficient numbers of patients, it wouldn't be terribly surprising to see one of those, in this case, divalproex, vary in its estimate from the overall meta-analysis, even if the truth was that the drugs do cause suicidality.

I just point out one other point, that for the two of the three drug that didn't have a signal. The confidence intervals for the estimates around the odds ratios in those cases did include the overall estimate of 1.8, which was itself statistically significant as I pointed out.

The third drug that didn't have a signal had no

events at all, so we couldn't calculate an odds ratio.

Regarding the second point about the disparate pharmacologic mechanisms, we have to recognize that we don't have any clear mechanistic understanding of the signal, which of course raises questions about the appropriateness of considering these drugs as a class to which results gained from several drugs should apply to all other members, although it is important to point out that we do consider the AEDs to constitute a therapeutic class--I will talk a little bit about that in a minute--and we do think that is of importance from a regulatory point of view.

In fact, I suppose one could argue that the widely different presumed mechanisms of actions of these drugs make any generalizable conclusion more or less implausible.

On the other hand, one could argue that defining of a signal in 8 of 11 drugs studied or, in fact, perhaps 8 out of 9 that had sufficient patients, by itself establishes that the signal, if one considers it real, is independent of mechanism and should apply to all AEDs studied and all AEDs not studied.

Here, the fact that the AEDs do constitute a therapeutic list is important to consider because

differential labeling of drugs approved for the same or similar indications of course can have profound effects on prescribing behavior.

In those cases, we, of course, have to be mindful of whether or not the data are sufficiently strong to support different conclusions for different drugs in that class. It would be very important that we avoid inappropriately shifting prescribing to members of a class that, in fact, have the same signal.

It is also possible that one can consider that the drugs are closer in pharmacologic action than we think because, whatever else they do, they do decrease seizures, at least in patients with seizures and, in that regard, I think it has to be acknowledged that we really don't understand how these drugs work even though we have some information about some of the pharmacological mechanisms that they display.

But in any event, regardless of the mechanistic argument and lack of understanding of that level, we don't really believe that there are very good reasons to ignore to us what appears to be a fairly clear empirical finding.

I would just point out that historically that this

is a situation that is more or less similar to what was seen with the antidepressants and where the meta-analyses showed a signal for increased suicidality. But there were a couple of members of that class that actually themselves did not have a signal. Of course, in that case, as you know labeling changes were applied and the conclusions were considered to apply to all members of that class.

Now, it is possible, of course, one could argue that there are more common mechanisms within the antidepressants than within the so-called class of AEDs but that is, I think, a point for discussion. Of course, we are very eager to hear what you think about that.

As you can also see, we are proposing that the product labels be changed to include a boxed warning and that a Medication Guide be given to patients as I mentioned before.

But, in particular, we are proposing that the language in product labeling be uniform across all drugs. That is to say, we are not proposing that there be drug-specific data included in labeling for specific products.

That is because, even though we believe that this is a real signal and that it exists for these drugs, we

don't really believe that we are capable of providing such precise estimates to know that there is actually a differential risk among the drugs.

So, of course, we are very interested to hear your views about whether or not our plans for labeling and a Medication Guide are appropriate or whether or not you have different views on that matter.

Finally, before I just read the questions into the record, I should point out that you will hear from, in the open public hearing, on the formal agenda, that there are folks who disagree with us. There is at least one company that will present its reasons for concluding that the signal does not apply to their drug. Other folks I think have different views about our plans to require a boxed warning, so you will hear all about that.

So, with regard to the one company that is going to suggest that their own analyses lead to a conclusion that their drug should not be implicated, the Agency will give a response to that particular presentation.

Really, here I just want to end by reading the questions that we would like you to formally vote on and formally discuss into the record and, as Dr. Goldstein had

pointed out, we are very much, of course, interested in the discussion part of the proceedings. Of course, the formal vote is very important to us, but we really do want to hear what you think. So let me just read the questions into the record that we would like you to vote on.

1. Does the Committee agree with the Agency's overall finding of an increase in suicidality for the 11 AEDs analyzed?

2. Does the Committee agree with the Agency's conclusion that the finding of increased suicidality should apply to all drugs included in the analyses, despite the observation that the estimate of the odds ratio for three of the drugs was below 1? If not, to which drugs do you think the conclusion should apply?

3. Does the Committee agree with the Agency's conclusion that the finding should apply to all chronically administered AEDs including those not part of the analyses?

4. Finally, does the Committee agree with the Agency's plan to require labeling changes for all AEDs including a boxed warning and the issuance of a Medication Guide? If not, do you want to offer guidance on other approaches to communicating this information?

Again, of course, those, as I say, are the formal questions that we would like you to vote on and discuss but, of course, if there is any other issue that is relevant that you would like to bring up, we would certainly be very eager to hear your views on those.

With that, I will just close. I will say thank you again for coming, for the work you have done in preparation for the meeting and for the work you are about to do, and with that, I will turn it back to Dr. Goldstein.

DR. GOLDSTEIN: Thank you, Dr. Katz.

Before we proceed, I would like to recognize Dr. Laughren for a brief presentation.

DR. LAUGHREN: Thank you.

In recent years, we have established a practice here of recognizing members of our advisory committees when they finish their tours of duty, and I think it's a good practice. Let me just say, as Rusty was telling you, we rely very heavily on the advice that we get from our Advisory Committees, particularly on issues like the one that we are dealing with today, and we really appreciate the hard work that you do. You know, we need outside comment from the academic and the clinical community, and your work

is very important to us, and we know that you do it in the interest of public service, not for the very small stipend that you get from FDA.

Without further ado, let me mention two members from the Psychopharm Advisory Committee who have recently completed their tours of duty. They are back here today as consultants.

Those members are Danny Pine and Delbert Robinson. Let me give you a plaque.

[Applause.]

DR. GOLDSTEIN: The questions are before us and I think it is a really interesting process that we go through. We have data. It's the interpretation of the data and then how to put that into a framework to hopefully guide the FDA and hopefully do some public good.

The next order of business is a series of presentations by the FDA. The first presentation is by Dr. Mentari.

Antiepileptic Drugs and Suicidality Background

DR. MENTARI: Good morning.

[Slide.]

My name is Evelyn Mentari and I am a Clinical

Safety Reviewer in the Division of Neurology at FDA. I thank you for this opportunity to discuss our analysis with you this morning.

[Slide.]

At the outset of this presentation, I would like to start by defining the term "suicidality" as one that encompasses both suicidal behavior or suicidal thinking.

[Slide.]

An antiepileptic drug sponsor approached FDA with concern of a suicidality signal in their controlled clinical database. In response, FDA initiated a study of suicidality events in controlled clinical trials across antiepileptic drugs.

Patients with epilepsy, and other illnesses for which antiepileptic drugs are prescribed, are reported to have increased risk of suicidal behavior or ideation, but risk estimates vary widely.

Without comparison to placebo-treated subjects, the background rate of suicidality events and the risk of suicidality attributable to drug are unclear.

[Slide.]

Ours was a standardized approach based on previous

FDA analyses of suicidality in children, adolescents, and adult treated with antidepressants.

In these analyses, pediatric and young adult patients treated with antidepressants were found to have an increased risk of suicidality compared to those treated with placebo.

[Slide.]

We included trials that were randomized, parallel-arm, and placebo-controlled, had at least 20 subjects in each treatment arm, had subjects at least 5 years old, had a duration of at least 7 days and trials without a randomized withdrawal study design.

[Slide.]

FDA specified a format for subject level data sets and information on suicidality events was part of the subject level data.

Sponsors searched adverse event reports for events related to suicidality or possibly related to suicidality, and search terms and procedures were specified by FDA.

[Slide.]

In our specified search strategy we used verbatim terms which are taken directly from adverse event reports

and also preferred terms which are translated into using the coding dictionary.

Our specified search included verbatim terms with the text strings: "attempt", "cut", "gas", "hang", "hung", "jump", mutilat-", "overdos-", "self damag-", "self harm", "self inflict", self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", and "firearm"; events were screened for false positives.

The specific search also used preferred terms with text strings "suic" or "overdos," including all events coded as "accidental overdose."

All deaths and other serious adverse events, and all adverse events coded as "accidental injury."

[Slide.]

After events were identified using this search strategy, structured narratives were prepared, and based on these narratives, events were classified by raters blinded to treatment.

[Slide.]

On this slide, we have the suicidality event categories. They include; no event, completed suicide, suicide attempt, preparatory acts toward imminent suicidal

behavior, suicidal ideation, self-injurious behavior, intent unknown, not enough information--fatal; not enough information--non-fatal.

[Slide.]

We requested for drugs known to have clinical trials which met our inclusion criteria, and on this slide we have the list of the antiepileptic drugs analyzed.

[Slide.]

Many of these drugs have approved non-epilepsy treatment indications. Carbamazepine is approved for trigeminal neuralgia. Divalproex sodium is approved for mania and migraine. Gabapentin is approved for postherpetic neuralgia. Lamotrigine is approved for bipolar disorder.

Pregabalin is approved for neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Topiramate is approved for migraine.

[Slide.]

Just as there are a wide variety of approved treatment indications for these drugs, there were a wide variety of trial indications for the trials analyzed. We categorized the trial indications into three categories; epilepsy, psychiatric indications, and other indications.

[Slide.]

Among the psychiatric trial indications were bipolar disorder, anxiety, post-traumatic stress disorder, depression, panic disorder, schizophrenia, social phobia, and binge-eating disorder.

[Slide.]

Among the other trial indications were neuropathy, migraine, obesity, chronic pain, agitation, impaired cognition, insomnia, spasticity, fibromyalgia, and tremor.

[Slide.]

To evaluate underlying mechanisms of suicidality risk, drugs were categorized by main mechanism of action.

Some drugs have multiple main mechanisms of action and for some drugs, main mechanisms of action are not universally agreed upon. Specifically, we would like to acknowledge the disagreement with the drugs groups voiced by the sponsor of pregabalin and gabapentin.

The subgroups used were based on drug prescribing information, published literature, and medical reviewer consensus.

[Slide.]

At this point, this concludes the background

information and next, Dr. Mark Levenson will discuss the statistical evaluation.

DR. GOLDSTEIN: Before Dr. Levenson presents, I just want the Committee just to have just a couple of minutes if there are any clarifying questions about each presentation. We will have more time to discuss them all together in detail at the end.

DR. PINE: When you listed the psychiatric indications for the anticonvulsants or the indications that the trials have tried to address, that was not comprehensive; is that correct? You said "among," so there are other--I mean in particular I was confused that I thought that there were trials of topiramate for alcohol abuse, and I was confused that that wasn't listed.

DR. MENTARI: You know, there are several trial indications and trials indications with very few trials that were not listed on that slide, that's true. There is a complete table within the briefing package.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: I have a question for Dr. Katz and one for Dr. Mentari, if I may.

For Dr. Katz, can you inform us about how these

recommendations, if we were to agree with all of the points that you have made, would pertain to antiepileptic drugs going into the future?

In other words, if a company were to develop a new drug and were to show no suicidal events or suicidal ideation, et cetera, et cetera, in a very large trial, would this necessarily apply to drugs in the future?

DR. GOLDSTEIN: Maybe we can hold those types of questions until the general discussion. I just wanted to make sure that there weren't any specifically clarifying the points that were made from these presentations. We will have plenty of time for these discussions. We will come to Dr. Gilman when we do that.

DR. LU: I have a question about those trials, because some of the drugs listed as adjunctive therapy, and some of them as monotherapy. For those trials when you have placebo groups, are they active control for the other drug that is not tested, or it's just purely placebo groups?

DR. MENTARI: The data that we collected did not include concomitant medications, because as you can imagine, there would be an inordinate amount of combinations possible. You know, we in some ways relied on the placebo-

controlled randomization. We in some way relied on randomization to supply a situation where things were relatively equal in both groups.

DR. LU: So, in other words, in the treatment group, there may be concomitant medicine; right?

DR. MENTARI: That's right. The trials included trials for adjunctive therapy and monotherapy, yes.

DR. GOLDSTEIN: Very good.

DR. TEMPLE: Just one comment. For the epilepsy trials they are mostly add-on studies. So you are right, the placebo group was getting some background therapy. In the psychiatric kinds of things, they are probably mostly placebo.

DR. GOLDSTEIN: Dr. Levenson.

Antiepileptic Drugs and Suicidality
Statistical Evaluation

DR. LEVENSON: Good morning.

[Slide.]

My name is Mark Levenson. I am a statistical safety reviewer in CDER. I will present the statistical review of antiepileptic drugs and suicidality. Dr. Mentari has already presented the background of the data and after

me will discuss the conclusions of the statistical review in the medical context.

[Slide.]

My presentation consists of four parts. First, I will briefly state the objectives of the statistical review. I will then discuss the analysis used in the review. This includes the endpoints, populations, and subgroups, and the statistical methods.

Then I will present the results from the review including trial and patient summaries, the results of the primary, secondary sensitivity analyses and the results from the subgroup analysis.

Finally, I will provide conclusions.

[Slide.]

The objectives were to examine whether 11 antiepileptic drugs as a group are associated with increased risk of suicidality relative to placebo and randomized placebo-controlled trials and to examine whether the risks of suicidality varies by individual drug, drug groups, studied indication and demographics.

[Slide.]

Now, I will discuss the analysis plan. The

analysis plan was specified prior to the review of the data. It was developed with consensus by the medical and statistical members of the review team.

[Slide.]

The primary endpoint was called Suicidal Behavior or Ideation. A patient had the endpoint if the patient experienced any of the four events; completed suicide, suicide attempt, preparatory acts, or suicidal ideation.

[Slide.]

There were two secondary endpoints; suicidal behavior and suicidal ideation.

Suicidal behavior consisted of the first three events. Suicidal ideation consisted of suicidal ideation only. Only the most critical event for each patient was used in the definition of the endpoints. Therefore, a patient with both a suicide attempt event and suicide ideation event would only meet the suicidal behavior endpoint.

[Slide.]

The primary analysis population was defined by the following trial and patient inclusion criteria. Trial were randomized parallel placebo-controlled. Withdrawal designs

were excluded. Open label extension periods were excluded. The trial durations were at least 7 days.

The trials had at least 20 patients per arm. The first period of crossover trials were included if they otherwise met the inclusion criteria. Patients had to be at least 5 years of age.

[Slide.]

Now, I will present the subgroups and special populations considered.

[Slide.]

For the subgroup analysis, each of the 11 drugs was considered individually. Three drugs groups were considered. As. Dr. Mentari has said, the groups were based on a consensus of the medical review team. It is recognized that the drug classifications are not unambiguous and recent discussion has highlighted other classifications.

Note that the drug groups are overlapping, topiramate is in all three groups. Each drug group was primarily compared to its complement; that is, the group of sodium channel blocking drugs was compared to the group of drugs that are not sodium channel blocking drugs.

[Slide.]

The three indication groups discussed by Dr. Mentari were considered. Note that these were studied indications and not necessarily approved indications or indications that were later approved.

Subgroups based on demographics were considered including age, gender, race, setting; that is, did the treatment have an inpatient component or was it outpatient only, and the location of the patient's clinical center.

[Slide.]

The primary analysis method was the exact method for a common odds ratio. The method allows trials to have different background rates of events, which is an important feature in meta-analysis. The method allows low even counts which we refer to as sparse data. The method does not make use of trials with no events, so-called zero-event trials.

The method assumes a common odds ratio for the trials. The unit of analysis was the patient, and the primary display was the odds ratio and is 95 percent confidence interval.

[Slide.]

In order to examine the robustness of the primary method, we conducted several sensitivity analyses. To

examine the consequences of zero-event trials, we used the Mantel-Haenszel risk difference method. This method uses trials with no events.

To examine the consequences of heterogeneity of the odds ratio across trials, we used the generalized linear mixed model with a random trial effect.

We also looked at the effect of trials that had large influence on the estimates.

During the analysis of the data, a small but significant difference in treatment duration between the treatment groups was observed. We used the exact method based on patient years to examine the consequence of this difference.

[Slide.]

For exploratory analysis, we examined the hazard pattern of events over time with Kaplan-Meier incidence curves and life table estimates.

[Slide.]

Now, I will present the results.

[Slide.]

First, the trial and patient summaries.

[Slide.]

The primary analysis group consisted of 199 trials. There were 43,892 total patients, 27,863 in the drug-treated group, and 16,029 in the placebo group. Note that more patients were randomized to drug treatment than placebo treatment.

(Slide)

This table gives the numbers of trials in patients for each of the 11 drugs. Pregabalin and topiramate contributed the most patients. Gabapentin, lamotrigine and levetiracetam were the next biggest contributors. Carbamazepine and felbamate each contributed relatively very few patients. The trial numbers reflect the patient numbers.

[Slide.]

The mean nominal trial duration was 14.2 weeks. The median was 12 weeks. The durations range from 1 to 112 weeks. 90 percent of the trials were between 3 and 39 weeks. 50 percent of the trials were between 8 and 16 weeks.

[Slide.]

This table compares the indication with the type of therapy, monotherapy, adjunctive therapy, or other

therapy for the 199 trials. The vast majority of the epilepsy trials, 92 percent involved adjunctive therapy, whereas, the majority of the psychiatric and other therapy trials involved monotherapy, 86 percent and 75 percent.

Overall, 57 percent of the trials involved monotherapy.

[Slide.]

This graph is a bar chart of the number of patients by drug and indication. In the interests of space, only the first two letters of each drug is given. For example, "ca" is for carbamazepine.

For the epilepsy indication, many drugs contributed comparable numbers of patients. For the psychiatric indication, fewer drugs contributed comparable numbers of patients. For the other drugs, several drugs, topiramate, pregabalin, and gabapentin dominate the group.

This disparity in the other indication group is somewhat reflected in the totals for the patients.

[Slide.]

I will now turn to the patient baseline demographics. Five percent of the patients were between 5 and 17. Eight percent were between 18 and 24. Ten percent

were between 25 and 30. The majority, 64 percent of the patients, were between 31 and 64. Thirteen percent were 65 or over. The mean and the median age were 44. The ages ranged from 5 to 100.

[Slide.]

The majority, 79 percent of the patients, were white Caucasian. Six percent were African American. Three percent were Hispanic. Three percent were Asian. Three percent were Other. Because of the small number in the subgroups, other than white Caucasian, these groups were combined in the analysis.

[Slide.]

Fifty percent of the patients were female. Eight percent of the patients had an inpatient component to treatment. 61 percent of the patients were from North American centers. There were no notable differences between drug and placebo patients for baseline demographics.

[Slide.]

Drug patients had shorter treatment durations and a greater discontinuation rate than placebo patients. The least-squares mean duration for drug patients was 73 days versus 77 days for placebo patients.

This discontinuation rate for drug patients was 36 percent versus 31 percent for placebo patients. The patient time and sensitivity analysis was conducted to evaluate the fact of these differences.

[Slide.]

Now, I will turn to the results of the primary, secondary, and sensitivity analyses.

[Slide.]

For the primary endpoint, suicidal behavior or ideation, 38 of 16,029 placebo patients had an event, which represents unadjusted rate of 0.24 percent.

104 of 27,863 drug patients had an event, which represents an unadjusted rate of 0.37 percent.

66 of the 199 trials, or 33 percent, has at least one event.

[Slide.]

This table breaks down the primary endpoint into the 4 component events. If a patient had multiple events, only the most critical is included. The most comment event was suicidal ideation with 96 events.

The second most common was suicide attempt with 38 of them. There were 4 completed suicides in the drug group

and none in the placebo group. For all event types, the drug group had higher percentages of events.

[Slide.]

This graph is a forest plot of the results of the primary analysis. Is shows the odds ratio and confidence interval of suicidal behavior or ideation for the 11 drugs and overall. An odds ratio of greater than 1, the area to the right of the dashed line indicates that the drug was associated with suicidal behavior or ideation relative to placebo.

The overall odds ratio was 1.8 with confidence interval of 1.24 to 2.66. The interval did not contain the value of 1. Therefore, overall, there was a statistically significant association between the drugs and suicidal behavior or ideation relative to placebo and these trials.

Eight of the 11 drugs had odds ratio estimates greater than 1. The confidence interval for individual drugs generally contained the value of 1.

[Slide.]

This graph is a forest plot of the secondary endpoints, the endpoint suicidal behavior and the endpoint suicidal ideation. For both endpoints, the odds ratio

estimates were greater than 1. Suicidal behavior had the larger odds ratio estimate and the associated confidence interval did not contain the value of 1.

[Slide.]

This graph shows the Kaplan-Meier incident curves for the endpoint suicidal behavior or ideation up to 60 weeks. There were no more events beyond 60 weeks. The graph suggests an increased hazard for drug patients over a range of time.

Analysis based on life table methods supports that the increased hazard at least into 24 weeks at which point data were insufficient for analysis.

[Slide.]

This graph is a forest plot showing the results of the Mantel-Haenszel risk difference analysis. This analysis examined the consequences of the zero event trials. Rather than odds ratio, the graph shows risk differences, a risk difference greater than zero, the area to the right of the dashed line indicates that the drug was associated with suicidal behavior or ideation relative to placebo.

Overall, the pattern for the overall result of the individual drugs were very similar to the primary analysis

based on the odds ratio. The overall risk difference was statistically significant. The estimate for each of the 11 drugs fell on the same side of the line of no effect.

[Slide.]

I will only present the results for the Mantel-Haenszel risk difference now, however, based on all the sensitivity analyses, we conclude that the results were robust to inclusion of trials with no events, the possibility of trial heterogeneity, and the differences in treatment durations between the treatment groups.

[Slide.]

I will now present the results for the subgroups.

[Slide.]

This graph shows the forest plot for the predefined drug groups. For example, the first entry is for sodium channel blocking drugs, and the second entry is a complement of this group.

Based on these two drug groups, there did not appear to be a notable difference among the drug groups and their complements.

[Slide.]

This graph compares the three indication groups -

epilepsy, psychiatric, and other. Epilepsy had a notably higher odds ratio than the other two groups.

[Slide.]

The higher odds ratio for epilepsy compared to the psychiatric group was related to the lower placebo background rate for the epilepsy group. This table gives the estimated odds ratio, the placebo and drug patient event rates, and the risk differences for the three groups.

The psychiatric group had a notably higher placebo event rate. The risk difference for epilepsy and the psychiatric groups were more comparable, 2.4 and 2.9.

[Slide.]

This graph shows the forest plot for the predefined age subgroups. Based on these results, there did not appear to be an effect of age.

[Slide.]

This graph shows the forest plot for a post-hoc finer partition of age. The 31 to 64 age group was further divided. Again, based on these results, there did not appear to be an age effect.

[Slide.]

This graph shows the forest plot for gender.

There was no clear effect of gender.

[Slide.]

This graph shows the forest plot for race. There was no clear effect of race.

[Slide.]

This graph shows the forest plot for care setting inpatient component versus outpatient. There was no clear effect of setting.

[Slide.]

This graph shows the forest plot for location. The non-North American subgroup had a notably higher odds ratio. This was not fully related to its lower background rate.

[Slide.]

I conclude with a summary of the findings.

[Slide.]

The 11 antiepileptic drugs as a group had a statistically significant effect on suicidal behavior or ideation. The odds ratio was 1.8 with a confidence interval from 1.24 to 2.66. Eight of the 11 drugs had estimated odds ratios greater than 1.

In terms of attributed risk, there were 1.9 per

1,000 additional patients with suicidal behavior or ideation events from the drug group compared to placebo.

[Slide.]

The higher drug hazard was seen over an extended period of time although this was not statistically evaluated.

Epilepsy had the highest estimated odds ratio, however, epilepsy and psychiatric indications had comparable risk differences.

Non-North America had a notably higher odds ratio.

Other subgroups--age, gender, race, setting, drug class--did not have notable effects.

Finally, the results were robust to the analysis method.

Thank you.

DR. GOLDSTEIN: Thank you, Dr. Levenson.

Again, any just clarifying questions? We will get to the meat of it in the general discussion.

Yes, Dr. Rizzo.

DR. RIZZO: What was the reason for always including suicidal ideation plus behavior together as an outcome?

DR. LEVENSON: Well, we did do--as secondary endpoints, we did consider them separately. But the primary analysis stuck with them combined, and that was the medical judgment what would the most appropriate outcome for this analysis be.

DR. GOLDSTEIN: Yes, Dr. Potter.

DR. POTTER: In the comparison of the North American and non-North American, were most of the trials combined American and North American, or did it turn out that the North American trials were just North American trials?

You see what I am saying?

DR. LEVENSON: Right.

DR. POTTER: Were these combined in one trial or were these totally distinct trials, do you know?

DR. LEVENSON: Maybe Evelyn would know more. The analysis based on location was at the patient level, so it depended on the patient center where they were, whether they were North America or non-North America.

I don't know if there are international trials or not. Evelyn, are you aware of the trials, were there many international trials?

DR. MENTARI: You know, in our discussions with the sponsors as they submitted data, it wasn't pointed out to us that there were trials that combined, that were both North American and non-North American. We had it coded as North American versus non-North American, and, you know, there is extensive dialogue between sponsors and our group at FDA, and a categorization didn't really accurately meet an appropriate description.

Usually, it was pointed out, and that was not pointed out to me. That is the best I can do. It was coded as distinctly North American versus non-North American trials.

DR. GOLDSTEIN: Dr. Schultz.

DR. SCHULTZ: I would like a brief clarification on Slide 19 where you have indication group by therapy. It indicates that most of the epilepsy patients were not on monotherapy, and 86 percent of the psychiatric patients, it was monotherapy.

In terms of defining that, I am assuming that is anticonvulsant monotherapy meaning the psychiatric patients were on one anticonvulsant whereas the epilepsy were on multiple, however, it wouldn't be psychiatric monotherapy

overall in the sense that they were probably covered with other psychotropics for their psychiatric indication, is that correct?

So, it wasn't global psychiatric monotherapy, because it would be unusual for a psychiatric patient to receive only carbamazepine.

DR. LEVENSON: Yes. I can't address that completely. That was based on a question, an individual patient level question, whether therapy actually--I am sorry--it was a trial level question whether the therapy was monotherapy or adjunctive therapy.

I guess it was left to the sponsor to interpret that.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: Thank you. Did you calculate the risk difference and the associated 95 percent confidence interval for completed suicide?

DR. LEVENSON: No, I mean there were only four events total. I think it would have had a very wide confidence interval. Obviously, the point estimate would have been greater than one with an extremely wide confidence interval.

DR. GOLDSTEIN: Dr. Goodman.

DR. GOODMAN: Really, my question is along the same lines as the previous one. You note quite clearly that the suicidality signals is higher among the epilepsy compared to the psychiatric, and I am still trying to tease out how much of that contribution is due to presence or lack of concomitant medications.

Did you do an analysis of that effect in terms of the--

DR. LEVENSON: In terms of concomitant meds?

DR. GOODMAN: Yes, in terms of concomitant medications or lack thereof.

DR. LEVENSON: Monotherapy versus adjunctive therapy is the only information that we have on that.

DR. KATZ: Ninety-two percent of the epilepsy trials were concomitant, so the results of analyses of concomitant versus non-concomitant would be the same as for the epilepsy trials presumably.

DR. PINE: I wondered if you could talk a little bit more about the fact that 66 or 67 percent of the trials contributed no events at all, and so, with at least your primary analysis standpoint, you are basing the conclusions

on only a third of the available data.

I mean obviously, based on your presentation you gave a lot of thought to that. Could you maybe speak to some of the issues that you considered in the analysis and how to draw conclusions for all of the drugs all together in light of the fact that two-thirds of the data you have basically generate no information?

DR. LEVENSON: When we were developing the statistical analysis plan, of course, we hadn't seen the data yet. But we were fully expecting for this level of sparseness in the data as we have seen in the antidepressant analysis.

That is the reason the sensitivity analysis of the Mantel-Haenszel risk difference plays a big role.

DR. PINE: Well, before you go on, I think in some ways it is similar to the antidepressant data. In other ways, it is very different in that most, if not all, the trials would have had at least one event.

Here, 67 percent of the trials have no events, which is very, very different from the antidepressant data, so I guess that is really--

DR. LEVENSON: Okay, yes, it is more extreme. For

the adult antidepressant data, I think you are probably talking about a 60 or 70 percent trials with events. I don't have the exact figure.

Well, again, getting back, the Mantel-Haenszel risk difference method, as I said, does make use of all the trials whether they have events or not, and we use that, you know. It's a very important sensitivity analyses, almost like a co-primary analysis and, when you compare the forest plots and the individual estimates between the odds ratio and the risk differences, you see the results lined up very well.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: Just to follow up that question about concomitant treatment. For the treatment group, would they have more than one drug among 11 drugs and, if so, did you separate them in the analysis or you just put them as one importance in this study?

The other question maybe just for the drug group study that you have at least one drug that appeared in all three groups.

DR. LEVENSON: That's right.

DR. LU: Did you do the sensitivity that if that

one is not there, what kind of impact would that be?

DR. LEVENSON: The first question has to do with how we grouped the drugs. Maybe you can explain more what you mean by that. Do you mean did we--

DR. LU: If they have two drugs in the treatment group, how do you evaluate individual drug effect?

DR. LEVENSON: So, if the treatment drug had two drugs compared to a placebo arm, well, that would have counted as adjunctive therapy and would have been included in the primary test drug, and the sponsor had submitted that data.

DR. LU: Okay. Primary one.

DR. LEVENSON: Yes.

DR. TEMPLE: Wait. Before you finish that, in these studies, the treatment group and the placebo group have the same background therapy. That is part of the background. They are randomized to the added antiepileptic drug or whatever versus placebo. So, they should be the same.

DR. KATZ: Right. We are not looking at two anticonvulsants versus none in those studies. You are looking actually at one added versus the same background.

DR. LEVENSON: Could you repeat the second question, please?

DR. LU: Just about drug groups, because there was one drug appearing in all three groups.

DR. LEVENSON: No, we did not do a sensitivity analysis where we moved the overlapping, but there was a point where each drug group was compared to its complement, so the complements were obviously not overlapping.

It wasn't so much a comparison among the three drug groups as a comparative between each drug group and its complement.

DR. JUNG: Along the same lines of what Dr. Pine asked about, what is the significance of just identifying the most significant suicidal attempt within each study?

DR. LEVENSON: What is the significance of using just the most significant event?

DR. JUNG: Yes.

DR. LEVENSON: As opposed to like all the events that might have occurred, well, in the antiepileptic data request, we did request for all events to be submitted, which was different from how it was done in the antidepressant analysis.

So, we received, out of the 43,000 patients, 9 patients that had multiple events. Part of that is actually ascertaining the events. Patients may have had multiple events, but we don't know about them.

In terms of what we know about multiple events, there is not--I have a back-up slide listing them all, but generally, the multiple patients had multiple episodes of ideation. One had two suicide attempts and one had one ideation and one suicide attempt.

I think the answer to your question is we don't really know a lot about multiple events, but the little we see it is still dominated by ideation.

DR. GOLDSTEIN: Dr. Temple.

DR. TEMPLE: Mark, the two striking differences that you had were epilepsy versus other, and North America versus non-North America. Did you do an analysis looking at those groups together, for example, epilepsy versus other in North America and the other regions?

DR. LEVENSON: No, I did not.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: Going back to the original classification of events using the Columbia algorithm, can

you remind us the number of raters used to sort events into the categories and what the inter-rater reliabilities were in general, and whether they differed as a function of the different levels within the algorithm?

DR. LEVENSON: I can't answer the question about the number of raters. The sponsors were responsible for actually conducting this, either through their own experts or contracting it out.

I do not know of that parameter the number of raters was fixed among the sponsors.

DR. DAY: Was that reported? I mean could it be found and could there be differences across different drugs and companies on this?

DR. LEVENSON: I do not believe we have that information at the moment. It could be requested.

DR. MENTARI: Just a note. In our instructions to sponsors, we specified that there should be at least two raters for each arm.

DR. DAY: I am asking this because in the original studies for the antidepressants, when the companies and the agencies, before they started using the algorithm, there were very different outcomes and number of events

identified, and so forth. I think it would be useful information to know the number the raters and the inter-rater reliabilities for the different drugs.

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: Yes. When you evaluated those strings of words to determine whether there were events, you mentioned that there was a false positive rate. I wonder what that false positive rate was, was it 10 percent or 50 percent, and if so, how did you account for it?

DR. LEVENSON: By false positive, what was meant there, that the text string search and like often parts of words--I won't be able to think of an example on the spot, but that part of a word falls in a completely unrelated word. It's a clear false positive, nothing to do with suicidal, like--I am not going to be able to think of an example. Does someone have an example?

DR. HUGHES: Say hang nail, if hang nail had been identified by searching for hang, or gastric identified by searching for gas, obviously, those aren't going to be suicide-related events. So that's what we mean by false positive.

Do we have information about the numbers of those?

DR. LEVENSON: No. I imagine no one really has that information because it is a very early stage of the process. Those are thrown out before blinded narratives are created.

DR. RIZZO: So, it is not merely that you sampled some of the records to see if there were false positives to determine the number, but everybody who screens positive is evaluated and then you make a judgment about whether they should be included or not.

DR. LEVENSON: Well, at that point, once a narrative is created, they are classified into seven or so events from completed suicide to not enough information, or no event. They could be classified at that point, but everybody at that point would get--

DR. KATZ: Right. The screening is done on those text strings, but I just want to--when you say "you," all of this work is preliminary categorization and the writing of narratives and the categorizing of narratives into one of these categories was done by companies blinded. It was done blinded, but it was done by the companies just so you understand that. We did the analyses of the results of their categorization.

DR. RIZZO: Thanks for that clarification. One other question is do you have information on false negatives?

DR. LEVENSON: False negatives, no more--no.

DR. RIZZO: Thank you.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: I have a question about Slide 20, if you can clarify. This was supposed to include every patient, not including the studies of zero events, right? So, if you look for zero events, would that be very different from the plot that you have?

This is the page for patients by drug and indication, month, number of patients contribute in the analysis.

DR. LEVENSON: That's correct. And what was your question?

DR. LU: Oh, the question is if you exclude the events, the trials with no events--

DR. LEVENSON: What would it look like?

DR. LU: What would it look like, yes.

DR. LEVENSON: I would not know exactly what it would look like. What I can say is the psychiatric

indication groups tend to have the higher event rates, so they would lose less trials than the epilepsy and other indications. So, if you are going to see a decrease from throwing out patients who were in trials without events, you would see that mostly in the epilepsy and the other indications, but that is all I could say about that.

DR. GOLDSTEIN: We are starting to get a little off from the clarifying questions, but that's okay, we still have time.

Dr. Leon.

DR. LEON: All these numbers, all the numerators here are based on spontaneous adverse event reports, correct? Particularly in the psychiatric trials, I would imagine there are also prospectively gathered information on suicidality. Was any of that looked at?

DR. LEVENSON: I am not really in a position to answer. I don't know the answer to that.

Does anyone at the table know more about that? I mean some of these were psychiatric indications, perhaps there were prospective instruments used in them, I don't know.

DR. HUGHES: We didn't analyze that information

for this analysis. We didn't request it.

DR. TEMPLE: We do know one thing from the depression trials, which is that the suicidality item or the suicidal item on the HAM-D didn't show anything even while the rest of the data, the spontaneous reports, did. So, I don't know what that means. Maybe you do.

DR. GOLDSTEIN: Dr. Winokur.

DR. WINOKUR: You pointed out that two of the antiepileptic drugs, topiramate and pregabalin, contributed a quite high percentage of studies in patients.

Can you say more about that and particularly how that was taken into consideration to make sure that that did not overly influence the finding across the large number of antiepileptic drugs?

DR. LEVENSON: Can I get the slides up again? It should be 28.

[Slide.]

The question is there are two drugs, pregabalin and topiramate, that contribute a large number of patients to the overall analysis.

There was no adjustment for that in the primary analysis. We do see that the other drugs, those two drugs,

fall in the pattern with the other 8 drugs that have odds ratios greater than 1. When you look at drugs individually, 8 of the 11 drugs seem to have a very similar pattern.

We did look at a sensitivity analysis where we looked at large trials that contribute, individual trials no matter what drug that may appear whether they have a large influence on the overall estimate. And it turned out only one trial had any significant, in itself, influence on the overall estimate and, when we removed that trial, the overall estimates were similar, slightly larger, but similar.

DR. GOLDSTEIN: Dr. Potter.

DR. POTTER: I was just trying to get at this same issue about the fraction of patients in the total size that contribute the two counts.

You talk about a lot of trials, but if you just ask the question how many patients of the total come from trials that contributed to your data analysis.

DR. LEVENSON: I don't believe I have that number.

DR. POTTER: So, in other words, are the findings the result of multiple things from the smaller trials, or all the findings coming from the big trials and there are

all these small trials with no events, just to put it in sort of common sense terms.

DR. LEVENSON: Again, when I looked at the influence of individual trials, there were very few trials really dominating. Well, there was one trial that had an effect of 120 for the overall estimate and other than that, no single trial had a significant fraction of influence to the overall estimate.

I am not sure that answers your question.

DR. POTTER: Let me try one more time. I mean you have 40,000, you know--let's say you have 40,000 people you are reporting in your totals. But you are saying a lot of the people, and I am saying how many of those 40,000 people were in those two-thirds of the trials that had no events.

DR. LEVENSON: I don't have the answer to that question.

DR. POTTER: Okay. It might be interesting, and what is the geographic distribution of that, because there are some very peculiar things that are just adding the data.

DR. GOLDSTEIN: Dr. Goodman.

DR. GOODMAN: I am perseverating on this concomitant medication issue.

As I understand it, there were some trials that involved monotherapy and it seems that more of those would be represented in the psychiatric than in the epileptic trials. Did you have enough of those monotherapy trials to conduct a separate analysis of suicidality risk? Again just looking at monotherapy.

DR. LEVENSON: Right. We probably had enough, but we did not. As you can see, 86 percent of psychiatric are monotherapy. So, in a sense, almost none of the epilepsy are monotherapy and 86 percent and 75 percent of the other indication categories, the monotherapy. So, in a sense therapy is very confounded with indication and, if you look at the results by indication, you are getting most of that information out.

DR. TWYMAN: In the statistical background, there was a comment about ascertainment bias and that ascertainment bias apparently did not play a factor here.

Could you elaborate further on that conclusion?

DR. LEVENSON: Evelyn, was there in your section, discussion about ascertainment bias?

DR. MENTARI: That is something I will discuss in my presentation that is next. Thank you.

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: Since the epilepsy patients were adjunctive, there were probably many patients on many different numbers of AEDs.

Was any effort made to look to see if the risk stratified with the number of AEDs or some other estimate of exposure to AED?

DR. LEVENSON: It is an interesting question, but no, we did not collect that data, and we could not analyze it that way.

DR. GOLDSTEIN: Dr. Jung.

DR. JUNG: Recognizing that the Agency's question is related to all chronically administered AEDs, and recognizing that this analysis was done only on drugs that had randomized placebo-controlled studies, where do you put phenytoin in all this? It is a very commonly prescribed drug. I know we don't have the data, but if you are going to try to classify the whole group, what are you going to do with this?

DR. KATZ: Well, again obviously, this is a larger question that we want the Committee to discuss, but I think our a priori view would be included just as the other drugs

that we didn't study that don't have adequately controlled trial data.

DR. GOLDSTEIN: Very good. Let's go on. I think the next presentation is by Dr. Mentari again.

Antiepileptic Drugs and Suicidality: Discussion

[Slide.]

DR. MENTARI: Next, I would like to discuss some issues related to our data and methods.

[Slide.]

First, I will discuss our use of placebo-controlled clinical trial data which is a strength of our analysis since placebo controls are necessary to understand the background rate of suicidality.

Patients with epilepsy and other illnesses for which antiepileptic drugs are prescribed are reported to have increased risk of suicidal behavior or ideation, but risk estimates vary widely.

Without comparison to placebo-treated subjects, the background rate and the risk of suicidality attributable to drug are unclear.

[Slide.]

Next, I will comment on our use of meta-analysis.

Individual clinical trials typically have few suicidality events.

However, this stands in sharp contrast to the fact that over the lifetime of individuals in a population, suicidal behavior and ideation are frequent occurrences that amount to a major public health burden.

In 2004, suicide was the eighth most common cause of death in the United States general population. However, in the limited time frame of clinical trials, large numbers of subjects are necessary to evaluate risk.

This meta-analysis provided the largest number of subjects used to evaluate this question to date.

[Slide.]

Next, I would like to discuss some limitations of our analysis. Our analysis used data that was collected retrospectively since the majority of clinical trial data for currently marketed antiepileptic drugs was generated prior to the recognition of a possible suicidality signal.

As we have discussed, large numbers of subjects are necessary to evaluate the risk of suicidality using clinical trial data.

However, while data was collected retrospectively,

the analysis was prospectively defined.

The trials included in this meta-analysis were not specifically designed to evaluate risk of suicidal behavior or ideation.

Differences between clinical trials analyzed for individual drugs limit the possibility of making reliable comparisons between individual drugs.

[Slide.]

Next, I would like to discuss some issues regarding our findings.

[Slide.]

Sponsors performed searches of their clinical trial adverse event databases.

With these methods, non-random differences in subject assessment, that is, ascertainment bias, may occur.

Drug-treated subjects may have a higher rate of adverse events in general, and this may lead to additional contact with clinical staff.

Placebo-treated subjects may have increased contact with clinical staff due to lack of treatment efficacy.

[Slide.]

With additional contact with clinical staff, subjects may be more likely to generate a suicidality adverse event report.

Prospective methods of assessing suicidality in randomized trials are not subject to ascertainment bias and will be useful in future studies.

[Slide.]

Ascertainment bias likely has less influence on the reporting of suicidal behavior than on the reporting of suicidal ideation.

Compared to placebo-treated subjects, drug-treated subjects had higher incidence rates for all categories of suicidal behavior or ideation events.

Also, the odds ratio estimate for suicidal behavior alone, which encompassed events of completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior was statistically significant with an odds ratio estimate of 2.92 and a 95 percent confidence interval of 1.44 to 6.47.

[Slide.]

On review of the suicidal behavior narratives, the majority of suicidal behavior events prompted notification

of the study investigator by an outside party; for example, notification during hospitalization, notification of death, or notification by a family member, or the event prompted the subject's discontinuation from the trial.

In these circumstances, reporting of suicidal behavior events is unlikely to have been driven by a generally increased rate of adverse events or by additional contact with clinical trial staff.

[Slide.]

Next, I would like to discuss the risk of suicidality with individual antiepileptic drugs.]

Antiepileptic drugs as a class were associated with a statistically significantly increased risk of suicidal behavior or ideation compared to placebo.

Estimated odds ratios were greater than one for 8 of the 11 individual drugs with data analyzed.

Two of the 11 drugs with data analyzed had a statistically significantly increased risk.

Nine of the 11 drugs with data analyzed had odds ratio estimates that were not statistically significant.

Reliable comparisons between individual drugs are limited by non-statistically significant odds ratio

estimates in the majority of individual drugs and by differences between clinical trials for individual drugs.

[Slide.]

Next, I will discuss our subgroup analyses and the consistency of results.

Consistency of results in subgroups of the data analyzed is important in confirming that overall meta-analysis conclusions are valid.

There is no clear pattern of drug effects seen among subgroups according to age, gender, race, or setting.

These was no clear pattern of drug effect seen among drug groups prespecified according to main mechanism of action.

[Slide.]

An increased risk of suicidal behavior or ideation was observed in all categories of trial indications evaluated. The majority of epilepsy trials involved adjunctive therapy, whereas the majority of trials for psychiatric indications or other indications involved monotherapy.

Because increased risk was seen in all trial indication categories, it may be expected that the increased

risk exists, whether the antiepileptic drug is used as monotherapy or adjunctive therapy.

[Slide.]

There is an increased risk of suicidal behavior or ideation seen in both trial location subgroups.

The estimated odds ratio for the non-North American subgroup was 4.53 with a 95 percent confidence interval of 1.86 to 13.18, and it was larger than that for the North American subgroup with an estimate of 1.38 and a 95 percent confidence interval of 0.90 to 2.13.

A much lower event rate in placebo-treated non-North American subjects leads to the elevated odds ratio and risk difference in the non-North American subgroup.

[Slide.]

Based on these data, we have concluded that there is a signal for increased suicidality for the class of antiepileptic drugs.

On January 31, 2008, FDA issued a press release and information for healthcare professionals.

[Slide.]

FDA plans for action which are up for discussion today include:

To propose product labeling for all antiepileptic drugs used chronically;

To propose that sponsors include a description of these findings in a boxed warning, as well as in the Warnings and Precautions sections;

To propose a Medication Guide describing this risk for distribution each time and AED prescription is filled.

[Slide.]

At this time, several areas for future investigation remain. Research using prospectively collected data is necessary to more systematically evaluate the risk of antiepileptic drugs and suicidal behavior or ideation.

Further development and validation of methods to assess suicidality, including suicidality rating scales, are necessary.

[Slide.]

Characterizing potential underlying mechanisms of increased risk of suicidal behavior or ideation with antiepileptic drugs is an area for future research, as well as research on whether certain patient subgroups are at particular risk.

That concludes my discussion. Thank you.

DR. GOLDSTEIN: Thank you, Dr. Mentari.

I think that sets up the discussions that we should be having now over the next half-hour and as I started to say earlier, this part should be more general in discussion, but again we can certainly direct questions at the FDA staff.

I again want to start off with Dr. Gilman who was going to ask a question earlier that I think sets up very well, as well.

Questions from the Committee

DR. GILMAN: Thank you.

My question was directed to Dr. Katz and it has to do with these four recommendations that you want us to consider assuming that we are in the affirmative as a committee for all four of them.

How does this pertain to drugs to be evaluated as antiepileptics in the future, would this pertain to them automatically? If so, is there any way that the sponsor could demonstrate that they do not have a suicidal risk?

DR. KATZ: I don't know that we have fully decided what we would do in that case. There is a couple of things.

I think if a drug were to be approved tomorrow or in the near future I think yeah, if we decided that this was going to be a general labeling change that applied to all drugs in the class that are currently approved, yeah, it would apply to the ones that are approved in the near future.

Again, our proposal is to apply it to drugs that are approved now as anticonvulsant but that haven't been studied. So I would say in an analogous way we would do it for the future.

But we are interested in the question of how best to get better data perhaps in the future and, perhaps in the future, if we systemically collect this data prospectively, and those are analyzed and it turns out. when you do it that way, there is really as a class there is nothing going on, that would affect our decision.

That is my answer to the question at the moment. The other thing is I think maybe we shouldn't really have the definitive discussion about these issues until we hear the rest of the presentations because, obviously, there are some dissenting views out there, so I wouldn't have the entire discussion, but that is how I would answer that question.

DR. TEMPLE: Can I just mention that for another setting, where we have got some experience--namely, antidepressants--we have been applying the labeling changes to new drugs. I mean the larger discussions, how do you ever make something like that go away. If somebody had a bunch of trials, I mean how would you know about the assay sensitivity of that person's method? Could it pick these up? It is a very challenging problem.

DR. GOLDSTEIN: One question that I just had. We are calling this a class, and the question really is how do you define the class. Here, we are saying antiepileptic drugs, but let's switch it. Let's say it was antibiotics. Do you use sulfonamides the same as beta lactams, the same as cephalosporins? They are all antibiotics.

DR. KATZ: That is obviously a critical question and a very complicated question. I would say that perhaps the distinction between this and antibiotics is that these at least all do the same thing ultimately. They decrease seizures.

Now, again obviously, a lot of these patients didn't have seizures, so that is an issue. I would say, though, the idea of a therapeutic class is something that is

worth discussing, as well, because, again, as I said in my opening remarks, if there is a group of drugs--let's not use the word "class--" if there is a group of drugs all approved for the same indication, you want to be pretty sure that your results either do apply to all or just a few, because you will shift prescribing behaviors.

You do need to think of them at least as a therapeutic class. Whether they are a pharmacologic class is a very thorny question that needs a lot of discussion.

DR. GOLDSTEIN: Again, by that analogy, the point about antibiotics holds. They all kill bacteria.

DR. KATZ: They all kill different bacteria perhaps. I mean again that's you go case by case. We can have that discussion.

DR. GOLDSTEIN: Dr. Rudnicki.

DR. RUDNICKI: The question about analysis; was analysis done looking at people who were in studies for depression, grouped with people who had a history of depression independent of why they were in a study, say, they were a seizure patient, but had a history of depression, so what role history of depression played on relative risk?

DR. LEVENSON: There was no subgrouping based on history of depression. It was purely by the studied indication of the trial.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I have three questions for Dr. Mentari's presentation. The first one was about the possibility of ascertainment bias and the comment that you made on Slide 10 that the majority of events were prompted notification of study investigator by outside parties.

Did you do that analysis, an analysis only relying on those events and what did that show?

DR. MENTARI: That statement was based on a review of the suicidal behavior event narrative.

DR. PINE: Right. So, did you do that analysis?

DR. MENTARI: I did that, yes.

DR. PINE: Did you repeat the analysis only treating those events as positive? Given that you reviewed all the narratives and that you classified them as either narratives where an outside individual, noted the behavior or not, it seems to me that you have the data where you could repeat the analysis only considering trials where an outside individual besides the patient noted the event, and

I would agree with you that if that were to show an association with the antiepileptic drugs, then, you would be right. I would agree that you have ruled out ascertainment.

Just noting that a majority of events are characterized by that is kind of only the first step in ruling out that possibility unless you repeated the analysis only considering those events as positive, you haven't ruled out that possibility.

DR. MENTARI: I will confirm that we took that initial step, but we didn't repeat the analysis with only those events with those characteristics.

DR. PINE: So, if you haven't, then, I don't think you have ruled out the issue of ascertainment if you haven't done that analysis.

DR. MENTARI: Sure. We were trying to touch on it, but I see your point.

DR. PINE: The second question has to do with Slide 11 where you said 2 of the 11 drugs with data analyzed had a statistically significantly increased risks. I thought I saw that some later material came in for 1 of the 1, and when that additional material came in, that the confidence interval then included 1. Could you clarify

that?

DR. MENTARI: Are you referring to the post-tox analysis with additional trials for lamotrigine?

DR. PINE: Yes.

DR. MENTARI: That slide refers to a primary analysis which did not include that data. If you would like to discuss our rationale for not including that data in our primary analysis, I would be happy to do that.

DR. PINE: But you still think that is the right thing to do to not include those additional data?

DR. MENTARI: Sure. Well, to bring the rest of the group up to speed about what we are discussing, in both the statistical review and in my review, we discussed that there were data from three additional lamotrigine trials that were submitted basically very late in the analysis, and our decision was that to allow a single sponsor to electively submit data for the primary analysis, despite existing instructions for a specific cutoff date, wouldn't be a risk for introducing bias to our analysis, and that is why we didn't use that in our primary analysis.

DR. KATZ: Could I just say also, right, I think the cutoff date is an issue. We could do this serially,

whatever, but for individual drugs, statistical significance really is not that critical for us.

It is just that the estimates all more or less go in the same direction. I think when you include those three other studies, statistical significance is lost for that drug, but it is still a signal that is consistent with the overall signal, if I remember correctly.

DR. PINE: But you can't have it both ways. You can't point out that two of them were statistically significant in your conclusions and then say that--

DR. KATZ: I think that just was an observation, I don't think we intend to make anything of that. In fact, our proposal, as you see, is to have uniform language in labeling that isn't drug specific. So, we wouldn't intend to make any regulatory hay out of that.

DR. PINE: Then, one last question on Slide 13. The last point on Slide 13 was because the increased risk was seen in all indication categories, it may be expected that the increased risk exists.

So, my reading in the psychiatric versus non-psychiatric odds ratio was that it was statistically significant in the non-psychiatric, not statistically

significant in the psychiatric or other, and you are concluding presumably based on statistics that that is just chance variation, that there was, in fact, no indication by drug interaction; is that correct or not?

DR. MENTARI: You know, in discussing differences between trial indication categories, I think we run into a same situation where, you know, the trials have differences where it is difficult to directly compare them.

I mean I think it can be said that in comparing the epilepsy trials and the psychiatric trials, due to the higher background rate in psychiatric trials, the odds ratio for epilepsy was higher, but the attributable risk was actually quite comparable. I am not sure if that entirely gets at your question.

It is an observation and I was basically pointing out that while it is not identical, and I don't know if--

DR. PINE: From a statistical standpoint, do you think difference between the odds ratio in the epilepsy and the other two categories, is that a statistically meaningful difference?

DR. MENTARI: I wouldn't necessarily say that, and that is my personal interpretation.

DR. TEMPLE: But that goes to the heart of all of this analysis. You get your best shot by throwing it all together. But nobody is going to sit here and argue that throwing it all together is the most logical thing to do. It makes the most sense. There could be regional differences, there could be disease differences, there could be, for goodness sakes, there could be drug differences, and that is really the problem we are presenting to you.

DR. PINE: But one of the first ones you would think about, if you are thinking about a psychiatric outcome, would be is the association different in the psychiatric patients or not.

DR. TEMPLE: It is and it goes in an illogical way. I would expect the people with psychiatric problems to have the bigger effect, but that is not how it works. You know, if that makes sense to you--that is why you are the advisory committee.

You know, that is at the heart of the problem with all of this, what do you do when your basis data is masked data and you are not very good at picking out the perfectly interesting, sensible differences within the data.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: I have a question of clarification for Dr. Mentari. On your Slide 18, you say that in the future we need additional development of methods to identify suicidality events. It was also in the briefing material as well.

Can you comment what types of shortcomings might be present in the methods currently used? For example, the use of text strings, I noticed in your previous presentation, there were approximately 19 text strings identified as being associated with possibly suicidal events, and I have been able to sit here and generate quite a few others.

So, are there any aspects of the current methods and the identification of events that you think needs attention in the future?

DR. LAUGHREN: We face the same problem with the antidepressant data. The information that we had on suicidality in those trials that were not designed specifically to look for suicidality was very sparse, and we tried to put together narratives that included all the relevant information, but obviously, in the conduct of those trials, the investigators had not asked all the relevant

questions.

They might have asked to try and define as precisely as possible what those events entailed, and that made it difficult to classify them into categories before we could do an analysis.

So, going forward, the hope is that we will develop better instruments for collecting information on suicidality in the conduct of trials so that, when we come around to doing a meta-analysis, we will have all the information we need to categorize those events into the bins before we do an analysis. There are some instruments that are being developed to do that.

DR. DAY: So, it is the initial collection of the data during the clinical trials as opposed to the use of the algorithm after the fact that you are particularly concerned about.

DR. LAUGHREN: They are completely separate things but related.

DR. DAY: That is very helpful. Thank you.

DR. GOLDSTEIN: Leon.

DR. LEON: The attributable risk that was presented, 1.9, that is worth paying attention to. I

calculated the number needed to harm, which is if about 800 subjects were treated with active med and 800 subjects were treated with placebo, there would be one more event on active, but just based on the numbers here.

So, to put that into context so we have an understanding of what is the impact on the public health, maybe I missed it in the book and I didn't see it in the presentation, what is the epidemiology of these disorders, or even more important, how many patients take antiepileptic drugs in this country? I have no idea of that number.

I am pretty sure at the antidepressant hearings we saw numbers like that, maybe just the early ones.

DR. KATZ: Certainly millions. I mean we probably have a lot of people in the room who know better than I.

DR. MENTARI: We actually have a slide on drug utilization that covers the 11 drugs in the analysis, not all antiepileptic drugs, but it's a start. I guess we could put that up if that is appropriate.

[Slide.]

This slide contains information from the Veruspan Vector One Total Patient Tracker, and it has information on unique outpatients who receive prescriptions in U.S. retail

pharmacies. This covers, not all antiepileptic drugs, but the 11 drugs that were in the analysis.

We have another slide that has a total of these, which we can switch to whenever people are ready.

[Slide.]

One thing that I tried to include in my second presentation is that, you know, in my mind it is important to note that our methods involve clinical trial patients for various reasons, but that is a very small snapshot of time for these patients, and that is what makes this analysis so difficult, but when we look at the potential for how many patients are affected over time, you know, it may be a very different issue.

DR. LEON: Now that I see the number 10 or 11 million, maybe, Dr. Levenson, can you put in context that attributable risk. What do we multiply that by, like 10,000 or something, to get us up to 10 million? You gave an attributable risk I think it was 1.9 per thousand.

DR. LEVENSON: 1.9 per thousand, yes.

DR. LEON: So we multiply this by 10,000.

DR. LEVENSON: By 10,000, yes, to get to 10 million.

DR. MENTARI: I guess one caveat I would include is that our data did not have much information on treatment beyond 24 weeks, so I don't know if it can be directly translated into an interpretation with that graph.

DR. GOLDSTEIN: Right, and I guess that also--that 24 weeks I think is an important thing for us to keep in mind, because the way the labeling or the regulation is proposed, it says chronically administered anticonvulsants, and we have data for a relatively short period of time, presuming that that would hold over longer periods of time.

DR. KATZ: What we meant by including that language or those other drugs, chronically administered, we meant to exclude drugs that are given for very brief periods of time, you know, injectable drugs that are given for a couple of days or perhaps maybe rectally administered drugs that are given for acute events.

So, we wanted--it wasn't so much to get at the question you bring up, but it was to exclude drugs that are given very briefly, very intermittently. We didn't think that the risk would necessarily generalize to that sort of treatment. That is why we said "chronically administered AEDs."

DR. LEVENSON: Continuing the fact of how many events could be attributed to these drugs, we saw throughout the durations of the trials we had the increased hazard, so there is no indication that we have that the hazard would go away at a longer time period. It may or may not, we don't know, but there is a potential that you will see, there would be attributable risk beyond the durations of the trials we have seen.

DR. GOLDSTEIN: Thank you. Just so the Committee knows what I am doing is I am going through in order, and what I am doing is looking at who has asked the most questions, and I am trying to get people who haven't asked questions a chance to ask first. But we will get to everybody I promise.

Dr. Caplan.

DR. CAPLAN: I want to follow up on what Dr. Pine mentioned and also Dr. Rudnicki. The issues, the issue of the psychiatric indications, one of the things that we do know is that the three categories of patients in these studies all have very high rates of depression, so there are very high rates of depression in patients with epilepsy, there are very high rates of depression in the patients who

were treated with neuropathy, the migraine, et cetera, et cetera, and, of course, in the psychiatric patients.

This is a commonality and the question is here are we talking about a therapeutic category in terms of drugs or we talking about a common diagnosis, psychiatric diagnosis that is associated with high rates of suicidal ideation.

I think we really need to give thought to that. The other thing is it is rather interesting that a third of the trials were the ones with events and what we do know about these populations and particularly the epilepsy and the chronic medical illness patients is that about a third of the patients have high rates of depression. So I think we really need to give thought to that.

DR. GOLDSTEIN: Dr. Armenteros.

DR. ARMENTEROS: I was wondering if the Agency is going to show to us some, you know, was mentioned before, epidemiology data on suicidality particularly in patients with epilepsy, so that the whole statistical discussion falls into some real clinical perspective.

DR. MENTARI: I didn't prepare a slide for this discussion, but I did review the data, and I can't see that my--I mean there are vast amounts of literature, and in my

review, the estimates varied very widely. I mean the rates, you know, are obviously defined in many different ways in many different populations, ranged from 3 to 25 percent. I mean it was wide enough that it was very difficult to use, and that is just a comment on my look at the literature.

DR. GOLDSTEIN: Dr. Jung.

DR. JUNG: Along the same lines of what Dr. Caplan and Dr. Armenteros mentioned, in your Slide 13, again the comment that the majority of trials for psychiatric indications and other indications involve monotherapy, again, talking about the other indications which are primarily pain syndromes, which have a very high rate of depression.

The other part of that is that you can't assume that those indications had monotherapy, because there may be other drugs involved that might change the statistics that were brought out on Dr. Levenson's Slide No. 20.

For example, pregabalin had a very high bump under other indications, and the question is are those patients pain patients that are using other medications that might change for the better or worse your statistics, and I think that is the part that it is not clear to me at least.

DR. HUGHES: But those other medications should be the same in the drug-treated group and the placebo-treated group. I mean we didn't collect information on concomitant medications, so we can't be sure. But that's what we expect.

DR. GOLDSTEIN: You might expect that unless these drugs are actually doing something, and then the open label adjunctive medicines might differ if the drugs that are being given have the desired effect.

DR. JUNG: True, or if there is some type of interaction, that's true.

DR. GOLDSTEIN: Dr. Temple.

DR. TEMPLE: As Alice says, this should not introduce bias and cannot explain the finding, but it remains possible that the people in whom the observation occurs is conceivably the subset of people with a history of depression or people who are on the other drugs. And I don't know the extent we could look at that, but it is something that one could consider certainly.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: A question for Dr. Mentari. You very nicely classified the other indications by diagnosis, and

also the psychiatric indications by diagnosis, but for the epilepsy, you just have epilepsy.

There are, of course, multiple types of epilepsy defined anatomically by semiology, by presentation, age, et cetera, et cetera. I wonder if you have any better indication of the kinds of epilepsy that were under consideration. I suspect many of them were complex partial, because that is the most frequent type and the most recent trials have been in that area.

I am wondering whether most of your data pertain to complex partial epilepsy or simple partial epilepsy, and is there any way to narrow that particular category down based upon the kinds of trials that were examined.

DR. MENTARI: Thank you for your question. We did ask about seizure type and, as you suspect--I don't have the exact figure in front of me, but my recollection is about 83 or 86 percent of the trials dealt with an indication for complex partial seizure. With that type of a number, we really weren't able to make differentiations between different types of epilepsy.

DR. GILMAN: My follow-up question, if I may, is do you have a subanalysis of just those cases? In other

words, does it come out more or less the same as the entire antiepileptic group?

DR. MENTARI: We did not perform an analysis of just the complex partial seizure trials, no, we didn't.

DR. GILMAN: Once more, these are people with common depression.

DR. KATZ: But, again, as with the adjunctive versus monotherapy, you would expect if 85 percent of the trials were complex partial, which is certainly consistent with our experience, you would expect that the estimates of the odds ratio would be certainly in the ballpark.

DR. GILMAN: I entirely agree, but we are discussing today not just a medication effect on a biological entity. We are discussing a medication on a patient with a predisposition.

DR. GOLDSTEIN: Dr. Goodman.

DR. GOODMAN: I don't know if you were planning to, but I would be interested in seeing data on other adverse behavioral effects or, say, adverse events in general comparing the drug and placebo group with particular emphasis on adverse behavioral and cognitive effects.

Obviously, when you do a drug versus placebo

trial, in general, you expect to see more adverse events in your drug group, so that shouldn't be surprising us. What was surprising when we encountered this with antidepressants in depression is we were seeing increases of suicide, which we considered to be one of the symptoms that should be getting better during the course of treatment.

I am still struggling trying to conceptualize what is going on here. But one thing I just wanted to explore is the possibility that, in a subset of patients with epilepsy or other disorders that are being treated particularly with combined or adjunctive anticonvulsants, it is increasing their general side-effect burden and maybe--as part of that picture, maybe there are other things that we could see like other cognitive disturbances, dysthymia, and maybe in an even smaller subset we are seeing suicidal ideation.

So, I would really want to see what other adverse behavior and cognitive effects were showing up in the data set.

DR. GOLDSTEIN: Dr. Winokur.

DR. WINOKUR: I have a follow-up question related to the epilepsy subset. We have recognized that virtually this whole group was in the add-on therapy, and Dr. Goodman

has raised a number of questions about that, which I shared the questions.

As not a neurologist, I have an impression that patients who would be studied in that kind of study would almost by definition by treatment refractory, that the only way they would get to such a study is having failed to respond to their current antiepileptic, you know--I know in theory I am more familiar where there are considerable differences between a general major depression in a study for treatment refractory.

I am curious about the idea that this is a special subcategory of patients--and I understand there was a different signal in those randomized to placebo, but I just wanted to bring it up for discussion both in terms of what further analyses the FDA has thought about and comments from the neurology colleagues about that kind of interaction of clinical focus challenging subgroup and perhaps greater sensitivity to medication effects could impact on the findings.

DR. KATZ: I would just confirm that the trials, the adjunctive trials for anticonvulsants in patients with epilepsy, those patients all meet some criterion of

refractoriness for seizures per month in the sort of baseline kind of thing, or by history.

So, they are at least by some operational definition considered not doing terribly well on their current regimen.

DR. TEMPLE: But that is in some ways why it is interesting that the psychiatric diagnoses, where they are not all adjunctive, although some might be, show the same direction.

DR. GOLDSTEIN: Dr. Malone.

DR. MALONE: As a follow-up on what Dr. Goodman said, I think in the panel on antidepressants, there was a lot of discussion about activation syndrome and agitation as kind of a mechanism that may have led to increased suicidality.

I think that data is interesting to look at side effects to see whether there was the presence of an activation syndrome or irritability. In my mind, I am trying to figure out some mechanism, some behavioral mechanism that would relate to suicidality.

DR. LAUGHREN: That is a very interesting question, but it is something that would have to be looked

at going forward. There is no way when you do a meta-analysis like this that you are going to have access to all that information. I mean this involved almost 40,000 patients. We had to go back to the companies to ask them for a very limited data set.

Obviously, we don't have all the kinds of information that you would like to have in trying to understand the phenomenology even of these events. The same was true of the antidepressants. I mean you would really have to form hypotheses and then go forward to try and understand the phenomenology of the events.

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: I had a question, to ask the FDA to clarify a little bit again on this issue of the therapeutic group. It would seem that a therapeutic group isn't defined by regulatory approval so how are you going to treat all--or are you considering treating all the medicines for which there is reasonable evidence of antiepileptic effect, but which are not approved for that, such as many of the antiarrhythmias, benzodiazepines, a number of others for which there is pretty well established antiseizure effects.

Should they all also carry the same black box

warning if that is recommended?

DR. KATZ: Well, at the moment we are considering, basically just considering those drugs which are approved for the treatment of epilepsy. I am not aware of the antiseizure effects of the antiarrhythmias or how well documented that is, but benzodiazepines, some are approved for epilepsy chronically, so those would at least by proposal be included.

But it is a fair question. I think in the antidepressant world, there might be drugs that are considered to have antidepressant activity which are approved for something else besides depression. I think those might have been included.

So, it is a fair question. But we were at the moment anyway proposing that only those drugs which are approved for epilepsy be included. Again, that does include some of the benzos, but not the antiarrhythmias.

DR. TEMPLE: That is, of course, until we do our anxiolytic meta-analysis, and then we will see.

DR. KATZ: Exactly.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: Thank you. Suicide is, of course,

a very serious adverse event. There is a difference that I calculated from the data presented is 5.8 per 10,000 treated patients. To me, it would help to put it in perspective to know whether other categories of death differed; in other words, was there an attempt to look at all-cause death between the two groups in the meta-analysis.

In some sense, if the only difference was suicide, that would probably by washed out by other causes of death. On the other hand, if the drugs cause beneficial effects that reduce the risk of death through other mechanisms, that would be important to know, and I would like to hear data on that if we have it.

DR. LEVENSON: We did not collect any data on all-cause death, so we do not have that data.

DR. GOLDSTEIN: We are just a couple of minutes after the top of the hour. We allowed about a five-minute wiggle room so we can take a couple more questions before we move on.

Next is Dr. Twyman.

DR. TWYMAN: I have a question around the data that went into the generalization that this is a class effect. I think someone else pointed out that there are a

lot of other compounds used in the United States that actually are not in this list per se. The data are obviously from more recently studied compounds and development programs.

My question is what potentially is the impact of the missing data--that is, the data from compounds in common use in the United States that are really not in this data set--and has there been an attempt to look at weaker data sets, say, the postmarketing vigilance database, to see whether or not there are some trending signals there because, obviously, we can't get at recent study data for these other compounds.

DR. KATZ: We have looked in at least one case of one drug at postmarketing for other purposes, and didn't convince ourselves that there was a signal. But I think we have long ago decided that postmarketing data are not the right data to look at, or we don't believe that for these sorts of things where there is a high background rate of suicidality so defined in these populations, I think we have concluded that postmarketing data is uninterpretable, and that is why we went to placebo-controlled trials.

It is impossible to know what the impact of other

non-studied drugs would be on this. Again, obviously, our proposal would say, well, we have studied 11, 9 which actually had enough patients to say something, about 8 of which all went in the same direction.

That is suggestive to us of a so-called effect. I realize we have to discuss that more. So, we don't know what would happen with other drugs not studied, but we do think that we do have pretty much all the relevant control trials done with these drugs in this analysis.

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: Did anyone do a forensic analysis to try to determine if the four people who committed suicide actually did it because of anticonvulsants or not?

DR. KATZ: I don't think we did a forensic analysis. I am not personally sure what that is. I think it is very difficult to tell from the individual case reports whether or not--narratives of those four cases--whether or not the suicide was related to the treatment. I think that is why we are analyzing controlled trials.

DR. RIZZO: What I mean is call up the authors and ask them about the suicide and try and determine what happened, and, if necessary, get medical records. That is

what I mean by forensic analysis.

DR. KATZ: I don't believe we did that. I think again the companies gave us presumably all the relevant data that they had. Whether they made efforts in those particular cases to follow up, I hope they did, but I certainly couldn't testify that they did that in those cases. Is that a fair statement?

Again, I think looking at the individual narratives to try and figure out causality is more or less problematic. Again, that is why we are looking at the controlled trial data.

DR. RIZZO: It's what the FDA does, it is what NASA does, it is what the FAR system does. It is a very common process.

DR. KATZ: Again, in any individual case, depending on what the event is, it might be fairly easy to do from a narrative. In some cases, it is undoubtedly more ambiguous. But again we haven't done that in this case.

DR. TEMPLE: But you can look at it and reach a conclusion. But I don't know if you remember the antidepressant situation beginning in 1991. There were these very interesting horrible cases of people becoming

suicidal. When this was taken to an advisory committee, they said, well, I don't know if that is the underlying disease or the drug.

The only way we eventually became comfortable in sorting that out in both children and adults was to look at suicidality, not suicides, in controlled trials, because these conditions are all associated with an increased risk of suicidal behavior. So, if somebody commits--has suicidal behavior or commits it, how do you know whether the drug did it or not?

That is what Rusty is saying, the control group helps you. The individual case is a formidable task in interpreting and knowing.

DR. RIZZO: But if there are only four cases it becomes much less formidable, and what I am just suggesting is to test the validity of the conclusions by trying to get extra data.

DR. GOLDSTEIN: Very good. I think this was an excellent discussion. I think you can all get a good feeling for the issues that are being wrestled with here. I think we will all be discussing these in a lot more detail as the day and the afternoon roll on.

We are going to take a 10-minute biology and Black Berry break. Be back at 10:15. Please remember, members of the panel, no discussions about anything related to the topic at hand. Thank you.

[Break.]

DR. GOLDSTEIN: We will come back to order.

We are beginning now to proceed with our guest presentations. I would like to remind the public observers at the meeting that while this meeting is open for public observation, public attendees may not participate again except at the specific request of the panel.

We now begin with the first set of comments and it will be by Dr. Wohlberg, from Global Medical Team, Lyrica, and head of Therapeutic Area Pain from Pfizer.

Neurontin/Lyrica: Potentially Suicide Related Adverse Events

DR. WOHLBERG: Thank you and good morning. I would first like to thank the Chair, the Committee, and the FDA, for allowing me to speak on behalf of Pfizer regarding this very difficult issue and what I intend to do over the next 20 minutes is present some of our ideas regarding primarily our data for pregabalin and gabapentin.

[Slide.]

These are the representatives within the sponsor section. I won't go through them individually, but they are there for the record.

[Slide.]

What we have heard this morning is really a difficult topic. These are rare events. We are talking about events that are approximately 20-fold less frequent than the antidepressant issues, and there are some basic assumptions that have been made that we would like to consider eliciting further.

The first of those is that these drugs belong to a class. The second is that the studies from these drugs are poolable, and then the third is that the effects seen are consistent across the drugs.

Finally, the overarching issue here is one of uncertainty. One cannot prove the heterogeneity where there is a lack of power and one cannot say that the drugs are necessarily different where the power doesn't exist to say that.

But we believe that primarily from an analysis of our products which we tend to look at very closely, that,

number one, pregabalin and gabapentin represent a distinct class of compounds with a unique mechanism of action and should be evaluated separately from other antiepileptic drugs.

The second is that Pfizer believes that the benefit-risk profile for pregabalin and gabapentin are properly represented in the current product labeling.

The third is that the available data do not support a boxed warning for suicidality for either product. Such a warning would misrepresent the available evidence for pregabalin and gabapentin, remembering that the warning applies to all indications, not just epilepsy, and that over-warning actually has the potential to negatively impact patient care.

[Slide.]

Based on the totality of data, there is no evidence of an elevated risk for potentially suicide related adverse events with either pregabalin or gabapentin regardless of the method that we accept to assess this risk.

Using updated data for Pfizer's products for studies completed through January 1st, 2008 we find a reduction in risk estimates using both the FDA's methodology

as well as our own.

Based on this updated information we have approximately 2,000 more pregabalin-treated patients, about 800 more placebo-treated patients and, within that, using the FDA's methodology of an odds ratio Mantel-Haenszel exact method stratified by study, the updated odds ratio is 0.94.

Furthermore, there is also a reduction in a risk difference which was low to begin with from the 2006 data, but has decreased from 0.52 per 1,000 patients to 0.13 per 1,000 patients for pregabalin.

Finally, we believe that the inclusion of all data from all available trials, including those without events, demonstrates no elevated risk of potentially suicide-related adverse events.

[Slide.]

Let me touch on the first assumption. Is this a class? There any many ways of looking at class. One can be therapeutic class, and the other can be a pharmacologic class. I will take them separately.

Does the fact that a common thread of effect in epilepsy mean that the drugs share all common principles? I think not. There are different adverse event profiles

across drugs, there are different molecular structures that would inherently lead to different adverse event profiles, and that these products are, in addition to having that common thread of epilepsy efficacy, have different efficacy in different indications, and are used in a broad array of indications.

[Slide.]

The example of antibiotics was brought up this morning, and it is interesting because we had tried to think of examples and came up with the antibiotic example of how antibiotics in different groups and different mechanisms may share common indications. But using the recent example of fluoroquinolones with a boxed warning for tendinitis and tendon rupture, although they share common indications with other antibiotics, that boxed warning was specific to the fluoroquinolones.

[Slide.]

So, what about a pharmacologic class? It is clear from the table here that the class of medication differs considerably by product. There are many different mechanisms of action proposed and while we won't speak to the remainder of these, we do know that for our two

products, pregabalin and gabapentin, extensive work has been done to categorize the mechanism of action of these drugs, and we are fairly clear that these drugs exert their effects through binding to the alpha 2 delta binding site on voltage gated calcium channels.

We refer to them as alpha 2 delta ligands. This commonality is not shared by any of the other products and therefore based not only on this common mechanism of action, but also what you heard before is a considerable contribution to the FDA's meta-analysis data set.

We feel that these drugs can actually be considered separately. Our two drugs contribute about 35 percent of the patient data to the FDA's meta-analysis data set, but contributed only about 8.4 percent of the adverse events.

In contrast, if you look two other drugs, which contributed about the same amount of information, they contributed, in composite, over 60 percent of the adverse events.

[Slide.]

Show graphically, in blue, you can see the patient representation for pregabalin and gabapentin, which again

combine totals about 35 percent, but a disproportionately low representation of adverse events.

In contrast, these other two drugs, topiramate and lamotrigine, seem to have a disproportionately high representation of adverse events. What does that suggest? Well, if you remove topiramate and lamotrigine and look at them separately, the incidence of adverse events is about twice what it is for placebo. But looking at the other 9 antiepileptic drugs, the incidence of adverse events, potentially suicide related adverse events, is essentially symmetric and, if it were not for this, we might not be here today.

[Slide.]

So, in summary, about class, we don't believe that there is a therapeutic or treatment class to speak of and that a common thread of effect in epilepsy does not imply equivalent risk profile across products. There is certainly differential efficacy across other indications.

We believe that there is strong evidence that there is a different mechanism of action to suggest that there is no pharmacologic class, and there appears to be unequal representation of events.

[Slide.]

Turning now to our data, and in response to the FDA's request for information in 2005 for their meta-analysis, we provided information, categorized using a Columbia system for pregabalin, shown on this slide, in which there were a total of seven events Category 1 through 5 versus three events for placebo in Categories 1 through 5.

But remembering that, in terms of the number of patients, there is slightly greater than 2 to 1 representation, so as a percentage we have 0.092 percent of patients with an adverse event in the active group versus 0.091 percent for the placebo group, about 1 in 1,000 patients, and it's symmetric, it's equal.

In terms of exposure, the number of events per patient year is similarly low and similarly symmetric between treatment groups.

[Slide.]

Looking at the data for gabapentin, the totality of clinical trials potentially suicide-related events is 3. They are all suicidal ideation. There are no completed suicides. Suicide attempts were preparatory acts within our clinical trials database.

Again, there is an unequal randomization here, so that, in terms of an incidence of event reporting, they are relatively similar.

[Slide.]

We have updated our database to include clinical trials data for those trials completed through January 1st, 2008. Based on that information, which included about 2,000 more pregabalin-treated patients, there were no new Neurontin trials that we could look at, and about 800 more placebo-treated patients.

Within that additional information, 27 percent more patient data for the active group, there is only one more event, and that was a completed suicide in the placebo group.

So, we now have a total for the alpha 2 delta's of 9 events versus 3 in 2006, it is now 9 events versus 4 in the 2008 database with a slightly greater than a 2 to 1 randomization ratio.

Furthermore, if we look at the specific patient in the pregabalin group that did commit suicide, that particular patient--as was brought up this morning very interesting discussion, this patient has a history of major

depressive disorder, was being treated with venlafaxine, and the event occurred approximately six months after the initiation of drug treatment within the trial.

[Slide.]

So, from the descriptive statistics, we have very few events, and it is clear that these are rare within the pregabalin and gabapentin trials, they are equally distributed between treatment groups, and the updated analysis shows greater symmetry in events between the treatment groups.

[Slide.]

If we turn to some of the statistical issues, this is really to raise awareness and to consider these points. The first is that there is a rarity of events. These are not common. They are indeed very rare events and that they could potentially lead to unstable point estimates.

Furthermore, different ratio-based methods, that I will show you in a second, in the presence of these rare events will give you different point estimates, highlighting the instability.

The majority of studies do not have an event in either treatment group. But that has been brought up before,

about 66 percent of the studies in the Pfizer data set don't have an event in either treatment group, and that constitutes in our data about 80 percent of the patients. So that within our data set, when you analyze using methods that exclude zero variance studies, you are only looking at 20 percent of the data.

[Slide.]

These are four different methods for calculating odds ratios. These are all valid methods. These are methods used by the FDA in their analysis of suicidality associated with antidepressants in 2006.

Depending on the method that is used, the odds ratio varies by a factor of 2 between 0.882 and 1.792, so half of the calculations give you an odds ratio less than 1, the other half give you an odds ratio, a point estimate greater than 1. But, again, you are using 20 percent of the data and none of these are statistically significant.

I should mention that this is for our data, the alpha 2 deltas combined, and it is highlighting the instability of these point estimate calculations in the setting of rare events.

[Slide.]

If you look at the primary analysis by the FDA, some of that instability can be seen in these confidence intervals--for example, gabapentin has a confidence interval ranging from 0.12 to 48. Clearly, the point estimate can vary considerably in those circumstances.

Pregabalin's odds ratio calculation from the 2006 data set was 1.88 in the FDA meta-analysis. In our analysis using the updated data through 2008, the odds ratio with just that one additional patient in the placebo group has decreased by 50 percent and is now 0.94.

[Slide.]

Again, turning back to whether the signals are consistent, the odds ratio calculated in an unstratified method--we don't have the study level data to do this by study--is 2.0 for lamotrigine and topiramate, which is statistically significant. It does not include 1 whereas the other 9 antiepileptic drugs, the odds ratio is 1.1 with relative symmetry of the confidence interval around 1.

Furthermore, pregabalin and gabapentin have been classified earlier as GABAmimetic drugs. We don't believe that that is true. We have no evidence that there is any effect on the GABA complex, but unfortunately, our generic

names are derived from the fact that we have a GABA backbone.

However that may be, if you look at the odds ratio within the GABAmimetic category, and exclude topiramate, topiramate has a odds ratio within that grouping, unstratified of 2.7 compared to 1.01 for Neurontin, Lyrica, valproate, and tiagabine.

[Slide.]

The next grouping that I will look at are some other points about ratio versus difference based estimates of risk. Ratio-based methods that don't account for the majority of data, those data with zero variance, may actually inflate the risk estimate.

There are methods that exist that allow the use of all available data and we can look at some of the variability of those point estimates when we exclude or include the zero variance data.

The non-ratio based risk estimates, or risk difference, may provide the most accurate point estimate of risk, because it does allow inclusion of all data.

[Slide.]

So, one method, not better, not worse, just a

different method is a Bayesian method and while the Mantel-Haenszel exact method does not allow zero variance data to be included, the risk difference Mantel-Haenszel does allow to be included, but gives zero difference in that analysis.

The Bayesian method does allow you to look at all of the available data, and does not assume zero variance for those studies with no events, so that there are some advantages, there are clearly some disadvantages to this method, but when we use it, we can look both at risk by exposure in terms of treatment days, and risk by event counts.

So, we have a median ratio of events. We are looking with a Bayesian analysis of a range of event likelihood, and the median is 0.95 for all pregabalin studies, but if we exclude the studies that were excluded using the Mantel-Haenszel exact method, that estimate goes up to 1.37.

Furthermore, the confidence interval becomes somewhat wider. We look at the odds ratio calculation, the odds ratio calculated using a Bayes method as 1.07 for all studies, and 1.52 when we exclude the zero variance data with again a broadening of the confidence interval.

We think that this shows that inclusion of all data provides a more accurate estimate, as well as a more precise estimate.

[Slide.]

The FDA did a sensitivity analysis looking at risk difference, and we believe that that risk difference data does show a lack of effect for both gabapentin and pregabalin. It is shown as a risk difference per 1,000 patients, and the results for gabapentin are 0.28 patients per 1,000 versus 0.52 patients per 1,000 for pregabalin with relative symmetry of the confidence intervals around zero.

[Slide.]

Again, we can replicate that analysis, the FDA's meta-analysis, and come up with the same risk difference. But, while we would not normally do this, what you can do is you can exclude the zero variance data and see what impact that has on the risk difference.

So, by doing that, you inflate that point estimate by 5-fold and significantly broaden the confidence interval around the point estimate.

Furthermore, in updating our data to 2008 studies, the risk estimate for all data has decreased by about 75

percent down to 0.13 patients per 1,000 compared to when we exclude data, still have a 5-fold increase in risk estimate, but even with the exclusion of that data, less than 1 patient per 1,000, this is really the take-home message that updating our database we have a decreased estimate of risk using either the FDA methodology or our own.

[Slide.]

Finally, the Mantel-Haenszel estimates of common odds ratio assume that the data estimates among the defined groups are consistent and poolable. As the Agency noted in the briefing document, there is insufficient statistical power to test for the poolability with rare events.

While they did do a Zalen test and they did a sensitivity test using a general linear mixed model, there is not enough power to really know what is going on, and there is a degree of uncertainty associated with that.

[Slide.]

So, in summary, analysis of rare events, pooling across these drugs may not be appropriate, and therefore Mantel-Haenszel based odds ratios may not be conclusive, the difference-based risk estimates may provide more accurate and stable estimates.

When all available data is utilized or our products, both the 2006 and 2008 analyses show no evidence of risk with pregabalin or gabapentin within clinical trials and again using either the FDA's methodologies or our own.

[Slide.]

So, what about indications? There are many different ways that these products are used. The primary usage of pregabalin and gabapentin is not in epilepsy. It actually is in neuropathic pain.

We have approvals in the United States as was shown earlier for DPN, PHN, and fibromyalgia in pain conditions, as well as adjunctive treatment of epilepsy.

When we look at these risk differences by indication, they are all small, but they are also different directionally, so that for the pain conditions, there is a negative risk difference relative to placebo where the majority of usage occurs.

In psychiatry, there is a very small positive risk difference, but it should be noted that within our GAD program, there were no events in either treatment group, and for adjunctive epilepsy, there is a very small positive risk difference although the instability can again be highlighted

by the fact that, with these two events driving this risk difference, if you have one event in the placebo group, the sign changes here to a negative.

Similar patterns are seen for gabapentin. In pain, there is a negative risk difference compared to a small positive risk difference in epilepsy, and overall, you have a risk difference of about 1 per 10,000 for pregabalin, 3 per 10,000 for gabapentin.

[Slide.]

So, therefore, it brings up the question: Is class labeling appropriate? We don't believe it is and there are several questions that go into that.

Do these drugs belong to a class? Pregabalin and gabapentin, as alpha 2 delta ligands, as I showed you before, are distinct pharmacologically.

One common effect does not suggest common risk profiles. Inconsistency of event reporting suggests that product-specific labeling may be more appropriate.

Is the risk uniform for all drugs? Again, it is difficult to know that answer by statistics, but the signal seen here may be primarily driven by two products. We do have updated information in the FDA's briefing document

regarding lamotrigine, but there is no evidence of risk for pregabalin or gabapentin.

Finally, is a boxed warning appropriate? There is no evidence of risk using all clinical trials data. The greatest usage is in conditions for which the risk difference is numerically lower than placebo.

Our updated analyses using FDA's meta-analysis techniques or our own show diminished risk patterns and the current data does not change the risk-benefit profile for either product.

[Slide.]

So, with that, I would like to conclude with the same thoughts. They are a unique class. There is no evidence of increased risk of potentially suicide related adverse events for either product.

Pfizer believes that the benefit-risk profile of pregabalin and gabapentin are properly represented currently, and the available data do not support a boxed warning for suicidality for either product.

Such a warning would misrepresent the available evidence relevant to pregabalin and gabapentin. An over-warning does have the potential to negatively impact patient

care.

Thank you for your attention.

[Applause.]

DR. GOLDSTEIN: The applause is appreciated, but please hold it.

Next, is Dr. Modell from GlaxoSmithKline.

DR. MODELL: There are technical difficulties here, so we will be back with you in just a moment.

DR. GOLDSTEIN: While they are treading water, does the Committee have any again clarifying questions at least for the last presentation? Maybe we can get some of those done. Dr. Leon.

DR. LEON: The last couple slides referred to risk-benefit ratio, and I wondered if they quantified the risk-benefit ratio either with the old data or the new data. I mean I saw risk data.

DR. WOHLBERG: If you are speaking specifically to how we would quantify a benefit, I am not sure how we would be able to do that. In terms of usage, I think that we do have indications where patients do benefit significantly from treatment. As we have heard, conditions such as neuropathic pain, fibromyalgia, epilepsy, they all have

increased background rates of suicide and comorbid psychiatric conditions, and so we are able to provide some relief of their underlying symptoms.

In Europe, we do have an approval for generalized anxiety disorder as well, and as I said, there were no events in either treatment group for that. How we would quantify benefit-risk? I am not quite sure how you would do that, but in terms of the risk itself, we feel that in this particular instance, there is no signal.

DR. LEON: But on your slides, you referred to risk-benefit. So would you just be willing to change those last two slides so you are only talking about risk?

DR. WOHLBERG: Yes, I think that in the absence of risk, it is difficult to say that there is a change in risk-benefit. But, if that is an issue, then, yes, we don't believe that there is risk, and therefore, that may stand on its own.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: Yes, I just want to clarify about the endpoints here, because I noticed that you have listed 1, 2, 4, and there is a comma, 5, and the matching was FDA. No. 4, I think was not in the FDA's list, but in your list and

was in one of the placebo group that you mentioned, so I just wanted to get it clarified.

DR. WOHLBERG: Thank you. That is a very good point, and in the original request for information in 2005, Categories 4 and 5 were actually flipped, so that Category 5 was suicidal ideation, Category 4 was preparatory act, self-injurious behavior, intent unknown.

What we have done because the presentations earlier listed Category 4 as suicidal ideation, and were presented that way, we presented it that way for consistency, but what we have analyzed are completed suicide, suicide attempts, preparatory acts, and suicidal ideation.

DR. GOLDSTEIN: Thank you. I think the technical issues have been resolved. Dr. Modell.

Lamictal (lamotrigine)
Analysis of Suicidality Data

DR. MODELL: Thank you very much.

[Slide.]

I am Jack Modell, Vice President for Clinical Neurosciences at GlaxoSmithKline. I want to thank you folks up here for the help with the technical difficulties, my

apologies for that, and also to thank the FDA and the Advisory Committee for having us here today and also for looking into what we consider to be this very important issue for patients.

I, like most of the psychiatrists, most of the physicians at GlaxoSmithKline, and probably throughout industry, practiced for many years before coming to industry, and we have seen the devastation that these illnesses, epilepsy, bipolar disorder, for example, untreated, can bring to patients and their families. And, in many cases, they don't have a choice but to take the medications to control these serious illnesses.

So, we think it is very important that any potential safety signal be evaluated very carefully, so that we can get the most appropriate information to patients and prescribers to make the best decisions around the use of these medications for these illnesses.

[Slide.]

I believe it was Dr. Pine who was asking earlier about the updated lamotrigine analysis, the additional data that were submitted later in 2007. By way of history, just to give you the background on this, when the request came

to have the initial data set submitted to the Fda, which it was in June of 2007, we still had three ongoing trials with lamotrigine, and I will show you more details of those trials in just a second, but they were three fairly large trials that we knew would be finishing within the next several months.

So, we thought it was most important especially with the signal that is relatively infrequent, to have as much data as possible and as complete a data set as possible. So, we did certainly submit the initial data set as you can see with 15 psychiatry, 16 neurology, and 1 healthy volunteer trials to the FDA in 2007, and notified them that there would be an additional 3 trials soon to complete. Again, in the interest of having as much data as possible, we would submit those as soon as possible after the data bases were frozen and analyzed.

So, as noted, there were three additional trials, two in acute bipolar depression, and one if epilepsy. Additionally, we also searched the previously non-database text fields from all of the studies to be sure, for example, in the case report forms if something was noted in the margins or something out of place where you might not expect

an adverse event to be reported, that we would be able to pick up any signals or any possible data from those, as well.

So, in total, the full updated data set for Lamictal, that included 35 placebo-controlled clinical trials involving almost 6,500 patients. The division there is about 3,000 in neurology indications and about 3,500 for psychiatric indications, and also 52 healthy volunteers.

[Slide.]

So, the additional data in the full updated data set submitted in November contained 706 new patients, 354 on Lamictal, and 352 on placebo. There were 13 new classified events of suicidal ideation, none for behavior alone.

Nine of these events, so the majority, came from the acute bipolar depression trials, 1 on Lamictal, 8 on placebo.

Four events came from the previously non-database text fields of the initial data set with 3 on Lamictal and 1 on placebo.

[Slide.]

So, just going over what I will show you here are the differences between the initial data set in this darker

blue and the full data set in the brighter blue colors. And what you will see for neurological indications overall--so this was now a combination of epilepsy trials plus neuropathic pain trials. Essentially, the odds ratios didn't change, approximately, from 1.1 to 1.2, neither statistically significant.

Looking at epilepsy alone, the odds ratios again not much change here, 1.8 to 2.0, again, not showing statistical significance, but I think it's important, as has been already pointed out this morning, that the important thing to look at here are perhaps point estimates across all of the drugs, and basically, to look at what those are rather than perhaps to argue over whether something falls at a p-value of 0.04, 0.05, 0.06., and that sort of thing.

[Slide.]

Looking at the psychiatric indications, these numbers change a little bit more because, as noted, the majority of patients from these additional analyses came from the psychiatric trials.

Here, the odds ratio was initially 2.29 and with the additional data from the two bipolar trials, that odds ratio is now 1.49, and does contain 1. Here is an example,

the p-value again going to the other side of 0.05. But the important thing still to note is we do have an overall odds ratio that is not really inconsistent with what we have seen across the aggregate data for all of the anticonvulsants.

Looking specifically at bipolar disorders, since that is where these trials were from, the odds ratio changed with the additional patients from approximately 2.3 to 1.3, and there are the corresponding ranges and p-values.

For all indications overall, the additional data changes the odds ratio again, not a lot, but from approximately 2 to 1.5 and associated p-values.

[Slide.]

Now, if we then look at number of subjects with definitive suicidal behavior by treatment group and indication, I can go through these quickly, because as noted already, there were no additional behaviors, so really, nothing changes here. The odds ratios stay the same for neurologic indications.

The denominators changed a little bit, but not the numerators. So, for epilepsy, the odds ratio is not really calculable because we have no events in the placebo group and only 2 in the Lamictal group.

Psychiatric indications again doesn't change, neither did bipolar disorder, neither would the overall odds ratios.

[Slide.]

In terms of GSK presenting these results publicly, within a couple of weeks of when we had the final full data set analyzed, GSK posted to its public web site for study results, these results under the heading or title analysis of suicidal ideation and behavior in lamotrigine clinical trials.

Additionally, these results have been presented at international meetings. You see the title of the presentations here, both at the American Psychiatric Association in May of this year and also at NCDEU.

[Slide.]

This is just an excerpt from the current Lamictal U.S. package insert actually around bipolar disorder. I realize that is not the focus of today's presentation, but just to say that it has been noted for bipolar disorder that there may be worsening of depressive symptoms and suicidal ideation and behaviors whether or not patients are taking medications.

But I think more importantly is the point that I, as a clinician, and I think all clinicians know, that patients with serious illnesses especially if associated with adverse consequences, suicidal ideation or behavior whether caused by drug or associated with drug or not, need to be closely monitored for clinical worsening including suicidality.

For that reason, we are actually grateful that this signal has been picked up, so that we can advise patients and prescribers appropriately to watch for possible emergence of these symptoms.

[Slide.]

So, in summary, I think it probably goes without saying that bipolar disorder, epilepsy, most of the indications we have been talking about are serious chronic illnesses that untreated carry significant morbidity and mortality, so we need to be able to treat these patients.

Definitive interpretation of these analyses is difficult as discussed already because of the small incidence in absolute number of events, the actual rates are very low. The retrospective nature of the analyses and therefore they are subject to confounding that we may not be

able to sort out for years to come, and potential confounding because the events of interest can be symptoms of bipolar disorder or epilepsy.

Now, saying that definitive interpretation is difficult is not to say that the results are unimportant, meaningless, inconclusive. They remain, nonetheless, an important signal that requires further investigation even if we don't fully understand what is giving rise to the signal.

The results from the Lamictal analysis, both the analysis submitted to the FDA and the final analysis submitted in November with the full data set, these results are consistent with the overall FDA anticonvulsant findings, and we do believe that the results of the FDA's analysis across all of these medications should be incorporated into the labeling for anticonvulsants in the interest of giving patients and physicians the most information possible to make informed decisions about risks versus benefits of treatment.

But also GSK strongly support additional prospective research for a more complete understanding of the observed associations in clinical trials going forward to really understand what the signal means, perhaps how to

best look for it, whether there are particular patient groups or situations where the risk is heightened.

So, again, I thank you for allowing us to present and I thank you for your interest in this very important issue. Thank you very much.

DR. GOLDSTEIN: Thank you.

Before we go on to the general discussion, I believe Dr. Levenson has some rebuttal.

Preliminary Statistical Comments on Pfizer Gabapentin and Pregabalin Analysis

DR. LEVENSON: Good morning again. I will now present some preliminary statistical comments on Pfizer's background package for this meeting.

[Slide.]

The sponsor made three major points. The first is that gabapentin and pregabalin have unique mechanisms and prescribing patterns.

The second is that additional pregabalin data are now available since the original submission to FDA.

Their final point is that FDA's analysis of rare events may lead to biased conclusions.

As a statistician, I will now address the first

point. I will briefly address the second point, mainly I will focus on the third point.

[Slide.]

On April 30th, 2008, the sponsor submitted additional pregabalin data on trials that were available as of January 1, 2008. According to the sponsor, no additional gabapentin data were available.

Again, according to the sponsor, the original submission had 10,429 patients, the updated submission had 13,314 patients. This amounts of a difference of 2,885 patients. There was one additional event, a placebo suicide.

FDA has not reviewed these additional data. We have not reviewed whether the trials meet our inclusion criteria, what indications are represented in the trials, and the duration of the trials.

The knowledge of these factors is key to understanding the data and its place in the overall analysis.

[Slide.]

Now, I will discuss the sponsor's analysis of rare events, which we will refer to as sparse data. The sponsor

considered three classes of methods, 4 classical odds ratio methods, 2 Bayesian models, and a risk difference method.

[Slide.]

The four classical odds ratio methods were Mantel-Haenszel, logistic regression, Mantel-Haenszel with continuity correction, and Dersimonian-Laird with continuity correction.

In 2006 statistical briefing document and review for the adult antidepressant analysis, we noted problems with all these methods except for Mantel-Haenszel in the sparse data setting.

In particular, the continuity correction adds proportionately more events in the placebo group because of unequal randomization. The effect is to reduce the estimated odds ratio.

[Slide.]

Here are the results of the various methods applied to the pregabalin data. The results for the FDA primary method agree well with those from the sponsor for Mantel-Haenszel and logistic regression.

The two methods that make use of continuity correction show the expected reduction in the odds ratio.

[Slide.]

I will now discuss the Bayesian models. First, I will discuss Bayesian models in general. Bayesian models have two components--prior information on parameters and a model of the data given the parameters.

Bayesian models have some desirable features. They produce probability statements rather than in confidence intervals, which simplify interpretation and use. They stabilize the estimation. In the present case, this allows for the inclusion of zero-event trials, and they allow the use of prior information on the parameters if such information exists.

There are some important caveats about Bayesian models. There are more choices to be made. Different prior information or different models can give different results. Because of this, sensitivity analyses with varying with varying priors and models are important. In addition, the estimation for Bayesian models is typically more complex than for classical procedures.

Because of this, diagnostics are important to judge the performance of the estimation algorithm.

[Slide.]

Now, I will discuss the sponsor's Bayesian models.

No justification is given for the particular model and prior out of many possibilities. It is not clear if the model is appropriate for meta-analysis. The model uses zero-event trials, however, it is not demonstrated that the model improves or worsens estimates.

Reference to analytical or simulation studies demonstrating the appropriateness and benefits of the model would be valuable in evaluating the model.

Finally, diagnostics and results of the sensitivity analyses are not provided.

[Slide.]

I now return to the forest plot to explain the FDA's primary result that I showed earlier. In this forest plot, the estimates for gabapentin and pregabalin are greater than 1 and are similar to other drugs, which together give the overall statistically significant result.

It is possible to define a drug group with an odds ratio of less than 1, however, our primary analysis was to look at the 11 drugs at as a group.

[Slide.]

FDA used the Mantel-Haenszel risk difference to

evaluate the effect of zero event trials. The risk difference is not directly comparable to the odds ratio. However, the method provides an alternative method for testing the drug effect and uses of zero event trials.

As stated in my first presentation, the estimate for each of the 11 drugs fall in the same side of the no effect line for the risk difference analysis as in the primary analysis.

However, I note here that the effects for gabapentin and pregabalin appear smaller in terms of risk differences than odds ratios relative to the other drugs.

[Slide.]

In conclusion, the sponsor's analyses do not support that the FDA's primary and sensitivity analyses led to biased conclusions.

FDA's conclusions for gabapentin and pregabalin were based on the overall patterns and findings of the 11 drugs.

Thank you.

DR. GOLDSTEIN: Thank you, Dr. Levenson.

We now have time for general questions for the speakers and some general discussion.

Questions from the Committee

DR. GOLDSTEIN: Before we get started on that, there is probably nothing more dangerous than an amateur statistician of which I consider myself a prime example, but we do have three full-time bona-fide statisticians on the panel, and I was wondering whether--I want to give you a chance to really talk about this for a minute to begin with.

I also know that you can draw a line among statisticians between Bayesians and non-Bayesians and get a war between the States as a result, so I think putting this in a little bit of context, I think may be helpful for the discussions that we have going on.

DR. LEON: I do want to make a couple of comments as a non-Bayesian side of the Mason-Dixon line.

Two comments based on the discussion this morning, and one, although we heard it from the people from the FDA many times, I still believe there is a misunderstanding among the group that there is confounding by indication, that we would have expected suicidality because of these diagnostic groups. But that's the beauty of having placebo in these trials, and all the comments, you know, a lot of comments this morning were concerned both by an adjunctive

therapy and about elevated rates of suicidality in pain and epilepsy and psychiatric disorders.

Placebo takes care of that for the most part. I mean with placebo, that's why we are not using observational data, and there is as lot of concern about that. So I hope you give some thought to that, that we use placebo as our base rate, and if there is an elevation, because they have those same problems, the same adjunctive therapy, the same diagnoses within a clinical trial as the active medication group does.

If we see an elevation in active relative to placebo within a trial, we can't attribute it to inclusion or exclusion criteria that are constant across the two groups within a trial.

The other is I also have concern about knocking out two-thirds of the trials because of zero events, and I have paid a lot more attention to the risk difference, the risk difference analyses which, when you look--and because that included all the data, and the risk difference being if we had a 1 percent rate in one group, and a 3 percent rate in the other group, the risk difference is 2 percent, and we saw that.

When you look at the plot of risk differences in Dr. Levenson's presentation, maybe it's around page 28 or 26 or something, and compare that pattern to the odds ratios that he presented, two or three pages earlier, the pattern is almost identical. I mean really the sensitivity analyses were really extensive, and I think that was the most important of the sensitivity analysis.

So most of my interpretation of this is based on looking at that risk difference plot because we are using all the data. I made the comment about number needed to harm, the risk difference is the denominator in the number needed to harm.

It is 1 over the risk difference, and now I forget--oh, yeah, it was 1 over I think it's 0.37 percent minus 0.24 percent. That is where I got really--when I said 800, it's 769, if you want to do the math, meaning again that we see an elevation there, and that is using all the data, not just one-third of the data.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: I want to comment on a couple maybe more technical side and for Pfizer's analysis. One thing about the patient analysis, I find the puzzle, you know, the

patient analysis you have set up some kind of prior distribution assuming that, you know, the underlying risk follows certain distributions. And then you have observed the data and you kind of weighted the average of the two in the general sense, so there your posterior data adjust what your pre-assumption as well as you observe the data.

Now, one thing that I don't understand about is the assumption of the model. I mean they give the reason that the prior distribution was assuming, you know, some kind of, well, it's more technical but assume it follows certain distributions, and they justify one other parameter, which is the mean of its ratio or the mean of the incidence, but they did not justify why they choose the precision variable, which I think is a very narrow, which basically nail down to zero for those unobserved data, and then when you do the Bayesian I would think they should allow flexibility between treatment and control group, so that the prior were less important for the placebo arm or treatment arm, so allow you to move.

But now in the finest model, it seems that they are only using one similar prior for both arms, so basically, if 80 percent of the data, as they said, has zero

observations, so you kind of like put a lot of weight on the prior, which you assume are the same.

So, that is why I am kind of puzzled about their odds ratio whether it's valid or not. I hope they did the sensitivity analysis as FDA asked, so that way we can see really the impact of those assumptions.

In terms of absolute risk difference, which means, you know, Dr. Leon articulated earlier, and of course, by including non-zero events, the overall risk reduced 5-fold, which I think clinically very important, but on the other hand, if you look for the confidence width, and the confidence width also shrink by the same proportion or even a little bit more, so that may not affect the statistical significance of the conclusions even though clinically it is important, because you want to distinguish the absolute risk magnitude.

Now, in terms of whether you want to look for individual studies or individual product versus all the class, I thought that the product was developed prospectively and for those rare events perhaps meta-analysis is the best approach, more evidence based and we look for individual studies.

The reason that you have to go through meta-analysis, there will be no hope for this rare event, that one trial can derive conclusion, you know, the valid conclusion that therefore you have to combine the study.

So, when you have a prospective protocol to list all the drugs and then afterwards you say okay, this was different from the other, therefore, I want to take it out. You need very strong justification in order to do that. Otherwise, there are always random variations, and you know that even in a trial, you don't see all people responded, and somebody may respond, somebody may not.

So, you can't say okay, my study is different just because I have a single observation that is different from the others because it's whole protocol, the whole analysis was conducted. That is my comment.

DR. GOLDSTEIN: Thank you.

Dr. Wohlberg, one of the things I guess that was asked for is whether you have the details of how the Bayesian statistical analysis was done on that, if you could maybe give to the statisticians, so that they could take a look at it.

DR. WOHLBERG: The Bayesian models were developed

in conjunction with three external statisticians--Dr. Normond at Harvard, Dr. Maddigan at Columbia, and Dr. Cabrera at Rutgers. But to the specific model features, let me have one of my statisticians speak to that, Dr. Whelan.

DR. WHELAN: The models are outlined around pages 30 and 31 of our briefing document that we sent down, and on page 31, you will see a short paragraph describing some of the sensitivity analyses that we did.

These included adapting the variability to an order of magnitude greater than what was in the base model, and also adapting the effect sizes an order of magnitude in each direction in our prior assumptions.

DR. GOLDSTEIN: That is on a disk and none of us have our laptops here. We don't have it printed out or a couple of us do maybe.

DR. LU: It's in the book. It's page 30 in their briefing book.

I tried to understand when you do the sensitivity analysis, you still apply the same prior to both treatment arms and placebo arm, right?

DR. WHELAN: Yes.

DR. GOLDSTEIN: Dr. Woolson.

150

DR. WOOLSON: I would agree largely with what has been said. Dr. Leon indicated specifically that a strong case could be made for using risk difference in a setting like this, and, in fact, as I went through the briefing book and materials sent ahead of time, and which you made available on the web site, I was somewhat puzzled why that wasn't the a priori analysis that was planned, and sort of expecting that those rates would be low for something like this.

I was not that surprised to see such a high fraction having zero events and the danger obviously in planning for something like a ratio analysis where there is relative risk or odds ratio is that you are going to be having things weighted essentially by the number of events rather than by the denominators, the numbers of patients. That is what essentially what ratio estimates do to you.

So, I was somewhat surprised. Anyhow, I find it heartening that the results did agree, and I think that was important to me. In looking through the materials that were sent to us by the sponsor, for two of their drugs from Pfizer, I compared the Bayesian analysis to the Mantel-Haenszel risk difference analysis.

151

Again, there was a similarity in their results for those analyses within their two drugs, and I thought, for me, the overall question was whether one could justify either putting those two drugs in the group of 11 as a single group, or whether they could justify having them pull that as a separate group, and I thought that was a larger question at hand.

The final thing I guess I wanted to say is that so much of our discussion here has been about the zero events and a number of statistical things that may be of interest to statisticians, that might not be of interest to a lot of other humans. [Laughter.]

But it seemed to me, as in most epidemiologic studies that, you know, the important thing we ought to be thinking about is what is the appropriate effect measure that we ought to be dealing with.

In some settings, it really is the relative risk in a prospective epidemiologic study and in case controlled studies we go to odds ratios because of the proximates, but I think that, to me, is the important thing in choosing one of these is which is the most appropriate measure of effect in the setting.

152

I think in this case that you could make a case either for odds ratio or for risk difference, and I might have chosen that risk difference beforehand and when looking at something like suicide or something with relatively low event given the work that has been done in studying those estimates and the bias.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I have two questions or points of clarification about some of the things that were said.

Dr. Leon, a couple of times you have brought up the risk-benefit or the harm-to-benefit ratio, and you said a few words about the number needed to harm and gave the number of about 800.

So, the first question is I wondered if you might just say again for the less statistically inclined, a number needed a harm of 800, how you view that from an effect size standpoint and how you think about that statistically, public healthwise when trying to evaluate the magnitude of a risk of an agent.

DR. LEON: That is a good question. Again, that 800 was really 769 to be exact. I will use that in my explanation. That is, if 769 patients were treated with an

153

active medication, and 769 other patients were treated with placebo, we would expect 1 additional suicidality event in those treated with active.

Then, the reason I asked that question about the sales figures, numbers of patients, if we take that 769, that we need 769 to see one difference, and then extrapolate to the 11 million people getting it, then, we see a pretty large difference, I mean there is a big public-health impact there.

DR. PINE: But I guess my question was more to the point when we look at a number needed to harm of other agents in terms of their risk, a number of 800 is generally small, right? I thought it was important. Some people could hear that number and think that is really big. But you interpret that in an inverse way, so a smaller number would be worse, and usually the closer a number is below 10, we get really, really worried. So 769, that is a pretty big number meaning a relatively rare event.

Am I interpreting that correctly?

DR. LEON: And if we were looking at efficacy instead of safety, we would want--depending on the prevalence of the disorder, we would want the number needed

to treat, not number needed to harm, but number needed to treat closer to 2 or 3 or, as you said, below 10 for the most part.

DR. PINE: The second question was, you know, you were making the point about randomization, which I agree, I think that was a really good point. I guess one of the other questions that the FDA put to us was how general this effect is across a whole bunch of different ways of carving the data, and we did talk about that. At least to my eye, it looked like there was an interaction in that the effect looked like it only applied in the patients with epilepsy.

Again, from a statistical standpoint, I wondered if you might comment on that specific. I mean I have the slide. It's Slide No. 35 from Dr. Levenson's presentation where he shows the odds ratios.

DR. LEON: If you got to page, Dr. Levenson's page number 34, I think this one addresses it pretty well. So, it is page 34 of Section 2. There, we see the risk differences, and not just the adds ratios, which a couple of us have advocated using, and there you see the risk difference actually is bigger for the psychiatric disorders than for epilepsy, which might, you know, be--so it raises

an alarm there that we don't see with the odds ratio.

DR. PINE: So, you are not reassured in other words.

DR. LEON: No. Initially, when you were making that comment earlier, I had to look, find the slide again, I mean this page again. Again, I would focus on the risk.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: I think we ought to put this into the patient's perspective just for a moment. Statistics are interesting and one additional case of suicidal ideation or behavior out of 800 seems like a small number. Nevertheless, we are not talking about withdrawing a drug from the market. Instead, we are talking about alerting patients and consumers to a danger here. I think that is a very different kind of statement, though, and that ought to be taken in the context of the statistics.

DR. GOLDSTEIN: Ms. Griffith.

MS. GRIFFITH: I appreciate what Dr. Gilman said, but what we saw after the antidepressant black box labeling was a significant fall off in prescription writing and also a real scare factor once the physician black box occurred. So, that is--in my mind, as a consumer, that is what we are

weighing.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: Thank you. I think the risk difference and number needed to treat discussions are very good. It also depends on which event you are talking about. For a completed suicide, I calculated that the number needed to harm was about 7,000, and for suicide attempt it was about 1,700, and the number that I gave before of a difference of per 10,000 people of 5.8, that was for attempt, not for completed suicide.

Overall, I think that the risks are modest in magnitude and uncertain and difficult to put into the context of the potential benefits of the drug. To me, that says that there ought to be a warning. But given what we know about the effects of black box warnings on prescribing, I am not sure that it rises to the level of a black box.

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: I direct this question to the FDA and to the pharmaceutical companies. I wonder if there is any way of recovering information on dose-response relationship to the outcome between the drugs and the suicidality measures.

DR. KATZ: Many of the trials I presume, at least in epilepsy, probably had fixed dose designs. I don't think we looked at that. We didn't ask for that information. I suppose it is possible to get that. We haven't done that. Again, it is very few events in total, so I am not really sure once you start splitting them out by dose, you are going to get terribly useful numbers. I guess we could inspect that.

DR. GOLDSTEIN: Dr. Robinson.

DR. ROBINSON: As we all know, the methodology in terms of assessing sort of suicidal events isn't ideal because these trials were not designed with specific suicide measures, et cetera.

So, one of the questions is always how much of potential events we are not capturing using the current methods, and so I would like--in the Smith/Kline presentation, there was a notation that when you looked at your data again, you added 4 new events that you found that hadn't been reported in the initial sort of report.

I would like potentially, if the people from Smith/Kline could tell us, what they found, you know, to give us a better idea about what they were finding that the

earlier FDA methodology wasn't finding, to give us some idea about potential much of people we may be missing, you know, in the earlier methods.

DR. MODELL: Thank you. I can only respond right now to say I think that is an important question and I will have to get back to you with exactly what those four events were, but I think that is worth looking at.

DR. MENTARI: In the correspondence that I received from GSK regarding those additional events, my understanding was that our request to have the comment sections of the adverse event reports searched was inadvertently admitted, so the additional events that were provided were actually an inadvertently omitted part of our requested search.

DR. ROBINSON: Also, for both Smith/Kline and Pfizer, one of the things I think the Committee has had sort of a question about is in terms of concomitant medicines or in some ways if anticonvulsants as a class have a potential to increase suicidal behavior, you know, would you find, if you are having a trial with multiple concomitant meds, more of it.

Obviously, for the FDA, you couldn't do that as

much because of what you had asked the companies, but when the companies were doing these detailed analyses, did they find any effect in terms of monotherapy versus concomitant meds, because obviously, you guys have your own data sets and you have been looking at that very closely.

DR. WOHLBERG: Specifically, for epilepsy, as I said during the presentation, we had two events in the epilepsy studies. One was a completed suicide. That patient had a history of major depression and was taking venlafaxine. The other patient was a suicide attempt with a history of major depression, taking fluoxetine.

When you have 7 versus 3 events, it is hard to know whether there is an interaction, but there are cases of concomitant medical histories or past histories of psychiatric conditions as you would expect in the disorders that were studied.

DR. MODELL: I will have to get you those data. We looked, they were relatively small number of concomitant meds, but I don't recall that we saw any interaction with concomitant medications.

DR. GOLDSTEIN: The estimates that we had for number needed to harm, that is based upon the total number

of events across all these trials.

I was wondering now that might change if you do it on a per-year annual basis. In other words, you know, how many people would you need, how many people treated for one year would be expected to have either the actual suicide event or this more global measure?

As a physician thinking about it, that is sort of the thing that people keep in their mind when we lose sight of the length of treatment. It sort of makes it a little harder to understand.

DR. LEON: I don't know if we had number of person years for each group. I might have seen that in one of these, but we would need the need the number of person years from each group to be able to deal with that.

DR. KATZ: I think we actually do have that somewhere. I don't know if we have a slide, but we did look at that, and I think Mark talked about that.

As Evelyn pointed out, we don't have any data beyond 24 weeks, so anything we would say--we do know that within the durations of the studies that we looked at, the risks seemed to at least be stable, if not increase over time. But we have no empirical evidence from these trials

beyond 24 weeks, and I don't think we have very many trials at 24 weeks either. I think the mean trial duration was 14 weeks.

We would really be extrapolating beyond anything we had if we start talk talking about what is the risk over years. I think that is a concern we have is that we saw it in short term trials, what will happen in long term trials, but I think that is a complete unknown.

DR. GOLDSTEIN: Dr. Lu

DR. LU: I just want to follow up a question actually I asked early this morning to Dr. Levenson, and I think Pfizer's presentation also raised the issue about the indication class.

If you look for the contribution of the drugs to each indication, the largest variation actually is in the other class. We know that one of the drugs that has a large contribution to all these, but in particular to the other section, is the drug called topiramate.

Anyway, this drug has odds ratio of 2 something, it is always in all these relative comparisons of 3 indications. I asked you this morning about sensitivity and if you excluded that, what happened.

DR. LEVENSON: I don't have much more to add than what I said earlier today. When you look at the forest plots of the individual drugs, topiramate is not really an outlier, it does have a lot of patients, but in terms of odds ratio, it is kind of right among the drugs.

DR. GOLDSTEIN: Dr. Rizzo

DR. RIZZO: I just want to make sure that I understand one point. Is there any evidence one way or another if the increased risk of suicidality, after stopping the medication, persists or stops? In other words, is it possible that a person would be having increased suicidality for weeks or years after taking the drug, and could you say anything one way or another?

DR. KATZ: Well, we excluded trials or events that occurred anytime later than one after the trial ended, so we have no information about what happens over time after drug is discontinued. We just didn't look for that. We didn't ask for that data, and we didn't look at it.

DR. GOLDSTEIN: Dr. Armenteros.

DR. ARMENTEROS: I was wondering, were the trials excluding patients that had suicidality on baseline, and if so, that is good, if not. Is the data available to

compare, not only the incidence of this event, but whether there is a difference between baseline data and then the occurrence.

In other words, if we have some events, you know, suicidality thinking at baseline, is there any way of measuring maybe the disappearance of such during the trial?

DR. MENTARI: Regarding your question on whether suicidality or suicidal thoughts existed at baseline, it is contained in my review. I don't have the data in front of me, but I can say that the exclusion criteria related to baseline psychiatric illness and suicidal thoughts really varied from drug to drug, but it is contained in the briefing packet if you want to refer to that.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I want to come back to the issue that Ms. Griffith and Dr. Hennessy raised, which I thought did nicely summarize some of the issues about black boxes and their potential unintended consequences, and maybe ask the FDA to talk a little bit more about the points that were raised by both people in terms of what have you learned from the black box experience with the antidepressants in terms of intended or unintended consequences that we should

consider and think about when we evaluate what the most appropriate action would be in the current situation.

DR. GOLDSTEIN: As an addendum to that, could there be a more nuanced approach rather than a black box, but just a warning or alert of possible concern rather than black box?

DR. KATZ: Let me just answer the second part, because that is easier. Of course, there could be--we are coming to you asking your advice on whether or not you think a black box is warranted, and if it is what should we say, and if it is not, where should we put it and what should we say.

My only view about putting something in labeling, even if the something is a bad thing like suicidality and a serious thing, is we have to be pretty sure we think the drug did it before we put it in labeling. Then, we can figure out where to put it in labeling. I mean that is the first thought of question, but certainly how we say it, where we put it, it is up for discussion, sure.

DR. TEMPLE: Before Tom tells us what our experience is, there is one other thing to think about, and that is, how much to say about the data. In the depression

one, we give the conclusions, but we don't give a lot of forest plots or anything like that.

One possibility here that the previous conversation has made me think about is that we might sort of have a section that describes the data with its infirmities. I mean it would be a big step to do drug by drug and say, oh, well, it doesn't look like this one did, but there is still things you could say about it and caveats, and even explaining the difference between risk ratio and actual numbers needed to harm or actual risk.

Those things seem like matters that the Committee was quite interested in, and those things are all on the table from our point of view. We don't have a rigid way.

It is our inclination, though, that if something is important, it gets noticed better if you put a box around it, and it doesn't mean--and Tom is going to emphasize this I know--it doesn't mean don't use this drug. It means pay attention, think about it, if the person gets funny, note that it might be the drug doing it.

But you are right, there can be unintended consequences, but I have interrupted Tom long enough.

DR. LAUGHREN: Clearly, when we were thinking

about what to do with the antidepressants, we worried a lot about unintended consequences. The Committees on both occasions are worried about that.

In terms of what the impact has been, we have some early results, but it is probably something we are not going to learn for some time. Actually, Andy Leon, in a nice editorial about this referred to that regulatory action as sort of a public health experiment.

I think what we have learned is that prescribing in pediatric patients of antidepressants has declined somewhat since the introduction of the black box. But the other part of that, you know, what has happened with suicides is less clear.

There was a lot of concern at the time that we had the Advisory Committee in December 2006 about a possible increase in adolescent suicides because the preliminary data from CDC had just come out, but now the numbers--that was for 2004--the 2005 numbers are down somewhat. They are not down to where they were in 2003, but they are down from where they were in 2004.

Actually, the change in antidepressant prescribing didn't occur until 2005, so I think the only thing we can

say at this point, it is not clear. It is not clear whether or not the black box has had any impact on the thing that you care most about, which is suicide.

You do know that prescribing is down somewhat. That could be a good thing, it could be a bad thing.

DR. PINE: Well, I guess on that point, that is from again an FDA perspective in particular, and again going back to where we were when the black box first came out, you know, were you surprised by that, did you expect that down turn and if yes or if no, how does that influence what we would think about now.

Given that it happened once, you know, should we be thinking that if we put a black box here. Maybe there is going to be a similar down tick in prescriptions of antiepileptics, and maybe that should be part of the equation what we discuss here.

DR. LAUGHREN: First of all, let me go back to what is actually in the box. As Bob Temple pointed out, it doesn't tell clinicians not to use the drug. It says that if you are going to use it, do basically a risk-benefit analysis, consider the risks, consider the benefits.

In terms of, you know, we didn't know really what

to expect in terms of prescribing. It is always hard to predict what the impact is going to be. It is something you worry about, but it is hard to know.

What has happened, I think everyone is in agreement that there has been a slight decline in prescribing in adolescents. There has not been an epidemic of suicides, but it is too early to tell. We will know over the next three to four to five years I suppose.

DR. PINE: Let me make one last comment and then I won't say anything more about this. I mean obviously, from my line of questions, I have a certain point view, and to be explicit, I voted against the black box both times, and I think that there was real concern at that time that there was going to be a decrease in prescribing, and I think a lot of people weren't that surprised when it happened.

I realize that you guys say that it doesn't say not to prescribe in the black box, and that you really do not--you want only people who need the medicine to get prescribed the medicine, you want physicians to think very carefully about that. But, given what happened in the past, I think it at least has to be on the table as a possibility that the actions here will influence the likelihood with

which medications will be prescribed.

DR. KATZ: Look, we have to acknowledge that even though we don't say don't use them, you put a box warning on, it affects people's prescribing or is likely to anyway. But again, it depends upon what the indication is.

I think we would assume--and this is obviously something for the Committee to discuss--but I think we would assume, for example, in epilepsy, if every drug approved to treat epilepsy has this language, it is very unlikely that people are going to stop treating people who have epilepsy. There is no alternative to turn to that is approved that doesn't have that in its label as well or assuming this comes to reality.

I don't think we would expect--but again there is lots of off label use. There are other things that are approved for that are perhaps not as serious as epilepsy, so as Tom points out, the decrease in prescriptions for antidepressants might be a good thing, it might be a bad thing. It may be that people who shouldn't have gotten them in the first place aren't getting them anymore, while physicians who don't really know how to wisely prescribe them aren't prescribing them anymore.

So, it's hard to predict, but yeah, we certainly acknowledge that just because we don't say don't use them, we know the box has an effect or expect it would.

DR. TEMPLE: The other thing, of course, is you can emphasize something at the expense of other things. The box for antidepressants now says the major reason for committing suicide is being depressed, so it says that. That was an addition.

Of course, one of the things that was at least somewhat distressing to me about the whole antidepressant thing is that we were looking at studies of acute depression, which is where this emerged, and if you think about what the likely benefit of an antidepressant is, it is preventing recurrence over the long term or at least that is my impression. I am not the shrink here.

Of course, there were no studies of that at all, so we are very conscious of trying to present a balanced picture and call for your help in doing that. But I think what Rusty says is surely right, nobody is going to stop treating epilepsy. That is hard to imagine.

DR. GOLDSTEIN: Dr. Potter.

DR. POTTER: I actually want to follow up on

something Dr. Leon was saying and perhaps ask him or the Committee about some implications. I think he drew very clearly the number needed to harm and, if you run the numbers over large numbers of people, you clearly have a public health problem potentially, which you want to alert people.

At the same time, given the statistical arguments, the conclusion of the statisticians is you can see no difference between drugs, but--and this is more than a mind game--but if you really believe that multiplied out, there is a significant health problem in the relative risk of a suicidal behavior, then, I would assume it would be very important to know if there are true differences between drugs and if the relative risk difference is shown in the FDA analysis from 5.4 to minus 4.16 on carbamazepine, just to take two numbers, if there is any reality in that, is that important to know, and are you losing that information or how does one follow up on that potential information?

It is interesting. I mean I understand from a risk point of view you emphasize the risk, but embedded in here is another question, are there real differences between drugs, and it seems very difficult to address that issue or

even talk about what one might do to address that issue.

I mean it is a point and obviously from society and a drug development point of view, it is extremely important for us to know how to go about this. But, frankly, one's concern is if the standards for saying that drugs are different and you lump them together with data like this, are so difficult to exceed, then, the likelihood that we, as a society, will invest what you need to do to show that one drug is different from another. It is something we all need to deal with, that is all I am going to say.

DR. TEMPLE: Can I just comment on that? Bill has identified what we I think said at the beginning, or Rusty said at the beginning, is one of the major fundamental problems here.

Our initial conclusion as you heard is that the sorts of differences that we have seen are expected with relatively small numbers, so they don't prove to somebody's satisfaction anyway that there was a difference.

But it is a profoundly good question and one of the issues I think is how much one should say in any box or other warning that you give about the variability and how

much you should dismiss it and how much you should emphasize it, and all kinds of things like that, and you are right.

Once you have a, quote, "class effect," the kind of evidence you would need to make it go away is daunting to even think about.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: I would like to address the issue of the unanticipated effects of putting a black box. Parents of children with epilepsy are really very concerned about adverse cognitive and behavioral effects on their kids. And the neurologists might continue their prescription patterns, but the parents make the decision if the children are going to get the medication or not.

We really don't want parents to withhold medication from their kids because of their concerns of these adverse effects, and seeing suicidal ideation I am sure would make parents very concerned.

The issue about withholding these meds from the kids, we also know that withholding meds have significant adverse cognitive, linguistic, academic, and other effects, so this really is a serious issue.

The other thing is in terms of adolescents and

young adults, the driver's license is a very important thing and one can easily see that patients might not tell the truth about suicidal ideation, because they want to get these meds because they need their seizures controlled so that they can have their driver's licenses.

So we really have to think about the different aspects of this.

DR. GOLDSTEIN: Dr. Goodman.

DR. GOODMAN: I want to add to Dr. Pine's comment and I think also to your's, Dr. Caplan. I also sat on those hearings and actually voted for the black box, and I shared the concern of unintended consequences, decreased prescriptions being written. But that was offset in my mind in part by wanting to alert the clinician and the consumer to the possibility that, during the course of antidepressant treatment, if one saw deterioration in mood or the emergence of suicidality, that you would think that that could actually be an iatrogenic effect that you wouldn't automatically assume it was just the underlying illness not responding to treatment, because I was concerned that the reflex action might otherwise be let's increase the antidepressant, in which case one would see more deleterious

results.

What I am not sure of, and I would be interested in hearing from my neurologist colleagues around the table, is whether there is an analogous situation here, and maybe there isn't. Maybe my reason in part for voting for the black box and depression doesn't obtain here in the treatment of epilepsy and that you may not be as concerned about changes during the course of treatment where you would want to back off.

DR. LEON: I wondered when Dr. Katz was talking, I wondered if--there is at least one device that was approved for--I know this is drug evaluation, the Center for Drug Evaluation, but there was at least one device approved for epilepsy. Did you look at the data, the suicide data there from their trials? No?

DR. KATZ: No, we didn't ask for that. That is a fair question obviously, but no, we didn't.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: Actually, my comment has been made by someone else. Thank you.

DR. ROBINSON: Just to sort of follow up on Wayne's comments. As somebody who also was at the

antidepressants hearings, I think one of the other things that we have to keep in mind is when we had the public testimony at that, and I don't know what our public testimony is going to be, but there were family after family who got up and who said nobody had told us that this was something that could happen, and then the worst thing happened, which is their child died.

It was very hard to make the argument that these people shouldn't have known about a potentially fatal side effect even if it's a very rare side effect.

The other issue, which I think also came up a lot in the public testimony was a lot of the families that were telling their stories, the medications were not being really prescribed by a psychiatrist. They were being prescribed by a general practitioner, et cetera.

The real question is, you know, GPs, are they really asking the patients about their level of suicidal ideation, that sort of thing. That is one of the things also I think we need to think about with these drugs when they are not being used in a non-psychiatric setting, how much of the time is the person prescribing really asking about suicidal ideation and during the sort of follow-up

about that.

DR. GOLDSTEIN: Dr. Malone.

DR. MALONE: This is also a comment about the black box for the antidepressants. I did vote for it. I think probably one of the big differences is at that meeting, we also had efficacy data, and one of the concerns was that there was not a lot of data to show that the drugs worked. But there was, you know, this--it wasn't a lot of data, but there was data to show that it may do harm and cause suicidality, so I would think it's a different situation.

Here, I think that we have data that the drugs--I am not a neurologist--but I guess that the data shows that they treat epilepsy.

DR. KATZ: We approved it.

DR. MALONE: Which is lacking in the child meeting, and I think that could make a big difference in your weighing of the significance of the side effect.

DR. GOLDSTEIN: Again, as a neurologist, the situation is not analogous. As was mentioned before, you had a disease where the outcome that you were treating also was considered to possibly be one of the side effects of the

178

drug, so separating those two is extraordinarily difficult.

Here, we have got drugs, if we are just talking about them as antiepileptic agents that are treating a condition, and there may be this has some potential side effect, and that is also, by the way, one of the things that we have to come to closure on that we haven't, do we think that there is a real signal here or not.

Dr. Griffith.

MS. GRIFFITH: By the way, it's Ms.

DR. GOLDSTEIN: Sorry. They don't tell me.

MS. GRIFFITH: To Dr. Malone's point, when we had the first set of hearings in '04-'05, indeed, the efficacy data wasn't there. By the time we met again in December of '06 to look at extending the black box labeling to a group 18 to 24, which was considered pediatric by some extension, we did have better efficacy data.

I voted against the black box label extension at that point because I had seen the precipitous drop-off and it really worries me, and to Dr. Caplan's point, there is a sense of needing to protect pediatric patients.

You have to protect the children. Obviously, they are not doing the risk-benefit analysis, and if the parents

179

are frightened they are not going to get the drugs. But one of the things that bothered me, and bothers me about this discussion, too, is I just don't want to see us rush headlong into a black box warning.

One of the reasons we did impose a black box label, Dr. Temple, when we were talking about this before, was the notion that we wanted a sense of consistency. When we put a black box on the labeling for pediatric patients, it was to be a consistent judgment that we extend it to age 24. I don't think that was a judicious move on our part, and I am afraid that we are just now going to look at all of these drugs and rush to the black box because it's expedient.

DR. GOLDSTEIN: Thanks. Again, nuancing this is certainly on the table as we discuss this, this afternoon.

We have about five minutes more, and a few folks that have questions or points to make, I would like to try to run though them, but try to keep them pointed, if you could.

Dr. Caplan.

DR. CAPLAN: I would like to address Dr. Goodman's comments and the issue about the iatrogenic effects. So,

180

what happens with the parents of kids with epilepsy, they rush to blame everything on the medication, and, in fact, we had a very, very high rate of undiagnosed psychopathology in these kids because the parents say that everything is due to the medication.

So, again, putting the black box here really will have the opposite effect .

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: Since some of this is inevitably a numbers game. If the risk were you had to treat 100,000 patients, the warning required might be different. So there is some magnitude effect, and there is pretty good data on death rates in epilepsy and also from some large cohorts of surgical treated patients who respond and don't respond, increased death rates in the patients who have unsuccessfully treated epilepsy compared to a cohort that had severe epilepsy that underwent the same surgery.

So, I think from your antidepressant data, you might be able to make some general assessment of, if prescribing decreased by this amount, given these risks of inadequate treatment, how does that weigh against what are confidences for the patients to harm, to at least give some

181

sort of sense of what might be the down side to placing a black box warning label versus what we believe is the down side to what is the current state of practice where it is sort of being done in ignorance.

It might help provide some sense of what is the appropriate response in terms of the magnitude of harm of labeling as opposed to not doing anything.

DR. KATZ: Again, we haven't thought about this, it's a fair question. I just think that there are so many assumptions you would have to make and so many unknowns about whether or not the prescribing habits that followed the change to the antidepressant label will be the same as in the anticonvulsant world where they are indicated for very different things.

Again, it is a fair question. We haven't entertained it internally, but it seems like there would be so many assumptions that you would have to make that you would be I think hard pressed to believe what you ended up with. But it is something to consider.

DR. ANDERSON: The assumption, I agree there would be a ton of assumptions, but they would at least be somewhat more numerically based than poling a room full of people

based on their idiosyncratic opinions based on their practice.

I mean at least you would be able to say, well, we know that this numerically happened for antidepressants, we know that this numerically happens in untreated epilepsy, so this provides some context for interpreting our expert clinical advice.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: I just wanted to make the point again that people with epilepsy, perhaps 50 to 75 percent of them are not well controlled on their medications. Those who are not controlled are usually given an additional medication, and that continues. Moreover, there is good evidence now that epilepsy, each seizure can be damaging to the brain, because of glutamate excitotoxicity.

So, we don't want people to have epileptic events. People with epilepsy do continue on to have their seizures and they continue to have medical care, and these are people often very disturbed, who may be depressed because of their seizure disorder especially in adolescence.

So, that has to be taken into account when we think about a black box or any of that kind of warning. On

the other hand, it is very important that the parents and the patient with the epilepsy be aware of this danger.

So, I emphasize the latter in my thoughts here. We need to make people aware that there is a danger here.

DR. GOLDSTEIN: Again, one of the things that could be done explicitly is say that this is an issue but that it is not any reason to stop treatment with an anticonvulsant. It is just a warning to be aware that this may occur, but not an indication for stopping.

Dr. Lu.

DR. LU: I think I heard a lot of discussion about epilepsy, that this black box labeling will not perhaps stop the treatment. But my understanding is that the black box will apply not just to epilepsy but also psychiatry as an indication including neuropathy. So, because I am not a clinician, so any discussion on the other side of the story?

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: If you don't mind, Dr. Goldstein, I will wait until this afternoon.

DR. GOLDSTEIN: That will be fine. Dr. Twyman.

DR. TWYMAN: I have a question for the statisticians. Let's assume that the effect is

generalizable to the class of AEDs. But, if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or do you need the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?

DR. LEVENSON: I would say that we need the entire data set in this case.

DR. GOLDSTEIN: We are going to take a lunch break. First, let me reiterate to the members of the Committee it is fine to talk about Duke basketball, it is not fine to talk about anything of substance or anything related to our discussions. Sorry.

We are going to reconvene in one hour at 1 o'clock.

[Luncheon recess from 12:00 Noon to 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

Open Public Hearing

DR. GOLDSTEIN: Would everybody please take your seats and let's come to order.

This is the open public hearing portion of our deliberations.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

As just a procedural thing, each speaker has been given four minutes to talk. At three minutes, an orange light goes on, on the podium. At four minutes, the microphone is turned off and the next person will be allowed to speak.

We will go in order and I will recognize the people just by number, if you will excuse that, and you can introduce yourselves. So, first, the first speaker, No. 1.

MS. CRAMER: I am Joyce Cramer, President of the Epilepsy Therapy project, a non-profit organization devoted to advancing development of new therapies for epilepsy, and my slides do not seem to be working. There, we are.

As I say, I represent a non-profit organization. In my role as President of this organization, I am here to represent researchers and patients with epilepsy. We do not support the findings of the FDA--I am missing a slide in here--that suggest that the suicidality risk is related to antiepileptic drugs as a class.

We offer data from the Department of Veterans Affairs database to demonstrate that suicidality and epilepsy is related to comorbid psychiatric diagnoses, and not the medications. These data demonstrate that the FDA data are not replicable in population-based studies and as you see in this slide, we have done a thorough analysis of a clean data set from the VA.

We know from history and from the literature that there are factors associated with an increased risk of

suicidality among adults. Our cohort looked at newly treated people on monotherapy with all diagnoses. We looked a primary outcome of suicidality including completed events.

Top line results. If you look at the bottom center of this slide, you see 6 cases or 0.08 percent among those with epilepsy, 0.06 percent among those without epilepsy and with other diagnoses, but using AEDs in monotherapy, newly treated, not statistically significant difference.

Top line results. The primary predictor of suicidality is a previous diagnosis of a psychiatric disorder usually depression resulting in odds ratio of 4.42 after initiation of an antiepileptic drug. No significant differences among the AEDs or among any indications. Note again that this was newly treated monotherapy.

What to change, if anything, in future controlled clinical trials? The problem obviously may be comorbidity. We have the advantage of being able to look back over four years and know what our patients were doing before they were treated with an antiepileptic drug.

We already have patient-reported outcome, screening tools that can observe effects on mood, as well as

MEDDRA spontaneous report data collection.

Let me give you an example of an ongoing or recently completed clinical trial of esclicarbazepine that included a quality of life instrument within which was the MHI-5 series of mood items, a well-known screener for depression, also included the Montgomery-Asberg Rating Scale in which the 10th item asks specifically about suicidality, and in this study, there was no signal of suicidality in this population. That should be adequate information.

We have tools that work and these are not class effect.

Another example is looking at some older data from levetiracetam, looking at the old COSTART data terms, we find that the difference in suicidal behavior that were reported was treatment responders and treatment non-responders as opposed to by class or versus placebo.

We have these screening tools. I am not in favor of developing new ones as an academic instrument developer I know, I am very familiar with the FDA guidance on instruments and am very concerned about these issues.

I want to remind you that depression in epilepsy screening is a practice guideline. The risk of suicidality

is probably not related to the epilepsy but to--[end of allotted time].

DR. GOLDSTEIN: Thank you. No. 2.

DR. REGIER: Good afternoon. I am Darrel Regier. I am the Director of Research for the American Psychiatric Association, and I am representing a professional medical association of approximately 38,000 psychiatrists.

Our concerns include the following: the adequacy of the statistical findings on which the recommendation for a black box warning is based; secondly, the potential impact on clinical practice of reducing the use of mood stabilizers; third, the public health impact of a black box on population mortality rates from suicide; and, fourth, an interesting concern is how we would communicate the proposed medication risk to our psychiatrist colleagues as part of our recently developed partnership with FDA and the AMA in this joint communication effort.

Certainly, these medications are not only for antiseizure purposes, but they are clearly used as mood stabilizers, and they are not all equal as mood stabilizers. Some of the medications being discussed are truly life-saving for the majority of patients who take them through

stabilization of severe mood disorders and a subsequent reduction in the associated high risk of suicide.

Numerous studies have documented that the highest risk of a suicide attempt in patients with bipolar disorder occurs when patients' symptoms persist or when the patient relapses, and certainly the data that the FDA studied does not seem to suggest that the risk of suicidal thoughts and behaviors outweighs the potential harm from medication changes of discontinuations that could result from a black box warning.

Now, in the fall of 2004, the FDA began this natural experiment of using the black box warning for antidepressant medications. There was a rather precipitous drop in the prescription rates as Dr. Laughren has mentioned, and, in fact, there was an increase around that time in the rate of child and adolescent suicide, an uptick that has not decreased significantly since that time.

So, with no clear understanding of the true public health impact of the black box warnings, it is vital that the Agency, first, do no harm, and one possible harm is the dilution of the impact of the black box warnings when they are applied on the basis of such minimal evidence.

An increase of reported adverse events of spontaneous reporting of suicidal ideation from 0.22 percent to 0.37 percent for all of the active medications needs to be contrasted with the epidemiological rates where we find that instead of less than 1 percent in this clinical population having suicidal ideation or behavior, up to 20 percent is found when there is systematic assessment, and putting it in this epidemiological context makes you really concerned about the ascertainment bias that exists with the current focus on adverse events that are spontaneously reported.

So, we are certainly concerned also in the memorandum that Dr. Katz provided, that the memorandum does not include, as occurred in the SSRI memorandum, a statement about the benefits of taking antidepressant medications to treat serious life-threatening depressive illness. A similar balancing of benefits and risks for the treatment of mood disorders and seizures would be considered, should be considered for this class of medications if, in fact, you decide to add a black box warning.

Finally, we want to reiterate the concern that there is a need for prospective systematic assessment of

suicidality as the FDA is moving toward as opposed to relying on these retrospective spontaneous report of events that are not the purpose of the original clinical trials.

Thank you.

DR. GOLDSTEIN: Thank you. No. 3.

DR. EGILMAN: I am Dave Egilman. I am a physician at Brown and also I have been a consultant to the folks from the Citizens' Petition.

I had a slide show, but I guess we will skip it.

I am going to start by taking off on Pfizer's argument, because I think it is a relevant argument. Pfizer comes here like the kid who kills his parents and pleads for mercy because he is an orphan.

In other words, they say, well, our drug is not used for epilepsy. Of course, that is because they fixed it so that people would use it for no indications that had any benefit whatsoever, and contrary to what their representative here said, neuropathic pain is not the majority use. Epilepsy is 2 percent of the use of Neurontin by example.

If you look at the drugs, and if I can get to the 7th slide, we will get to, this is the Pfizer slide, I urge

you to look at that slide. That righthand column is the percent non-epileptic use, 98 percent of Neurontin is non-epileptic. You have got to get two-thirds of the way down the chart, and the big drug prescription numbers are at the top of the chart. Neurontin is the big drug here in terms of number of scripts, 12 million. You are way down in the hundreds of thousands when you get to the bottom of the chart.

So, we are talking about not epilepsy, we are talking about back pain 8 percent, migraine 4 percent, bipolar 15 percent. There is some suicidal risks, so now we are adding to that with bipolar disease.

Other psychiatric, 23 percent. So, when we are talking about warning, what you are doing is warning physicians who are mostly GPs, who are using these drugs for diseases for which there is no benefit, no proven benefit, and that is Pfizer's number, okay, and don't think that the other, which they put as postherpetic, which is an approved use for Neurontin, has fewer than 100,000 treatable cases of that per year, and trust me, they are all not getting Neurontin as hard as they try to market it.

So, the impact of the warning will not be on

epilepsy treatment. It will be on all these other diseases for which there should be none of these drugs prescribed in the first place.

A couple of comments on warning. There has been some talk about whether the word "chronic" should go on. Well, I think that is going to be--I look at that from a different perspective. You have got data that goes to 14 weeks. You have got a separation on Kaplan-Meier curve really immediately, but certainly after a week.

Three months of use, which is your average data, is not chronic in terms of epilepsy, so if you put chronic, people will think in years, when you really have data for weeks and months. So, it is really not chronic, it is really short-term use that has been associated, because short term for epilepsy is three months.

Now, in terms of just data, it seems like there is a lack of data here. We are debating or you are debating, you know, how many angels can fit on the head of a pin, and not only that, you want to know if they are fat angels, skinny angels, or how many of the angels were saints. But data is not there for that. But there is some data that you are not considering, you are not doing, you are not ordering

them to do case-controlled studies with large data sets, observational data, and you haven't presented the challenge/rechallenge data.

Somebody asked about what evidence is there when you go off the drug, whether the risk goes away. In the Pfizer data set, there are at least two Neurontin cases, maybe more, where the person on the drug suicidal, off the drug not suicidal. Rechallenge, suicidal. That is powerful, powerful evidence, and that evidence exists for some of the other drugs. I don't know why it hasn't been presented here.

The last is the mechanism. You heard a lot about why the mechanism isn't there. Well, the mechanism, that is evidence under Hill's consideration, you know. Increase GABA, decrease serotonin, decrease serotonin, increased depression, increased depression, increased suicide.

Antidepressants drugs are used to increase [end of allotted time].

DR. GOLDSTEIN: Thank you. No. 4.

MR. FINKELSTEIN: Thank you. I am Andrew Finkelstein. I am an attorney in New York and Chairman of the Neurontin Federal Multidistrict Litigation in Boston and

lead counsel in the Neurontin coordinated litigation in New York State Court.

My firm represents over 250 families of victims of suicide and over 500 people who attempted suicide while taking Neurontin. During the course of the litigation, we have discovered documents which illustrate both Pfizer, then Warner Lambert and the FDA have known since 1992 that Neurontin is associated with suicidality.

At that time, FDA's clinical reviewer voiced concern over Neurontin's capacity to lead to suicides. Given the limited population which approval was sought, which was adjunctive treatment for refractory seizures, the clinical reviewer and the Advisory Committee recommended approval for use in a specific population.

However, Pfizer's illegal marketing of Neurontin off label was in direct violation of FDA's limited approval. When they did, Pfizer failed to disclose their knowledge of the increased risk of suicidality caused by Neurontin.

Their action resulted in direct harm to thousands of American families across the nation. Now the FDA has recognized that the data from its meta-analysis in fact shows the increased risk, something that has been known for

16 years by Pfizer.

When someone has a sudden mood change, emergence of or worsening depression or suicidal thoughts, the proposed warning will inform that it might be drug induced. As a result, the patient will be more willing to speak up to tell a loved one or a physician. Family members and physicians will be on the lookout for these mood changes, whereas, up to now, they are not.

Without such warnings, thousands of people will continue to be left thinking their changes must solely be them, without any consideration that their new or worsening thoughts may be related to their prescriptions.

One must not overlook the search terms FDA left out when they told pharmaceutical companies here to collect the suicidal events for their analysis. The companies did not include adverse event reports of increased depression, anxiety, hostility, akathisia, mania, or hypomania.

As the 2000 FDA alert states, symptoms of anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Yet, those events were not even collected or analyzed as part of the FDA work year. As a result, the analysis did not consider many events relevant

to suicidality.

FDA does not know, and did not include as part of this analysis, how many people in the submitted clinical trials dropped out because of increased depression or increased anxiety.

In Neurontin, for example, the preapproval clinical trials had 5.3 percent of the total exposed population report depression as an adverse event, which amounted to 78 people out of the clinical database of 2,048.

Importantly, of the 78 people who reported depression, 19 had no history of depression at all, and 9 of them had to withdraw because of the severity of their drug-induced depression.

Yet, FDA did not ask pharmaceutical companies to collect the treatment emergent depression. I know the FDA can have all the documents we get in this litigation. They don't see the manipulation by the drug companies when they minimize the adverse events by coding self-inflicted stab wound to the chest as psychosis with chest wound rather than what it really was, a suicide attempt.

I strongly recommend you ask the companies for the case report forms related to depression, hostility and

anxiety, and you will surely find many more qualifying events.

The FDA is not asking for a recall here, nor are we. We are asking solely [end of allotted time].

DR. GOLDSTEIN: Thank you. No. 5.

MR. ALTMAN: My name is Keith Altman. I am the Director of Adverse Event Analysis for Finkelstein & Partners, a law firm in Newburgh, New York.

By way of disclosure, my firm represents individuals and families that have been harmed by adverse effects associated with Neurontin.

In March of 2004, my firm contacted the FDA because of the large number of calls we received reporting suicidal behavior and Neurontin. The vast majority of these calls were for off-label uses and about half of those were for uses other than psychiatric conditions.

At that time, the FDA urged us to obtain experts to review the data. We have done so and brought copies of these reports for the FDA and the Committee.

In May of 2004, after detecting an increased reporting of suicidal events for Neurontin, I submitted a Citizen's Petition for the Neurontin label to be enhanced to

one of suicidal events. The petition was based upon data that existed before my firm became involved in September of 2003. In March of 2005, I submitted 258 Medwatch reports with completed suicides after which the FDA stated its review of suicidality in part because of the submissions by my firm.

Aside from the review of the placebo-controlled trials, I would like to point out to the Committee that there is much additional information. The expert reports I provided are comprehensive analysis of one of the drugs Neurontin. These reports were prepared using the same methodologies used by industry reviewing the safety of a drug.

A review of all of the available data on Neurontin shows that in the original 1992 NDA clinical review, they were concerned that the drug could lead to suicidality. The FDA medical reviewer stated that Neurontin may lead to worsening depression and suicide as there were suicidal attempts in the clinical trials. The clinical trials also showed several suicidal dechallenge events, and there was one very well documented dechallenge/rechallenge event with tight time association.

A review of postmarketing safety information is also instructive. There were numerous reports of the very behaviors that the FDA suggests should be included in the Med Guide for AEDs. As the current slide shows, the percentage of serious Neurontin AEDs associated with suicidality compared to that of the background shows there was a strong signal by the middle of 1999.

In the past, the FDA has required labeling changes and requested products be withdrawn based upon similar postmarketing data. It is also important to consider the extensive off-label use of many of the antiepileptic drugs. I make no comment on whether or not this practice is appropriate.

This slide shows the approximate breakdowns in about 2003 of several of the AEDs. Since we have focused on Neurontin, the chart shows that 7 percent for epilepsy and a small portion of the neuropathic pain used were for on-label indications.

This means that on the order of 85 percent of individuals using Neurontin were without any clear guidance on safety and efficacy. Furthermore, Pfizer was well aware that many of the trials in off-label populations failed to

demonstrate efficacy.

A review of the Neurontin clinical trials shows that for the off-label indications, there has been little, if any, testing. For example, psychiatric conditions representing 38 percent of the use of Neurontin were tested using 144 people and 21.49 patient years of exposure.

With a background rate of about 1 in 250 patient years, it is unlikely to see suicidal events in this population. Other indications are no different. In many of the studies, individuals with serious psychiatric conditions were excluded.

Looking at Pfizer's internal adverse event database for suicidal events by indication, one sees that there is a very strong signal associated with psychiatric uses. Although this chart is not, by itself, meant to prove that the drug is responsible for any of these events, the totality of the data is strongly suggestive of an increased risk.

Therefore, in conclusion, it is crucial for the Committee to consider that the placebo-controlled trials are the tip of the iceberg and that a more detailed review of one of the individual drugs Neurontin shows that the entire

experience is consistent with an increased risk of suicidality.

Furthermore, the Committee should take the off-label use and lack of adequate testing into account when recommending what action should be taken and provide meaningful warnings in that context.

Lastly, contrary to Pfizer's conclusions that the lack of statistical significance for Neurontin is evidence that there is no increased risk, the totality of the information says otherwise.

Thank you.

DR. GOLDSTEIN: Thank you. I am told there is no No. 6, so on to No. 7.

MR. BRIGGS: Thank you. My name is Andrew Briggs and next to me is my mom, Robin Briggs. I must first disclose that she has a pending lawsuit in which Finkelstein & Partners represents her for the death of my father due to Neurontin use.

I come to speak to you on behalf of those affected by the suicidality caused by the epilepsy drugs that we are discussing today. My father, Dr. Douglas Briggs, was a well-known and very well liked family physician in a suburb

outside of Charlotte, North Carolina.

After attending medical school, he built a successful practice by caring, by caring for his patients' well-being and doing everything he was trained to do to help with their maladies. However, anyone who really knew him, knew of his devotion to his wife and my brother and me is what gave him true purpose.

Whenever my dad was not working, he was with my mom, my brother, and me. My dad never suffered from epilepsy. He had a back problem for which he had three back surgeries. Following a third surgery, he took longer than expected to recover. A colleague of his, a neurologist, suggested the off-label use of Neurontin for his pain and gave him boxes of samples as well as a prescription.

At no time was he warned about an increased risk of suicide and my family was never told to pay close attention to the day-to-day changes in mood behavior or his actions.

Shortly after beginning the treatment, my dad became more dour and sullen. Suddenly and completely uncharacteristically, he began to worry about his job and whether he even wanted to continue practicing medicine. He

began withdrawing from friends and even our family.

He quickly transitioned from having a great interest in my academic career, the frequent phone calls, long discussions, to minimal contact. I knew there was something wrong and didn't even think that the sudden mood change could be related to the new drug he was taking.

When I came home from school for Christmas break in 2004, my father was not himself. On December 23rd, we were all watching TV together and out of nowhere my father asked us if we had a choice for a method of dying, what would that be. I will never forget how strange that question seemed and my father's sudden preoccupation with death.

We all dismissed the question as another one of my father's questions trying to engage us in spirit discussion. It seemed that he would just not let the conversation end. Two days later, on Christmas Day, during our traditional Christmas rituals, it was clear that my father was withdrawn and unengaged.

That afternoon he suggested that my mother, brother, and I go to the movies, and when my mother refused, he insisted and spoke in a forceful manner and which I had

never seen or heard before.

Reluctantly, we all went and upon our return we opened the front door and we found that my father had hung himself in the foyer of our house. During the last few months when my father was on Neurontin, he was not the same man that I grew up with, that raised me and took a remarkable pride in me and my family and, most importantly, in himself and his work.

In hindsight, there were so many signs we could have seen, it seems so easy to look back in hindsight now and pinpoint every instance when my father said something or had done something that would have raised red flags and alarm bells, however, we didn't know what to look for, we didn't know what the signs were and after listening to this morning's discussions, presentations, and reading the January 2008 FDA report, I wished that he was told of the increased risk of suicidality related to Neurontin.

Whether my dad would have decided to take the drug or not after being told of the risk, I have no way of knowing, however, I have no doubt that if we, his family, were told what to look out for, we would have contacted his doctor shortly after he started using Neurontin. We

certainly never would have left him alone that night.

Please don't let another family suffer the way my family has suffered by not providing an enhanced warning on these drugs. Thank you for your time.

DR. GOLDSTEIN: Thank you.

Again, I am told there is no No. 8, so on to No. 9.

DR. FRENCH: Hi. My name is Jackie French and I am a neurologist, epileptologist, and I am here to kind of represent the view from epileptologists. I am speaking today on behalf of the American Epilepsy Society, as well as the American Academy of Neurology.

What I want to tell you is that suicidality and epilepsy is very multifactorial. We know that there is a bidirectional relationship between suicidality and epilepsy. Probably a lot of you don't know that people who have a history of depression and suicide attempts, et cetera, have a higher risk of developing epilepsy. There is a biological relationship.

One thing that I am very concerned about, even after listening to the last few speakers, is there is such a high prevalence of depression within epilepsy, not only

because of the social problems with epilepsy, but also just the biological predisposition that when people do have suicidal thoughts, which many of them do, and many of them will, they are going to get very confused when they see that black box warning, and they are going to make presumptions and say I need to switch my medicine, I need to come off my medicine, and just, you know, to return a point from the FDA in terms of everybody with epilepsy knows they have to be on antiepileptic drugs, that makes sense in one way, but when you think that a lot of people who are on antiepileptic drugs, they are actually working.

That was another question that came up, and they are seizure free, so in their mind, and I see this in clinic all the time, they may not realize that they have to maintain their antiepileptic drug in order to maintain seizure freedom, and when they get concerned, because they are depressed and they have suicidal thoughts, which they will and they do, they may respond to that by coming off of antiepileptic drugs.

The other thing I wanted to point out is that changes, suicidality may occur in the context of epilepsy both when you go onto drugs, also, when you come off of

drugs. And I wanted to point to a study, a placebo-controlled study of antiepileptic drug withdrawal, 38 percent of patients developed moderate to severe psychopathology on withdrawal of antiepileptic drugs.

We also know that other therapies related to changes in seizure frequency also changed mood and increased suicidality, so if you do epilepsy surgery, which is not a drug, you also increase the risk even when people become seizure free with epilepsy surgery, there is a period of time when they have an increased risk of depression and suicide, so it is changes, it's perturbation that leads to changes in mood and perhaps suicidality. It is not a 1 to 1 correlation with drug necessarily.

We do have some issues with the analysis. A lot of them have been discussed before, so I am not going to go into them in detail. Another thing I want to absolutely point out is the consequences of antiepileptic drug noncompliance, if people stop taking their drugs because of a black box warning.

A recent study of antiepileptic drug noncompliance using a Medicaid database showed a 3-fold increase in death with apparent noncompliance as well as increase in emergency

visits, hospitalizations, automobile accidents, and injuries. I looked back at that study while I was sitting here, and if you want to know the number needed to harm, people who didn't take their antiepileptic drugs, the number needed to harm was 1 in 30, that the would die from having seizures and from epilepsy, so keep that in mind.

Finally, my conclusions are that changes in medicine regimen should absolutely be a time of closer observation for changes in mood. We all know that. That is a message we want to get out. But the label should at least--I mean, first of all, why put a black box warning on when you are not really sure yet about the cause-effect relationship, and is this drugs or is this a change, a perturbation in therapy of any kind.

So, the label should at least emphasize [end of allotted time].

DR. GOLDSTEIN: Thank you. No. 10.

DR. GILLIAM: Thank you. I am Frank Gilliam. I am a neurologist and Professor of Neurology at Columbia University. I am here representing the Epilepsy Foundation. The Epilepsy Foundation is a non-profit organization that represents more than 3 million people in the United States

with epilepsy.

The Epilepsy Foundation is very concerned about the possibility of a black box warning related to the association of AEDs with suicidality. This is based on two major reasons.

First, as has already been emphasized, but the Epilepsy Foundation would like to echo this strongly, the danger of patients stopping antiepileptic drugs or not beginning appropriate new therapies to better control their epilepsy due to concern about suicidality.

That concern by the Epilepsy Foundation is based on, as they describe, an overwhelming onslaught of telephone calls and electronic communications after the FDA alert was made public regarding the suicidality issue.

The second concern is based on the misassignment or the inappropriate emphasis of the risk of the association of AEDs with suicidality compared to the background problem of depression and anxiety as comorbid problems in epilepsy that can cause suicidality. I would like to discuss that in some detail for the next couple of minutes.

The prevalence of depression in epilepsy is 20 to 55 percent, depending on where these patients are selected,

in refractor epilepsy. But multiple studies including a large population-based study in the UK found that depression was 5 to 9 percent in seizure-free patients although those patients were all taking antiepileptic drugs, suggesting that the major influence of depression is not due to the drug.

Another community-based study with a valid and reliable instrument used to identify depression was published a couple of years ago, and in this study, about one-third of patients with epilepsy--again, this is community based--endorsed significant symptoms of depression. This was increased over asthma. That has been replicated in other studies showing increased depression compared to other chronic illnesses, such as diabetes.

So, this issue of depression as a comorbid problem in epilepsy is very large and is a major concern and effort related to the Epilepsy Foundation.

This is data from 17 prior studies of suicide and epilepsy. These studies summarized 11.5 percent of all deaths were from suicide in the epilepsy samples compared to about 1 percent in the general population.

These studies were all completed before the

approval of newer antiepileptic drugs, suggesting that the new drugs may not be the major factor in suicide in epilepsy.

Similarly, a multi-decade study from Denmark recently published found that, as opposed to patients with epilepsy and no comorbid disorder, the suicide rates were 2.4 times greater in patients with only epilepsy. But, if you added epilepsy and affective disorder, it was 32 times increased over the general population, again emphasizing the magnitude of the problem of comorbid psychiatric pathology in epilepsy as a primary factor in suicidality.

Another study looking at suicidality from a structured psychiatric interview in five outpatient centers in the United States found that 12 percent had suicidal ideation within the past two weeks compared to [end of allotted time].

DR. GOLDSTEIN: No. 11.

DR. GREENHILL: Good afternoon. I am Larry Greenhill, President-Elect of the American Academy of Child and Adolescent Psychiatry, a medical membership association of over 8,000 child and adolescent psychiatrists dedicated to treating and improving the quality of life for an

estimated 7 to 12 million American youth under 18 years of age who are affected by emotional, behavioral, developmental, and mental disorders.

We are acutely concerned about the safety of medications that may be used in the treatment of these children and adolescents and appreciate the FDA Committee's concern and attention to the suicidality from the AED medication trials.

Adverse psychiatric events that appear during treatment of children and adolescents with mental disorders have not been reported in conjunction with the use of various medications.

It is challenging at best to try and reevaluate data from multiple clinical trials, few of which were ever designed to assess such parameters. In the case of children and adolescents, often individuals with suicidal tendencies are excluded from those trials, and that makes the analysis even more difficult.

Analysis based primarily in a retrospective review of reports not systemically designed to assess causality of suicidal thoughts or behaviors cannot provide us with adequate information to fully understand the relationship

between medication treatments and these adverse events.

However, the data as presented today, can raise questions and help inform needed future research. The data reviewed today strongly indicates the need for large-scale prospective studies which evaluate the incidence of serious side effects including suicidal ideation and behavior in a systematic prospective manner utilizing consistent assessment tools and techniques.

The American Academy of Child and Adolescent Psychiatry is concerned about possible ramifications and impacts of the FDA recommendations for patient care using these medications and based on these data reports.

As we have learned from previous experience, the FDA's decisions regarding use of black box warnings significantly influence physicians' prescribing practice and ultimately impact patient care.

We ask the Committee to carefully consider their message to the public regarding these medications. These medications are helpful and even life saving for many people with neurological disorders, but patients currently on those medications could face life-threatening effects if they choose to suddenly discontinue their medication without the

advice and guidance of their physicians.

The American Academy of Child and Adolescent Psychiatry support the FDA's practice of approving safe and effective treatments for our patients. We strongly urge the FDA Peripheral and CNS Drugs Advisory Committee and the Psychopharmacological Drugs Advisory Committee to consider all data available on the relationship of antiepileptic medications and suicide when determining decisions about labeling and ramifications of action based on currently available data.

While protecting and informing the public, we urge the Agency to very carefully weigh the impact of black box warnings on current practice and have demonstrated effectiveness of these medications to treat our child and adolescent patients and to consider the most beneficial manner with which the recommendations are released to physicians and the general public.

Thank you.

DR. GOLDSTEIN: Thank you.

That is the last registered speaker that I have. The open public hearing portion of the meeting has now been concluded. We will no longer be taking comments from the

audience.

Committee Discussion

DR. GOLDSTEIN: The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public's comments.

We have specific questions that the Committee was given that we will be addressing later, but I think this portion would be worthwhile having a more general discussion and basically just to summarize again the sort of questions that we are generically trying to address is:

Is there a signal at all? If there is a signal, is this a signal of concern? If there is, do we believe that this is a class effect, and if so, what is the class? Should there be a warning if that is the case, and if there is, then, what form should it take?

A lot of the discussion has focused on the black box and the unintended consequences that that might have. Before the general discussion again, we have heard some other information from the public, particularly some statistical and other analytic information.

I would like to again ask the statisticians

amongst us if they have any comments about that or anything that they would like from just a purely technical standpoint to discuss before we move on.

DR. LU: Yes, just add a comment that, you know, we don't have time to really review their analysis before, so it is hard to weight, you know. But I observed that most of them are based on observational studies and just remind us that this meta-analysis was based on randomized clinical control, which at the current standards, the best way to control the confounding factors.

DR. GOLDSTEIN: Dr. Leon, anything?

DR. LEON: No.

DR. WOOLSON: I think just to emphasize the point that I think there is a big difference between observational and clinical trial data, and I think I would want to be assured. I wouldn't want to be in a position to have observational data trump clinical trial data in any strong way.

The other issue I would want to point out is that there has been somewhat of a call for large-scale prospective studies and from the standpoint of design of studies, when you have something that is a very, very rare

event, prospective cohort study is not usually the optimal way to design that study. One usually thinks of case control types of investigations simply because it would take millions and millions of individuals in order to really do those kinds of comparisons.

DR. GOLDSTEIN: Thank you. I am opening it up now for a general discussion. Dr. Day.

DR. DAY: Just a brief comment to the last speaker. Last week there was an FDA Advisory Committee on potential signals for serious heart events while taking drugs for diabetes, and the topic of that meeting was how would you design studies to do all this. So a lot was brought forward and some things were figured out, and should this group think that that would be a way to go, the transcript and materials from that meeting would be helpful.

DR. JUNG: Just a quick question for the FDA staff. What is the criteria for setting out a black box warning versus other warnings that are set out?

DR. KATZ: There are no formal criteria. We choose to typically put a black box or box warning when we think it's a serious event, and we think people ought to know about it, or might be able to prevent it.

It is really a judgment. There are no rules that I know of that say this is, you know, if it's different, sometimes you do it if it's the only drug in a class that has a particular serious event. It has to be serious and it has to be something we think people really ought to know about.

As Bob was saying earlier, if it's the kind of thing that you really think people ought to pay attention to, that is sort of a seat-of-the-pants sort of a rule because it is the most prominent way we can describe it.

DR. TEMPLE: It might help to look at what we have said about when we think there should be what is called a Med Guide, patient-directed labeling, because some of the considerations are similar.

The two main reasons for having a Med Guide are when the thing in question, the adverse effect in question is something that you really want patients to know about before they decide whether to use the drugs, so they can participate in the risk-benefit decision. That is one.

The other is where there is something you can do to prevent a problem, for example, knowing that it might be a problem, knowing that the drug can do this. I think box

warnings come in something like the same category, it has to be a severe problem or you wouldn't do it.

You have to be reasonably convinced of a causal relationship although, you know, who is ever absolutely convinced, and then there needs to be something that you can do about it, whether it's the physician deciding whether to use the drug, or the patient deciding whether to use the drug, or taking appropriate warning steps.

I mean for antidepressants, for example, the main thing we have told people is watch out, not not use it.

DR. JUNG: Well, the reason why I asked is that coming from the consumer advocate standpoint, the use of the antiepileptics in general neurology I think is not just for epilepsy, and so as the other indications were pointed out, a lot of that is for pain management.

The alternatives for pain management are not good, so, you know, it was interesting, I got an e-mail during lunch from one of my patients asking, trying to get off his antiepileptic, which is used for neuropathic pain.

The alternatives that were allowed by the FAA, for which this patient was asking, are anti-inflammatories, which have risks associated with them, kidney failure and GI

disorders. We run into that issue as well as the chronic pain patient whom we are trying to get off narcotics.

So, at what point do you say that one alternative is better than the other? Certainly, suicide is a very significant adverse effect, but the risk associated, losing a job or be unable to work because of pain, or dependency issues are also significant.

The reason why I asked about the black box warning is that it is not clear to me that there is set criteria for it, so are we jumping to establish some type of ruling that may cause the clinicians to have difficulty in terms of convincing their patients to switch therapies.

DR. GOLDSTEIN: Dr. Rizzo, I think you had a comment before lunch that you were going to hold over.

DR. RIZZO: Yes, I guess. I hope I can say this the right way. I wasn't in on the discussions with the psychiatrists about suicidality and antidepressants, and they understand far better than we neurologists do what suicidality is, and this is one of the things that confuses me.

One of the issues is the construction of validity of suicidality, what does it mean, is it a disease like

dementia, is it a condition that predicts something? In a way it seems to me it is a concept that links together apples and oranges.

If you think of a triangle with a wide base at the bottom where you have ideas, and at the top you have actions, and at very tip you have very infrequent actions which are actions that lead to suicide, there is a relationship between the different levels of the triangle.

So, there is a relationship between ideas and there is a relationship between actions, but what are those relationships, and is it fair to lump them all together?

I was trying to think about how the concept of suicidality would relate to some sort of mechanism, and so you can imagine that a change in medications would lead to a change in moods, which would lead to a change in ideas or the willingness to report ideas, which would lead to a change in behavior and actions, which might lead to suicidal attempts or suicide that was successful, but how that mechanism, which I would put out as a plausible mechanism, or chain of causality would relate to this concept of suicidality, I don't really understand.

It seems to me that throughout the discussions,

people have been talking about suicide, they have been talking about suicidal actions, they have been talking about suicidal ideation and depression, and all of these ideas have been interchanged, and I am not sure that we are all clear on the distinctions that we are making about ideas and actions and what we are really worried about.

It seems to me that what we are really worried about is suicide or near suicide events, and I don't think that comes out very clearly in the discussions today.

So, I would ask our psychiatric colleagues to explain better the concept of suicidality.

DR. PINE: I actually was going to say something else, but let me speak to that since a few of us, as we have commented, have kind of watched the development of this issue over the last five or six years, and I think maybe a few of us can comment on it.

I think you raise a lot of points that have really occupied a lot of time and a lot of thought, and there has been some progress, and I will try to describe it to you briefly and quickly.

The first thing to say is that when this issue first came up with antidepressants, many of the concerns

that you raised occupied a lot of time including the fact that the term as it is currently defined and as it was used in the analyses that were presented, lumps together a lot of things that maybe shouldn't be lumped and there was a fair amount of thought about that.

The other thing is that it doesn't conform to the usual way we think about medications as being applied to at least disorders or syndromes that hang together, but ideally, things where we have some understanding of etiology.

There was a fair amount of time spent classifying and reclassifying events, and I do think, speaking as an individual and as a psychiatrist, that my sense is after a few years, the FDA did about as good a job as one could do given the inherent problems in that, problems that you rightfully point out and that I think are not going to be easily solved.

I also think you raise a very important issue that what we really care about is not suicidality as it is defined currently in the measure that we are using, but ultimate, completed suicide.

The problem is that, thank goodness, ultimately,

completed suicide is a very rare event. But, on the other hand, the best predictors that we have of completed suicide is a history of a suicide attempt.

So, when looking at an outcome that can be about the best proxy for the potential risk for completed suicide, some constellation of suicidal ideation and suicidal behavior is about as good as we can do and, as the statistical analyses from the FDA made clear, when that signal is clearer for behaviors, because the link between suicidal behavior and future suicide completion is stronger than the link between suicidal ideation and ultimately completely suicide.

When you see a stronger association or at least a strong association with behavior from a medication, it raises a lot of concern.

I think the last thing to say is that because, in thinking about behavior disorders more generally but mental disorders in particular, suicide is a major emergency for us as psychiatrists and something that really makes all of us think very, very carefully.

The response has been over the last few years, in thinking about this, that we should have a very low

threshold for alerting the public and for raising concern, and for not getting too bogged down in imperfections in the definitions of suicidality because, no matter what the imperfections are, I think we have all ultimately agreed, number one, that it is about as good as we are going to get as far as coming up with a decision when there is a specific question about medications before us, number one, and then, number two, the way it is currently described is a reasonable predictor of risk for completed suicide.

So, given all of that, I think the way in which the current measure of suicidality, which is the exact same measure that was used in the three hearings about the antidepressants is thought about, I think that among the committee that includes a lot of psychiatrists, there has been reasonable comfort in basing decisions about risk and risk-benefit ratio with the definition that we are currently working with given all the flaws in the definition.

Then, maybe you can ask me questions, but I will be interested to hear other comments from other psychiatrists.

DR. ROBINSON: Also, I think there are a few sort of methodologic things that maybe those of us who have been

through the antidepressant sort of trials, it is sort of second nature. But, if this is the first time you have started thinking about it, it might be worth bringing up.

One is we have talked about the randomized controlled clinical-trial data has lots of advantages, but has some disadvantages in the sense that, for example, these are patients--and I don't know about epilepsy, but in psychiatry it's very routine for there to be criteria for suicidal patients when they go into the trials.

So, one of the things is a lot of the psychiatry patients may have been systematically filtered out, the patients at most risk, because you can't get in the study because of an exclusion criteria for human subjects protection.

The other thing is that if people are in a trial and they develop ideation, usually, their participation in the trial is truncated because, if you are treating somebody in a trial and they start to have suicidal ideation, they are often taken out of the trial and we do some other interventions because you don't want to go on to full suicide.

That is one of the reasons why suicidal ideation

is really important in these sorts of trials, because nobody wants to progress to the next level, which are attempts, et cetera.

DR. RIZZO: Can you tell us anything about the tools that measure suicidal ideation, what is the test, retest reliability, what is the interrater reliability? Is it a thermometer that reads 30 degrees in 1 second, and 50 degrees the next second?

DR. ROBINSON: I think the main difficulty--I mean basically, I remember the methodology is they are using spontaneous adverse-event reporting. Then, those reports are then classified using the Columbia system, and as Dr. Pine was talking about, there are limitations to the Columbia system of classification. But it is as good as anybody can come up with.

I think the main difficulty is that we are dealing with reports of spontaneous AE's in a case report form, so I think it's like getting the data is the problem. Now, there are scales that actually do measure suicidal ideation, in fact, in psychiatry, there is at least one drug that's specifically got an indication, which is clozapine, for patients with schizophrenia who are suicidal, it has a

specific indication for that.

In that study, there was wonderful measures of suicidality, but that was a study that's totally designed for that purpose. Obviously, in these epilepsy trials, people weren't wanting to do specific suicide scales. Maybe in the future they might, but we don't have that sort of thing now. So, I think that is a big limitation is the data that we are basing all this on is spontaneous reports in a case report form.

Obviously, in that method, you are probably missing stuff.

DR. RIZZO: So, if you were doing a prospective study, what tool would you use?

DR. ROBINSON: As I said, I mean there is at least one instrument that has been used successfully for an indication, so there are scales. But its like everything, it's a specific scale. It takes time, et cetera, et cetera, and, in a global trial where you are looking at many other--I mean if you are in an epilepsy trial, you are probably interested in lots of other measures, and it is always the balance about what you put in versus what you measure.

But you can do it, it's possible.

DR. PINE: One thing related to that, and Dr. Temple mentioned this but it might have been lost on people who are not psychiatrists or were not at the other hearings, that, for the antidepressant hearings, there were a subset of the trials that had acquired data prospectively on a group of patients specifically asking about suicidal ideation or behavior with reasonable reliability.

One of the vexing questions of those data was that you could see the signal, the association with suicidal ideation and behavior in the spontaneous event reporting data. But, when you looked at the prospective systematic measurement of suicidal ideation and behavior on the trials that had those data, there was no association with antidepressant use.

So, it really raised a lot of questions, as Dr. Robinson was just mentioning, about exactly what we are picking up with these events.

But the thing to remember is despite that, the feeling around the room at the time, even though there was this discrepancy between the spontaneous event reports, which showed pretty much uniformly acknowledged by both committees, a clear signal with suicidal ideation or

behavior, an association I would add that was no stronger than the association that we are seeing in the data today.

So, despite that contradiction between the prospectively collected data and the event reports, both committees felt that the data were conclusive enough to say that there was a causal relationship between antidepressants and suicidal ideation and events.

So, even if we had those prospective data here, if this committee viewed the data the same way the other two committees did, one would be forced to conclude that that still would not contradict the fact that the spontaneous event reports have shown what at least I look to see a fairly clear association from a statistical standpoint.

So, having the better scales would not really help us right now because, if they showed something, maybe we would feel a little more comfortable in concluding there was an association. But, if they showed nothing, that would basically be exactly what we had with the antidepressant data, which was not reassuring enough to a group of people who spent a lot of time thinking about suicidal ideation and behavior.

DR. GOLDSTEIN: Thank you.

Dr. Hudson.

DR. HUDSON: My question was addressed because I wanted to know what were their quality of life for mental health data that could anticipate a high-risk profile patient who might suicide, were those routinely done with any of these randomized controlled trials that were included in the meta-analysis?

Even if it's not going to make a difference in our deliberations today, I am curious, are those types of outcomes collected in these studies and was that data evaluated?

DR. LAUGHREN: We don't have good instruments for predicting suicidality, but we do have better instruments now for prospectively collecting information on suicidality when it emerges. That is really what has been missing from these trials.

We have relied on spontaneous reports. The frustrating thing is that these reports have been very sparse and very difficult to classify prior to doing an analysis.

Columbia has an instrument that they have developed, the Suicide Severity Rating Scale, that

prospectively collects detailed information on suicidality that hopefully in the future will allow us to do a better job of looking for suicidality in future meta-analyses and future analyses of clinical trials data.

There are some other instruments that are being developed, but it is something for the future. It doesn't help us right now with what we are dealing with today.

DR. KATZ: But just to answer your specific question about quality-of-life scales and those sorts of things, we didn't ask for those data. Some trials I am sure had that. I am sure many trials didn't I would assume anyway, depending on the indications. We can't answer that definitively.

DR. GOLDSTEIN: Dr. Temple.

DR. TEMPLE: Just one thing is worth remembering. We don't quite know what the phenomenon we are looking at is. For example, in the depression trials, the people on treatment were, on the whole, less depressed.

So, you might ask, well, why are they more likely to be suicidal. The suicidality is a relatively rare event compared to their underlying depression. They are all depressed, after all. So, we don't really know what the

characteristics here are. It looks like it behaved like something that was sort of an odd thing that happened to a small fraction of people.

So, you don't really know whether your scales are going to pick it up. I must say in line with Dr. Rizzo's question, that is more persuasive for a suicidal act than it is for suicidal thinking, which you might think happens more commonly.

But a lot of what we pay attention to is the suicidal acts. According to the analysis that the Columbia approach is, you have to reach a conclusion that it was a serious attempt to do yourself harm. Obviously, a judgment call, but that doesn't happen that often, but it does happen more often in the people on treatment, or at least it seems to.

I can't help adding one other thing. We have always wondered whether this was a greater likelihood to report events that were already there in equal numbers. That seems more of a worry with suicidality to me--you guys have to think about it--than it does with suicidal acts, you know, putting a rope around your neck and stuff.

But, you know, we don't really know the answer to

those things yet.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: Throughout this discussion I have been wondering about the basic question of whether there is a signal here and is it an important signal. I would just like to spend a minute or two about those thoughts.

First, as I review the data, we have epilepsy, we have psychiatric disorders, and then we have other indications that are in the mix of data that we evaluated. We looked at forest plots that are, to me, very convincing, they cut across 8 of the 11 medications that you looked at, all antiepileptic drugs so called, but used in a variety of indications.

I am struck again that those patients who are in these trials, are people who have illnesses that frequently come with depression. They include diabetic neuropathy and other kinds of pain that are often depressing, that often happen to people who have pain and therefore are depressed.

They happen in psychiatric disorders where depression is common, and people with epilepsy, you heard from Dr. French and as I have commented earlier, who are often depressed people.

So, I, for one, as I am thinking through this, see a biological substrate of group of patients who commonly are depressed because of their illnesses or for other reasons, the two go together, the pain and the depression go together.

The question is whether there is a common mechanism and at least from the pharmacological point of view, there appears not to be, but we have, as Dr. Katz put it, an empirical piece of data here showing that there is some sort of relationship, that is, these are all antiepileptic drugs used for different purposes and yet we have this commonality here.

So, I am at least leaning towards the conclusion here that we have an important signal. It may pertain to a small percentage of the total cases evaluated but we have at least a reporting phenomenon; that is, these are people in clinical trials. They were placebo matched. This is as good as one can get in clinical pharmacological evaluation.

I am concluding myself that there is a signal here, that it is an important signal even though it pertains to a small percentage of people. I think what the FDA has come up with is important and to me it is real. That is all

I wanted to say.

DR. GOLDSTEIN: Thank you.

Dr. Goodman.

DR. GOODMAN: Going back to Dr. Rizzo's question, I don't know if it has been completely answered yet, but my own conceptualization of what is going on here or with the antidepressants is that there isn't a switch in the brain, a suicide switch, that one day it is off, and the next day you take an antidepressant or an antiepileptic drug and all of a sudden it's on.

I have always imagined as a clinician that there was some sort of intervening state change. In the case with antidepressants and their use in pediatric depression or other pediatric conditions, we all had our hypotheses and discussed them.

Those hypotheses included a state shift. We all know that with an antidepressant there is a risk in susceptible individuals. You may induce a shift into bipolar, into mania, and that could account for some of the emotionability and irritability, and other manifestations that could then lead to suicidality.

That certainly seemed to fit with the data and

also clinical experience. There is a thing called "activation" syndrome, which is not very well characterized, but includes features like irritability, dysphoria, disinhibition, that you can see if you have been treating enough kids with antidepressants, and you could imagine if that was an unrecognized state over a period of time, that that could lead to suicidal behavior.

At least on my part, and I think probably on some of the other psychiatrists who have examined this issue, thought about this issue, that we don't think that--we think that there is some sort of intervening antecedent process that occurs.

It is not going to be depression, I mean we don't think that we were making patients more depressed with the antidepressants. We conceptualize that as a sort of behavioral toxicity that occurred in a subset of individuals who are susceptible to that side effect, and if unrecognized, if the dose wasn't changed or the medication wasn't decreased, or, in fact, you increased the dose, it might actually further exacerbate that problem.

What is going on here, I don't know. One of the areas of discomfort is I don't have a good theory, as much

as I thought I had a testable hypothesis in the case of the antidepressants here because it's not inducing mania. I mean we use these drugs to treat mania, so it's unlikely we are getting stage shift.

We are not making them more depressed, because some of these are useful for depression. I don't hear anything that suggests activation syndrome although we haven't really discussed that.

So, the only thing I can think of that might be an intervening behavioral change is some sort of side effect burden and certainly we know with some of these drugs, in some patients, they can experience dysphoria, they have cognitive dysfunction, they may be feeling loggy.

There are words I can think of that I don't want to use in public that may cause, over time, for them to feel that life is not worth living, but my guess is as good as anybody's. I don't know really what is going on, but I don't have a neat fit with a construct here.

A simple answer to your question, I don't think that you are flipping into suicide. There is something going on in between and I just don't know what that is.

DR. LEON: I have two points I want to make. One

is following up on something Dr. Pine said. Although the strength of the association between medication and suicidality is the same in these data, the antiepileptic data, as we saw in the antidepressant data, the rates of suicidality in the antidepressant was about 6 times what we are seeing in the data today. That is one clarification there.

The other comment is regarding we saw some new data today that were presented that weren't included in the meta-analyses. And I think it is important, you know, when we are looking at efficacy data or safety data, we use the a priori goal, the a priori analysis, and the a priori primary outcome. It has been defined in advance before the studies began.

To start piling on new data that may or may not agree with the data that we agreed to look at to make a decision, that muddies the water. Although it doesn't seem to agree, the data that we saw today doesn't seem to agree with the bulk of the data, I dismiss it at this point.

I don't know, there might have been some other trials conducted by other companies that we didn't get those data, but the ground rules were set before the data came in.

The agreement was we would make a decision based on these 199 trials, not 202 or whatever the additional number. That's it.

DR. GOLDSTEIN: Thank you.

Dr. Katz.

DR. KATZ: Just something perhaps for people to think about or discuss it. A number of comments have been made today about how the signal is much smaller than it was for the antidepressants. But at least if you look at the odds ratio, it is basically 2, which is what it was for the antidepressants, if I remember correctly, it was 4 percent to 2 percent versus here, you know, whatever it is, which is absolutely the rates.

Of course, that is a function of who was in the trial and what the placebo rates were. If you believe it is twice on drug what it is on placebo, you could translate that, and folks have said from the audience it is dwarfed by the background rate of depression or perhaps suicidality in the population at large, up to 20 percent depression rates, this sort of thing, in epilepsy.

But if it's twice what it is on placebo, then maybe the rates are 40 percent on drug out there. So who

knows. I wonder whether or not the fact that the absolute incidence is much smaller than it was with the antidepressants really can be generalized to say, well, it's less worrisome in some sense. I just wonder what people thought.

DR. GOLDSTEIN: Dr. Rudnicki.

DR. RUDNICKI: Given that some of the benzodiazapams are chronically used to treat epilepsy, particularly, clonazepam, how is that going to fit if there is a warning that comes out?

DR. KATZ: As proposed, our proposal was to include any drug that is approved to treat epilepsy, approved to be used chronically. Again, I think there is some perhaps misunderstanding, and I talked about it earlier today, about why the word "chronically," the whole point of that--and you could pick another word, the whole point of that was to exclude drugs that are used only very acutely, very intermittently, where we thought this signal might not necessarily apply.

So, whether the chronically is three months or five years is a matter for discussion, but that was why we threw the word "chronically" in there. But anyway, to

answer your question specifically, those would be included by our proposal--

DR. GOLDSTEIN: Dr. Hennessy.

DR. KATZ: --if they have a claim, which some do.

DR. HENNESSY: Thanks. One of the points that was recently discussed was should an equivalent relative risk in one setting to another mean that the risk-benefit balance is the same in the two, and it doesn't.

Are the risks that you get from a drug--has to do with the risk difference, you know. If you double a very small risk, it is a lot different than doubling a big risk. The other point I would put forward, just because an event happens to be fatal doesn't necessarily mean that it needs to result in a black box warning.

There are plenty of adverse events, I think, and somebody can correct me if I am wrong, that can be fatal but don't occur with enough frequency or aren't well enough documented to result in a boxed warning.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: Two things. First, just to respond to Dr. Katz and to make it explicit, my view of the data here, and I hope I am consistent in saying this throughout the

day, are that I view the strength of the association very similarly and I base it on whichever metric the statisticians would tell us is the most correct one, whether it's the relative risk or the odds ratio, that the data appear to me reasonably compelling.

I would agree with the summary about 10 minutes ago from this side of the table, that it seems fairly clear to me that there is an association here, that it is important, and that seems to me by far the easiest of the three main questions before us.

In other words, whether or not there is an association, and it is important, I would say absolutely. Does it apply equally to every group and every medication? That's a tough one, and what to do about it, that is a tough one. But I am not sure if it was Dr. Leon and my discussion, but I have heard a fairly consistent opinion around the table. I haven't heard anybody say that this doesn't look like a real association yet.

I think maybe if somebody felt that way, it would be good to hear why, because I don't feel that way. I feel it looks like a real association that I believe.

DR. GOLDSTEIN: Dr. Potter.

DR. POTTER: Perhaps Dr. Pine or someone else can remind us. People continue to say, well, this looks pretty much alike except for the absolute numbers. But the relative risk and the pattern seen for the antidepressants, and just sort of point of information since I should know this, but I don't recall, among the SSRIs, if you looked at the relative risk or the odds ratios, were the patterns distributed essentially the way we saw here, across a range of plus 5 when you take the European studies for an odds ratio down to minus 2.5, did the SSRIs really distribute across that same range?

DR. PINE: I would say, if anything, the data are more consistent here probably just because the numbers are so much bigger. At least in the initial analysis, there were only 4,000 patients, right, so that is 10-fold fewer patients now.

DR. POTTER: That's not the question. What I am asking is if you look at the plots that were used, and remember here in this particular analysis, what I just trying to get at it is, by chance, is the distribution of odds ratios by chance, because you have multiple drug classes, and with the SSRIs you had the advantage of looking

at one true biochemical class of drugs where we have a much better sense of what they do, and did we get the same distribution of risk and odd ratios across drugs.

DR. PINE: Maybe we should ask Dr. Laughren.

DR. POTTER: Did it go down and above, or could they cover that big a range.

DR. LAUGHREN: If Mark Stone is here, he could probably respond with more precision, but my recollection is that there were at least two antidepressants that did have an odds ratio less than 1.

DR. STONE: First of all, we have to be clear about whether we are talking about the initial analysis of pediatric trials or the second analysis where we looked at all ages.

Now, in the second analysis with all ages, it was shown to be age dependent, and there was an increased risk in the 18 to 24 age group, no increased risk in 25 to 64, and a reduced rate in under age 65.

Looking at the 25 and under, and you can pretty much say the same thing whether you include the pediatric trials or just the young adults, you see a pretty consistent effect across classes. We are talking about SSRIs, SNRIs,

tricyclics, drugs that don't fit in like buproprion and what have you.

The numbers certainly varied from drug to drug in terms of the point estimate and the odds ratios. What is interesting, and it wasn't published, is that in some additional analysis, the slope of change with age was very similar in all drugs regardless of whether the overall risk was high or low, which kind of says that, for this particular drug, there was a therapeutic effect that lowered the overall risk.

But you still saw the age dependency, which was the effect that was associated with suicidality, and other drugs you may have had a higher basic risk because you were dealing with patients that were refractory to the drug or the drug was just less effective in terms of treating depression and suicide associated from the depression rather than the drug.

But I think there was an extremely impressive consistency in the age dependence of the effect, that you were always seeing more suicidality for drug relative to placebo in younger patients than in older patients.

DR. TEMPLE: But, Mark, in answer to the actual

thing that is worrying Bill, there were drugs that were below the one line and there were drugs that were further above the one line than some of the others and it made no pharmacologic sense. It just reflected the variability of the data. But again this was a pooled analysis with 4,000 people in it.

The adult one is 70,000, but on the pediatric it had 4,000. But there was a similar kind of scatter, which is a small numbers issue probably, I mean who knows.

DR. STONE: Again, if you look at all adults where the point estimate was like 0.86 for all adults, and class by class, they were all like between 0.83 and 0.90 class by class. Drug by drug, a lot more variance.

DR. POTTER: That is very helpful, because what I was trying to understand and to get at was the class versus the individual and what is one's confidence or not that this data does or does not suggest that there might be differences between drugs. And it is so hard to figure out. I mean this is a big dilemma.

DR. STONE: But it's worth emphasizing again that in the antidepressant situation, there were different pharmacologic classes, as well. We have been talking about,

well, antidepressants, they all have a common mechanism but, in fact, the signal seemed to occur across pharmacologic class.

DR. POTTER: That is why I asked, among the five or six SSRIs, however you classified it, were the spreads observed just within that subclass because there you have five or six, and if it did, then, that just tells you it is just the numbers.

DR. STONE: For example, again, in the overall analysis, sertraline was pretty low, fluoxetine was fairly low, citalopram and S-citalopram were on the high side, and that's only just within the SSRI group.

DR. TEMPLE: The results varied by study, I don't know if you remember this, but the first three studies we had of Prozac were all sort of below the line, and then along comes the NIMH study, and that brings it way above the line. I mean nobody can make sense out of this, and you are looking at very small numbers, which is why we put the data in a pooled way, because the individual cases don't have enough.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: I would like to address the point

that Dr. Pine made about the association between antiepileptic drugs and suicide. I don't want to sound simplistic, but yes, there is evidence for association. But that really doesn't mean cause, just association.

And I would like to bring up again the issue that our epilepsy colleagues here have very clearly shown prospective data on patients with epilepsy with high rates of depression, suicidal ideation, and that were unrelated to antiepileptic drugs.

I think that that is prospective data, whereas, the current data that we are reviewing is retrospective data. The other point that I want to make is--which at least in terms of what Dr. Goodman was talking about, trying to understand the mechanism--the situation here is very different from the situation with the antidepressant drugs.

We have got very different classes of drugs here, they act by very different mechanisms, and it is very difficult to use these different mechanisms as the explanation for an increase in suicidal ideation in a very, very small subset of the sample.

Again, what I would like to suggest is that at least in terms of patients with epilepsy, the biological

aspects with the increase in depression and suicide need to be looked at prospectively and, given that the other two populations, the psychiatric patients and the patients with pain, et cetera, all have high rates of depression, I really would hate to have a confounding variable here that we are not considering despite placebo ticks.

I just want to add something about the placebo. At least in terms of the patients with epilepsy, if you are looking at monotherapy versus polytherapy, we do know that polytherapy can increase adverse cognitive and behavioral side effects.

The patients who are on placebo weren't exposed to that, so it is not the exact same trial.

DR. LEON: I mean if you are addressing that comment to me, I am assuming, the difference, though, the only difference between the two groups--I mean maybe both groups got polytherapy, but one of them also got an additional antiepileptic and another also got placebo.

So, the only difference between the groups would have been adding on one antiepileptic versus one placebo, and I think with that we can look at causality. I would rather look at retrospective clinical trial data, randomized

controlled clinical trial data than prospective observational data.

I mean the big advantage to prospective designs now is we can build in better assessment tools, but I really would like to have randomization.

DR. CAPLAN: Can I just say one more thing, though? But I do think that these prospective studies did have very good tools, so I think that is an important issue. In other words, it wasn't just subject reporting, but these questions, specifically, suicide, depression, et cetera, were very specifically addressed.

DR. HENNESSY: Arguing for causation is randomization, which gets rid of confounding on average, and the fact that across the different measures, there is consistency.

On the other hand, we have small numbers for completed suicides, we have zero versus 4, and the group in which the 4 occurred was larger than the group in which zero occurred, and we have one meta-analysis of randomized trials that weren't designed to look at this.

So, there is reason to have pause in jumping to a causal conclusion even though they are randomized data. The

data are still very early at this point, and I suspect that additional data will be forthcoming. And I wouldn't want to jump to a black box warning before the data are convincing and before we have enough data to make that assessment.

DR. ARMENTEROS: We are going back and reviewing the child experience, which is I guess the only experience of this sort that we have had. I think we should be a little bit careful in doing so, number one, it is an entirely different group of patients, starting with a different condition all together.

Now, just to go further a little bit, the fact that even the risks are similar in the suicidality between that type of data and this data, in entirely different groups of patients and entirely different groups of medications. I think it makes the whole situation more complex. I don't know exactly what is it that we are identifying whether the actual methodology employed is contributing to what we are observing.

So, I think we should be a little bit careful in continuing to make these comparisons.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: I was going to say something similar

to that, but it is a little different, so I will go ahead. I don't think it is very helpful to go back to compare a previous trial or previous set of data with respect to antidepressants and suicide risk.

Also one never has the perfect trial. We have what we have before us. I think what we have is a very interesting data set, that is, we have the advantage of a large placebo population and a large population of people who are treated in a randomized, controlled study.

That has given us a signal. Now, it is true it is not perfect, because not all of these individual studies were done with the same number of patients, nor were they done with the same drug. They were done with different drugs that have different mechanisms, but they were aimed at, more or less, the same indication, that is, epilepsy or psychiatric disorder or another indication.

That has given us a signal. It is a very clear signal to me. It varies in power between the individual studies but, nevertheless, it has the tremendous advantage that there is a placebo-controlled group along with the active group, and I think that is, to me, the most important aspect of this data set.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: I agree with Dr. Gilman. I do want to comment on what Dr. Hennessy said. I think it would be years, maybe a decade or more, before we had another 43,000 subjects enrolled in clinical trials to add to this body of data.

So, although it would be nice to have three, four times as much data here, this is a big data set which we will probably never see anything like this again to address this question. I wouldn't want to wait for a couple more trials to come in.

DR. GOLDSTEIN: Dr. Temple.

DR. TEMPLE: Just a couple of things that have come up. We are accustomed to concluding when you have a result from a controlled trial that any effect you see is causal. We are constantly encouraged by people who own the label, to use the word "associated with," but not for controlled trials. The whole point of them is to reach a causal conclusion within the limits of the data.

The other thing I would just like to mention is that one of the things I worry about with meta-analyses is that you frequently know what the result is going to be

before you do it because you have seen the large trials that you are putting into it.

That is one potential bias that this analysis did not have. We went looking here without knowing what the result was going to be. So, there weren't 25 hypotheses or anything like that, that we went scattering about. This was the one thing that was being looked for and that is not a common feature of all meta-analyses. So, I just wanted to mention that there is one bias that this didn't have.

DR. GOLDSTEIN: Other points? Dr. Lu.

DR. LU: For me that takes care of data, I mean really different from the people who take care of patients. I heard a lot of comments from professional associations this afternoon. I would like to hear also from clinical side, clinicians, or FDA, about practical implication.

Also, what are consequences if, later on, because they call for research for this topic, if they find a biological mechanism that can explain partially the reason, how often will FDA go back to revisit black box warning, or I mean that will be last forever. I mean what are the consequences here that we are talking about?

DR. KATZ: I didn't hear the last part. Was the

last part of the question--

DR. LU: Updates with the new knowledge.

DR. KATZ: Again, as I mentioned earlier, we don't know. And, as Bob has said on several occasions, it is difficult to get a labeling statement removed in particular a boxed warning. If things look better in the future, one could argue, well, the box is working, so it can almost be circular. But I guess one view is you continue to get data, maybe better data.

We have been talking about how to prospectively or contemporaneously during trials get better data, and I suppose it's possible if we got a large enough cohort of data that we really thought was prospectively collected and then analyzed again, and there is absolutely no signal, I suppose it's possible we could look back and say, well, we did the best we could at the time but the data capture was so poor and variable that that is what gave rise to what we would now think would be a spurious result.

So, it is possible there are ways to amend labeling. But it would be difficult and it would probably take a while, and it took a while to get this sort of a data set.

DR. TEMPLE: But we did amend the antidepressant box, both adding the adult data, which depending on how you feel about it, softens it or strengthens it, but also took note that suicide and suicidality are consequences of the underlying disease, reminding everybody that there is something to treat. That was at least in part to the same kinds of worries that people have expressed today.

DR. KATZ: Right. Certainly, we could amend language, and that we do. We certainly do amend language when it comes to our attention, for example, that there is an unintended consequence that we think we could prevent with amending the language. But the fundamental finding and its description is hard to reverse.

DR. GOLDSTEIN: Dr. Schultz.

DR. SCHULTZ: We have been talking a great deal about a neurobiologic mechanism, but I am sitting here thinking of the complexity of suicide and how we know clinically it is driven by social, environmental, cultural factors, access to alcohol, et cetera. So I am curious as to others insights on the compelling finding that the data were driven by the non-North American studies.

I don't know from an epilepsy management

standpoint if there might be cultural differences that might be adding to this finding. It's a major finding that we really haven't brought into the discussion and again how that might even affect the labeling and communicating this information that is a strong finding that we might want to communicate.

DR. GOLDSTEIN: Any comments about that? Dr. Malone.

DR. MALONE: I don't have a comment about that, but it was really about labeling and changes. I mean if you think about the label for the antidepressants, it already had a warning about suicide in it before the black box was added. It was an old warning. So, in a sense, you took that warning and stepped it up.

Here, I don't think there is any warning in most of the antiepileptics about suicidality, so any statement would be a stepping up or a changing of the warning, which was not true for antidepressants.

DR. GOLDSTEIN: Dr. Leon, did you have your hand up?

DR. LEON: I want to follow up on what Dr. Temple or Dr. Katz just said, have you considered including--it was

Dr. Katz--including something to the effect that untreated epilepsy, pain, mood disorders themselves are risk factors for suicidality in the black box?

DR. KATZ: I don't know if we have had that language in the box that we proposed in the package. We probably didn't but, certainly, it is something we would consider for sure.

DR. GOLDSTEIN: I think we have had a great discussion. I think what I would like to do now, let's take a 15-minute break. We will come back at five to 3:00.

When we come back, what we will start doing, is really trying to attack each question separately and in turn. I remind again the Committee no discussions about anything related to what we are talking about.

[Break.]

DR. GOLDSTEIN: Let's go ahead and reconvene.

Dr. Schultz had raised a question when we left about the comparison of North America versus the rest of the universe data. The FDA does have some additional analysis that they can show us about that before we go on.

DR. MENTARI: As I discussed in my discussion slides and also as brought up by Dr. Schultz, there is a

notable difference in the subgroups according to location. I mentioned in my discussion that that was something that could be attributed to a lower event rate in the placebo-treated non-North American subjects.

[Slide.]

Here we have the exact numbers as was shown during the discussion presentation. The non-North American subgroup had an estimated odds ratio of 4.53 with a 95 percent confidence interval of 1.86 to 13.18.

The North American subgroup had an odds ratio estimate that was 1.38 with a confidence interval 0.90 to 2.13.

[Slide.]

On this slide, we have a table that shows events according to treatment arm and location in the placebo-controlled trials. As you can see, the comparison between drug and placebo in both the North American and non-North American subgroups are qualitatively similar for the suicidal behavior events, namely, completed suicide, suicide attempt, and preparatory acts.

However, you can see that the results are different for the suicidal ideation events. In the North

American subgroup, suicidal ideation in drug versus placebo was nearly identical, however, in the non-North American subgroup, the number of suicidal ideation events was very different, and it is important to note that the rate of events was much lower in both groups but is notably lower in the placebo group.

That was the main category that was driving the difference in estimated odds ratio between the two subgroups.

[Slide.]

This table breaks down suicidal behavior or ideation event rates and risk differences by treatment arm and location, and it doesn't differentiate in this table between suicidal behavior or suicidal ideation. But, as you can see, as a group, placebo patients with events had a much lower event rate as compared to the other subgroups.

[Slide.]

Other characteristics were similar in North American and non-North American trials, and they included trial indication groups, the proportion of trial indication groups, age, gender, race, and treatment setting.

[Slide.]

Of primary concern I think is the question of whether given these differences between the North American and non-North American subgroups, whether our methods can reliably and reproducibly capture suicidal ideation between the two different locations, however, in comparison, suicidal behavior events were much more consistent.

In addition, the slide just lists a very general overview of other differences between North American and non-North American locations that may be contributing to these differences.

We can open up the floor for discussion or I can stay up here and take questions, either one.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: Maybe I missed it, I missed your first slide or two, but did you show the indications by North America and non-North America?

DR. MENTARI: The proportions of trial indication groups were similar when I looked at North America.

DR. LEON: So, there wasn't more bipolar disorder?

DR. MENTARI: No, there wasn't really a notable difference.

DR. TEMPLE: But it would be of interest to look

at those rates in the two subgroups, because they were so--I mean the rates are so different in the epilepsy and other group, it would be interesting to have a four-part table that showed epilepsy, other North America, other, just to look.

DR. MENTARI: Sure. Just to allow the Committee to know where to find that data in the briefing package, it's in the clinical review on pages 44 to 46, and then also on page 52.

DR. ANDERSON: For a non-North American trial, who translates or is there a translation of a reported adverse event into the text strings that you searched for, and how is that done?

DR. KATZ: I don't know if we know. We didn't do the translation. This was all done by the sponsor. As I said before, the primary work of identifying the cases, categorizing them by the Columbia scale, the translation if necessary, it is all done, it is sort of opaque to us, it is all done by the sponsors.

DR. ANDERSON: That would seem a possible systematic difference, whoever is performing the translation chooses terminology that is different or distinct from that

which is spontaneously reported by North Americans, then, it doesn't show up when you look for ideation.

DR. HUGHES: We didn't give specific instructions about translation.

Discussion and Questions to the Committee

DR. GOLDSTEIN: Very good. What I think we would like to do now is to turn to the specific questions that we were asked to discuss. We have really talked a lot about many of the issues, if not all of the issues, that these questions address.

As we go through them, though, I would like to sort of take each one in turn. Each question in turn is sort of conditional on the one before it, but the answer to the one before it doesn't dictate the answer to the one that follows.

Let's put Question 1 up. The first question is: Does the Committee agree with the Agency's overall finding of an increase in suicidality for the 11 AEDs analyzed?

The real crux of the question is do we think that there is a signal here, is there a signal. Again, don't think about where this is taking this on later questions because we could answer yes now, and have something else

later on, so don't jump to yes here and Question 4.

Each one is conditional, but the answer to one doesn't dictate the answer to the next.

Firstly, do we think that there is a signal. Again, before we have a just general discussion, I would like again the statisticians just to make sure we have them on line about this.

Are there issues related to the analyses that were conducted or the other information we heard at the public comment time that would alter that in any way, anything technical with the way the analyses were done that you have issues with?

DR. WOOLSON: I think I am okay after the discussion. I think I concur with the analyses. I put more weight on the risk difference kinds of analyses, and I think we have heard issues with regard to separating out the suicidal categories into behavior versus ideation, and I put a fair amount of weight on the behavioral aspects.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: I don't have anything new to add. I agree with the way it was done and I focused more on the risk differences.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: I don't have anything to add. I think the analysis won't change.

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: Just one clarification. What we are trying to get at here is whether or not you think there is an overall signal. It says for the 11 AEDs. There is a subsequent question, which asks if you think there is a signal, to which drugs do you think the signal applies.

So, I don't want you to be distracted by that 11. Is there an overall signal.

DR. GOLDSTEIN: So, again the question is given the information that we have based on the analyses that were presented, firstly, are they valid, are there technical issues with the way it was done, that the statistical members of the Committee have an issue with, and the answer to that from what I am hearing is no.

Given what we have, the next question is do we think that there is a signal. Again, forget about the 11 AEDs analyzed part of this, do we think from the information that we have here that there is a signal.

Comments? Dr. Gilman.

DR. GILMAN: I have made two previous comments and my answer is yes, there is a signal here. I have given the rationale previously, so I won't repeat it.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: I am going to repeat what I said before, but maybe a little better. I still am concerned that without knowing what the rate of depression was in the treatment arm and amongst the patients who received placebo, we have problems coming to the conclusion that AEDs are, in fact, a causal effect of suicidal ideation.

DR. GOLDSTEIN: Comments about Dr. Caplan's question?

DR. GILMAN: Yes, if she is going to repeat, then, I will repeat. We had placebo-controlled groups to compare it with the patients who were seen as having active suicidal ideation, therefore, I think that we do have a very good data set here.

DR. CAPLAN: Can I respond to that?

DR. GOLDSTEIN: Sure.

DR. CAPLAN: I agree that the data is good, but I think that the conclusion about the causality of AEDs is problematic if we have a high rate, much higher rate of

depression amongst the treatment arm versus the placebo arm.

DR. LEVENSON: Could I make a comment here?

DR. GOODMAN: As I understand it, there were no baseline differences on depression or suicidality. I don't know if we have a measure, but there is no reason to believe that there is any difference between the two treatment arms with respect to baseline measures of suicidality or any other psychiatric phenomenon that could be related to it.

DR. CAPLAN: Earlier this morning, I believe that question was asked and there was no data available for baseline.

DR. GOLDSTEIN: Dr. Levenson.

DR. LEVENSON: I have to interrupt the voting for one moment.

DR. GOLDSTEIN: We are not voting, we are discussing.

DR. LEVENSON: No, we do not have data directly on baseline depression. Everything we do have data on shows that the randomization in the trials seemed to work. But there were balanced treatment groups in everything we did measure, so there is no reason to believe there would be a poor randomization for this attribute.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: Particularly with 43,000 subjects being randomized, if we had 43 subjects being randomized we might expect some imbalance, but with 43,000 randomized in 199 trials, I wouldn't expect imbalance on an unmeasured variable--it wasn't unmeasured, but one unavailable to us.

DR. GOLDSTEIN: Dr. Winokur.

DR. WINOKUR: I am going to jump in and agree and reinforce comments that several people have made. I think, in balance, this is a significant data set because of the really large number of studies and population, and the placebo-controlled design. There clearly are some potentially confounding factors. but I think the fact that we are strictly looking at randomized placebo-controlled trials results in our seeing a signal that I think is an important one for the field to be aware of.

DR. GOLDSTEIN: Very good. Any other Committee members have any other points? Sorry, Dr. Hennessy.

DR. HENNESSY: Thank you. As the question is worded, I would say yes. But suicidality actually isn't found in the dictionary on the one that I just looked at. It is not in the dictionary, thank you.

If you ask the question, is the rate of suicide different, it is not statistically different. It is 4 versus zero and the sizes of the denominators are different. I agree that suicidality and suicidal ideation points to a potential problem. But the thing that we are really worried about, suicide, which is the fatal event, has a suggestion for an increased risk but it's not statistically elevated.

DR. GOLDSTEIN: I think that gets back to the issues that were discussed with the depression drugs. I think this is an empiric definition of what they are calling suicidality and it's operationally defined.

Yes, Dr. Schultz.

DR. SCHULTZ: Just briefly, to clarify the question, you are asking, concerned about an increase in suicidality based only on these up to 24-week roughly trials, which, as was alluded to earlier, represents sort of an acute perturbation of a system.

Are you asking simply about that or whether we think that is relevant to all antiepileptic treatment overall, which we know is chronic therapy over years of time?

DR. GOLDSTEIN: That is a later question. Again,

we are going to do each one of these separately, and again, the answer, you know, if the Committee votes we think there is no signal, the rest of the questions become moot. If we think that there is a signal here, then, the next one is to start addressing some of the other issues that you so appropriately bring up.

DR. SCHULTZ: Okay. So, the signal question is only about the acute trials, period.

DR. GOLDSTEIN: Each one separately. The next is conditional on it, but it doesn't dictate the answer to the next.

Any other discussion? Yes.

DR. ARMENTEROS: One point. We are not implying, or maybe we are, causality? Clearly, implying causality, is that correct?

DR. GOLDSTEIN: I think that the first question is, is there a signal in this group, how one interprets it--causality is related, but not the same question.

DR. PINE: What I heard the FDA to say, and maybe they will restate it, is if association is observed in a randomized, controlled trial, by definition, they have viewed that as a causal association or causality, but maybe

you want to restate that.

DR. KATZ: No, I think that is right. I think in controlled trials you see a signal, it is statistically significantly different from placebo, that is operationally defined as causality.

DR. TEMPLE: Once you rule out bias, error, and other inconveniences.

DR. GOLDSTEIN: I think in answer for a prospective randomized trial and what we are looking at here is that these trials were not prospectively randomized to test this question. So this is an observational analysis that is nested in a series of randomized controlled trials that we are analyzing.

Now, whether one concludes that this is causal or not I think is open to debate. But the bottom line is this is the data we got; these are the results, do we believe the signal.

DR. JUNG: That has got to be two separate questions.

DR. KATZ: We are interested in whether or not you think, when we use the word "signal," we mean whether or not you think there is a statistically significant increase in

episodes of suicidality, which to us we interpret that as causality.

We should be very clear. The trials were prospective trials. They were randomized trials. Data were collected contemporaneously, prospectively. The trials were not designed to specifically solicit information or elicit information about suicidality necessarily. Some probably were depending on the indication, but they weren't globally, specifically set up to capture that information.

But the information that was captured, was captured the way information is captured in clinical trials, contemporaneously, and you can think of that as prospectively.

What was done retrospectively was the manipulations after that, which were searching the database and categorizing them into these categories, and the meta-analysis, as has been said before, was prospective.

We set up a hypothesis, we set up a primary outcome variable, and we set up a method of analysis before we had looked at the data. So, much of this in a sense is quite prospective. They just weren't set up to capture the data perhaps in the best possible way.

DR. MENTARI: As I understand the discussion that we are having, we are dealing with the question of whether there is causality, and we do have a statistically significantly increased result for the class of antiepileptic drugs, and as I understand it, most people consider that causality.

There is a separate question of generalizability, I mean there are several issues with these trials that may make one question about how generalizable they are, namely, that several of them have exclusion criteria, including history of suicide attempt, suicide risk, substance abuse, personality disorders, which may affect how generalizable they are and how we might use the data, and that is a very relevant question.

Also, the issue that has been brought up several times of the short-term nature of the data is also something that we need to look at to assess how generalizable it is. But, to me, I think that is a slight different question from whether it represents a causal association.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: If I could get additional explanation. So really, the outcome measure, which in this

case is suicidal intense behavior ideation, was as you indicated with collected--it was actually collected retrospectively, but looked at prospectively. So the study wasn't a study that was designed to look at suicidality as an outcome measure, and I think we really need to clarify that.

DR. GOLDSTEIN: I think that that is hopefully clear that again this is a retrospective post-hoc querying of data that was tried to be done in as reasonable a way as is possible for these types of analyses, but the studies weren't prospectively designed to test this hypothesis.

DR. TEMPLE: Before you leave that, the meta-analysis was planned to study only that. It wasn't a scatter shot look through any conceivable association. It was directed at a particular thing, which means it was prospective although the studies were designed for something else.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: Since the question has been raised, I think we should direct our attention to the book page 8, Table 1, it's Suicidality Events in Codes.

There has been some question about that

suicidality means, and I think it is very clear here from the coding.

It goes from 7, not enough information, 6 not enough information, fatal, self-injurious behavior is No. 5, suicidal ideation No. 3, preparatory acts towards imminent suicidal behavior, 2 suicide attempt, 3 completed suicide.

I think that essentially defines suicidality as indicated here in this data set, and I think the idea is that there is a sequence of events leading to actual suicide, and that suicidal ideation is a serious event as is suicidal behavior.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: I would like to spend a minute or two on causation or not, and randomized versus not. Except for mathematicians who proved things by theorems, the rest of us work by inference and, while I will agree that, in general, you can make stronger inferences from randomized studies than from non-randomized studies, it is not an all or nothing thing.

Randomized trials do not prove causality, nor is it the case that you can never draw causal inferences from non-randomized trials, so we are always making inferences.

I don't think it is as simple to say because it was randomized, and there is a statistically significant association, therefore, we approve in causality.

DR. GOLDSTEIN: Dr. Jung.

DR. JUNG: I think along the same lines. I would like to hear from our biostatistician colleagues whether or not having that signal point is the same thing as causality because I am still struggling with that.

DR. WOOLSON: I can offer my view. I think anytime you look at a study, and we see an outcome and it's a positive outcome, there are really four explanations, really only four for the difference that we see.

The difference could be the way we handle the patients over time, could be the way we made the assessments. Those are two reasons. It could be a real difference, and that is what we are looking for, and at the end of the day, what we do as statisticians it could still be chance. So chance is always on the table, and that is the 5 percent, p, less than .05 kind of thing, so that is always there.

So, I think what we have done with a study like this, if we have taken care of the first two reasons, which

are randomization and objective assessment, and so forth, to really help us with, then, we are really down to a real difference versus chance, and then right now we are saying the chance of this being a chance outcome is so small that it is very, very unlikely.

That still is not perfect cause, it is not 100 percent, because you are never 100 percent unless we go to infinity with sample sizes for things.

I wanted to make one or two other comments, if I could, just about randomization. Even though we don't have some of the factors measured we would like to have reported here, they may have been measured. But the nice thing about randomization when done well, and Dr. Levenson has told us that it was done well in these 199 studies, is that you will get balance on the measured factors as well as the unmeasured factors on average, and that really is the beauty of randomization.

If you did, indeed, pick a particular variable, a baseline variable, and do a comparison, and if I found there was a statistical difference, I don't need to make too much of it, because the reason there is a difference, it's chance. That is the explanation, because I assign

individuals at random to receive these treatments.

So, I think the randomization and the on-average aspect, as Dr. Leon would say, when you have 47,000 individuals, it really gives us a lot of comfort for some of the issues, and I think there are legitimate issues to have on the table, But I think there are methodologic strengths here that really help us enormously.

DR. GOLDSTEIN: Dr. Lu.

DR. LU: Just trying to clarify technically when you say "causal effect," it means the condition on treatment minus condition on untreated given everything else equal. So randomization is the only mechanism that can wash out everything else equal. And it doesn't mean the case controlled studies or prospective studies cannot prove the relationship, but it is hard to argue about call a relationship than clinical trial can.

So, for this one, I think there are potentially the conditioning was in each treatment, which basically the difference only come from the treated, untreated. Now there may be bias. Some of study may contribute more than the others because of the weight also, not only count by the difference of the risk factor, but also the variation of the

study. And another way when they put zero there, it is really weighted on the randomization size.

So, in that case, some study may contribute more than the other, but if you believe there is a common--there is no way to distinguish among the studies, and there is a common factor, and the way the estimate should be unbiased in the sense that approach to the truth, you know, that is to the limit of the data that we have.

DR. GOLDSTEIN: Thank you.

Dr. Day.

DR. DAY: I have two things to say. First of all, I think the question is very simple. Is there a signal? There were two groups. Things were done with the data, the data collected, they were analyzed. Is there a signal? Is it statistically reliable? I think the answer is yes.

This whole discussion of causality, of course, is really important, but I don't think it needs to be addressed in this first question. It certainly will be later.

My second point is the concept of causality causes lots of problems in a lot of settings, and it is partly because it sounds so all or none; it does or does not. And so, if I use terms like relative risk or is associated with,

or is consistent with, it downplays it. In many settings in everyday life, people don't want to step up and say causes. And I will just point out that even within the FDA documents presented to us of things we might take action on later in the proposed medication guide, which we are not discussing now, but it does say this medication may cause suicidal thoughts, et cetera, et cetera.

So that is one way of saying it, yet, in the public health or the information for healthcare professionals that has already been posted, it says what it says and then there is the boilerplate language at the bottom, "Posting this information does not mean that FDA has concluded that there is a causal relationship between the drug product and the emerging safety issue."

So, it is partly a linguistic problem, and I don't think that is part of Question No. 1.

DR. HUGHES: I just wanted to mention that the reason for that disclaimer was because we issued that back in January when we had just finished the analysis and we were still reviewing it, and it was still considered preliminary at that time. So, I think there are probably lots of examples of inconsistent language in our proposals

in terms of causality. But that specific disclaimer is because it was preliminary rather than because we--

DR. DAY: Oh, so you are more comfortable with saying causality now?

[Laughter.]

DR. DAY: I withdraw the question.

DR. HUGHES: I am.

DR. KATZ: We are unequivocally comfortable with using the word, the "c" word with saying that this establishes causality. Again, we have talked about this a fair amount. This is how we determine causality, this is how we base our findings of effectiveness for drugs.

We do randomized trials, we analyze them prospectively, we have an outcome measure, and if it's statistically significantly different from placebo, we say the drug caused it, you know, once you rule out chance and fraud and bias and that sort of thing, which we think we have done here.

So, yes, we are quite comfortable with saying there is causality. And you have mentioned the Med Guide, where we said this drug "may cause." That was, of course, predicated on the view that we had concluded that the drugs

caused this. That is a document to be given to lay people and we said "may cause," because even though we have established causality, it doesn't mean it causes it in everybody.

So, we said, well, it might cause it or it may cause it in a particular person, and that was the implication, but it wasn't meant to step away from the conclusion that the drug is responsible in those cases where it happens.

DR. TEMPLE: Probably should have said "can."

DR. GOLDSTEIN: I think we have said ample discussion about the point. I think we know the question that is before us based upon the data that we have available, do we think that there is a signal.

The question itself is written up there exactly in the text that we are voting on, but that is the aim of what the question is trying to get at.

For those of you on the panel, there is a new way of voting we used to go around the table and everybody yea or nay. We still need to do that, but what we are going to do first is have voting without knowing what your neighbor thinks. There is a little button on your gizmo here. It

says Yes/No and it's flashing all sorts of colors now.

What you do is you press Yes or No, and then once that is done--or Abstain, sorry--and remember some of the people on the panel are non-voters, so do they press Abstain or not vote? Don't touch a button. Do something really bad. The Voting Committee members please place your votes now and they will show up on the screen and then we will go around because we still have to do it the old way, as well.

[Voting by Committee members electronically.]

DR. GOLDSTEIN: I think what we have to do is even though that is the way it shows up, we then need to go around and have everybody vote orally to affirm that that is what their vote was just in case there is a short circuit here or the same people that are doing the voting in Florida run this thing.

DR. WAPLES: I need to read the results in for the record.

Question 1, there were 20 Yes, 1 Abstain, 0 No.

DR. GOLDSTEIN: Dr. Schultz, let's just go around. Just say your name and how you voted.

DR. SCHULTZ: Susan Schultz. Yes.

DR. ANDERSON: Anderson. Yes.

DR. HUDSON: Hudson. Ye.

DR. LU: Lu. Yes.

DR. MALONE: Malone. Yes.

DR. RIZZO: Rizzo. Confess. I am the guy who abstained and it's because I still don't understand the question. I would vote Yes if the question were worded that there is a statistically significant increase in suicidality, but I cannot vote Yes if the issue is causality.

DR. GOLDSTEIN: Very good.

DR. WINOKUR: Winokur. Yes.

DR. LEON: Leon. Yes.

DR. WOOLSON: Woolson. Yes.

DR. JUNG: Jung. Yes.

DR. PINE: Pine. Yes.

DR. ROBINSON: Robinson. Yes.

DR. GOLDSTEIN: Goldstein. Yes.

DR. GOODMAN: Goodman. Yes.

DR. RUDNICKI: Rudnicki. Yes.

DR. GILMAN: Gilman. Yes.

DR. HENNESSY: Hennessy. Yes.

MS. GRIFFITH: Griffith. Yes.

DR. CAPLAN: Caplan. Yes.

DR. ARMENTEROS: Armenteros. Yes.

DR. DAY: Day. Yes.

DR. GOLDSTEIN: Very good.

On to Question 2. Does the Committee agree with the Agency's conclusion that the finding of increased suicidality should apply to all drugs included in the analyses, despite the observation that the estimate of the odds ratio for 3 of the drugs was below 1? If not, to which drugs should the conclusion apply?

This is getting at the issue of generalizability, and we have also discussed in some of the give and take that we have had about drugs that have these properties being antiepileptic drugs that aren't in the analysis at all or drugs that may be developed in the future. Trying to prove a negative with very rare events is virtually impossible, so what they are looking for here is that guidance.

Should this be a generalizable conclusion applied to all antiepileptic drugs or drugs that have antiepileptic properties? The only other proviso is that word chronic and what does chronic mean. Dr. Leon.

DR. LEON: As a point of clarification, there were

only two below odds ratios below one. One of them was undefined, and the other, whatever is left, eight were above one, so we should either say all but three were above one or two were below one. That should be corrected.

DR. DAY: Excuse me, Mr. Chair, I disagree with your interpretation of the question. You were talking about this extending more generally. I think this is still restricted to the 11 drugs in the study and that the misleading word in here is "all."

So, if we take in line 2 and make "all" each, so, does the finding of increased suicidality should apply to each of the drugs included in the analyses, and I think it is then in Question 3, when it is applying to other ones that were not studied.

DR. GOLDSTEIN: That is perfectly fine.

DR. DAY: Thank you.

DR. GOLDSTEIN: Not a problem.

Dr. Gilman.

DR. GILMAN: Mr. Chairman, I have another correction to what you said, but not what is written here. You said applied to drugs in the future. I don't think that should be part of this question. It is not written here.

DR. GOLDSTEIN: We can do that in Question 3. That is sort of what they are trying to get at there.

DR. KATZ: This is intended to address just the 11 drugs.

DR. GOLDSTEIN: Just the analysis that we have before us.

DR. TEMPLE: It is about what to do with the diversity of responses in a situation like this.

DR. GOLDSTEIN: So, everybody clear? Okay.

Dr. Hennessy.

DR. HENNESSY: I would like to make the point that, you say that the results apply, we are really talking about an assumption, so there are a couple of different things you can assume either in the absence of data you can assume that any particular drug that hasn't been shown to be dangerous is not, or on the other side, you could assume that all the drugs are the same unless proven different.

For a safety concern, the conservative thing to do is to assume that all drugs in a particular class, and whether that be pharmacologic class or therapeutic class, shared the same risk unless proven otherwise, that is a reasonable assumption to make in a safety context.

But I think we should be clear that we are making an assumption and that we are not able to use scientific reasoning to make the inference that each one of those individual agents has an increased risk.

So, we make an assumption from a public policy perspective of what we will do from the label, but I would say that the data aren't there for the individual drugs.

DR. GOLDSTEIN: Thank you.

Dr. Pine.

DR. PINE: So, two things. One thing. Just to second what Dr. Hennessy said. From a safety perspective, I think that we have to look for the presence of data to suggest that we should do something unusual with one or another medicine. Do we single it out as particularly good or particularly not good, and in the absence of statistical evidence, from a safety standpoint, I think it behooves us to not single something out unless the evidence is there.

The second thing is I want to come back to the point that Dr. Temple made, that I think it is a good trend in recent communications from FDA that there is an emphasis on data and particularly alerting the field to the paucity of data, so really thinking very carefully about how exactly

limited the data are in terms of saying anything specific about any of the 11 medications would be really important, you know, to get across again in data the scatter that you see.

DR. GOLDSTEIN: Other comments?

If everybody is okay, then, I think we can move that one to a vote.

Again, the question is: Does the Committee agree with the Agency's conclusion that the finding of increased suicidality should apply to all or each of the drugs included in the analyses, despite the observation that the estimated odds ratio for 2 of the drugs was below 1? If not, which should the conclusion apply?

I think we do it in two steps. The first step is the first question mark and then we can do the second question mark additional on the first.

[Voting by Committee members electronically.]

DR. GOLDSTEIN: Did everybody press their buttons that they are supposed to?

DR. WAPLES: For the record, 18 Yes, 3 No, and 0 abstain for Question 2.

DR. GOLDSTEIN: Let's start this way this time.

DR. DAY: Day. Yes.
DR. ARMENTEROS: Armenteros. Yes.
DR. CAPLAN: Caplan. No.
MS. GRIFFITH: Griffith. Yes.
DR. HENNESSY: Hennessy. Yes.
DR. GILMAN: Gilman. Yes.
DR. RUDNICKI: Rudnicki. Yes.
DR. GOODMAN: Goodman. Yes.
DR. GOLDSTEIN: Goldstein. Yes.
DR. ROBINSON: Robinson. Yes.
DR. PINE: Pine. Yes.
DR. JUNG: Jung. No.
DR. WOOLSON: Woolson. Yes.
DR. LEON: Leon. Yes.
DR. WINOKUR: Winokur. Yes.
DR. RIZZO: Rizzo. No.
DR. MALONE: Malone. Yes.
DR. LU: Lu. Yes
DR. HUDSON: Hudson. Yes.
DR. ANDERSON: Anderson. Yes.
DR. SCHULTZ: Schultz. Yes.
DR. GOLDSTEIN: Very good. Did the number add

up? Good.

I guess the second portion of the question then is moot, so we can go on to Question 3. Does the Committee agree with the Agency's conclusion that the finding should apply to all chronically-administered AEDs, including those that were not part of the analyses?

I guess this is the question that I semi-muddled with the last one, but we are addressing this separately now. This gets to the generalizability issue.

Comments? Dr. Anderson.

DR. ANDERSON: I will have trouble voting on this as phrased, because I am not sure that I understand with sufficient specificity what the FDA's definition of an AED class is. So, for example, if I work for Pfizer and I have another alpha 2 delta agent and I make sure that I never test that agent for antiepileptic efficacy, but I only test it in pain, is that going to have to carry whatever warning, is that going to be defined as an AED?

You are going to get clozepam, but no other benzodiazepine unless it's regulatory approved, and so without knowing more specificity about the definition of the class, it is hard for me to feel that I could say yes or no

on this question.

DR. KATZ: Fair question. I couple of things. I don't know that we have a definitive answer. It's an excellent question. There are I think examples, as I said before, with the antidepressants with drugs that are considered to work the same as other antidepressants, but are not approved for depression. I think they have the boxed warning, so there is some sort of mechanistic carryover, if you will, even if they don't have the indication.

You can make this I suppose simpler if you just want to consider the question to apply to only those drugs that currently are approved for an indication of epilepsy. Then, at least for the moment, we don't have to worry about --it would be interesting to hear your comments about the future. But really, here we were mostly trying to get at the other drugs that are currently approved for epilepsy, but were not included in the analysis.

That is a simpler question which we would very much--you know, they are almost equivalent questions although I agree they are not exactly. And one issue also that has just been mentioned to me--as we mentioned earlier,

most of the studies that we included were for complex partial seizures for epilepsy. There are some drugs approved for seizure types that don't include partial seizures. There are a couple. I think just for proof of just some generalized seizures, I don't think carry a claim for partial seizures, if you would like to discuss that. But our proposal was to include all drugs that are approved for any kind of seizure type.

We couldn't just limit this to the ones currently approved. That would at least make it easier I think.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: So, we are changing the question then, because I do think that it's an easier question to think about based on what Dr. Katz just said. Is that right?

DR. GOLDSTEIN: Dr. Katz, just to clarify, so it would then read: Does the Committee agree with the Agency's conclusion that the finding should apply to all currently approved, chronically administered AEDs, is that what you are proposing?

DR. KATZ: We can certainly do that at least as a first step, because again I think that is mostly what we were getting at. We will, of course, have to deal with the

fact that tomorrow there may be an anticonvulsant approved, and we will have to deal with that if you don't want to vote on that question. We will deal with it and we are likely to apply the same labeling.

DR. PINE: Just to clarify the thinking there why you asked the question, I think you said it this morning, and I think I understand it--but maybe to just make it explicit, you are concerned that if we limit it, the warning, just to the 11 medications that we have already discussed, or limit the conclusion, that there will be a movement away from these medicines to other medicines. Is that what motivates the question?

DR. KATZ: That is the generic concern. Whether that is a real concern in this setting given what those other drugs are, I don't know, but yeah, that's the overarching concern that we can shift prescribing to other drugs that might very well have the same signal. They just weren't included, yes, that's the general idea.

DR. GOLDSTEIN: Very good.

Dr. Gilman.

DR. GILMAN: I would just like to make sure that we are now talking about current medications, and we are not

projecting into the future. I would be happy to discuss that. I mean I think maybe we should discuss what we do about future AEDs, but right now it would be easier if we just voted for this as it is stated.

DR. GOLDSTEIN: I think that they actually amended the question with somewhat different wording, taking into account the clarifications that were just mentioned, so that it now reads, "currently approved chronically administered AEDs."

Dr. Hennessy.

DR. HENNESSY: Thanks. I would like to make a similar comment to last time that in my view, this is more of a policy question. What does one assume in the absence of data rather than a scientific question what do we know about the effects of drugs that weren't studied.

Obviously, we don't know about the effects of drugs that aren't studied. The question is from a public policy perspective what do we do about that. To me, the question becomes much easier when you think about it in those terms.

DR. GOLDSTEIN: Dr. Katz or Temple?

DR. KATZ: Right, largely that. You take into

consideration what you think you should take into consideration, but certainly it is, in our view, largely a policy question, or in part anyway.

DR. TEMPLE: But it's presumably informed by what the perceived consistency across the drugs studied so far is. I mean it will be informed by that, but it is ultimately a policy question.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: Can you just clarify to me--I am sorry--but if this is a policy issue and we are lacking all data, I mean again what is the indication for treatment with patients, all patients, for example, and I am particularly talking about patients with epilepsy, are going to be warned that their medication might cause suicidality, that is what we are voting on?

DR. KATZ: Right now I think you are voting on should we apply the conclusion that we have come to, to all those other drugs, and the operational definition of apply the conclusion is to change the labeling in a similar way.

DR. CAPLAN: Right, but the impact of this, for example, on the epilepsy community is going to be tremendous. Basically, it is going to be saying to all

patients that any medication that they take might make them suicidal, right?

DR. KATZ: Yes.

DR. CAPLAN: That is what we are voting on.

DR. KATZ: We are voting on changing, in effect, changing the labeling to include some description of these results in that labeling.

DR. CAPLAN: Despite the absence of data.

DR. KATZ: Well, that is what we are asking you. We are saying we didn't study these additional drugs; should we take the same action, specific action yet to be determined by the way--that is Question 4--but should we take the same action we are going to take with these 11 with these other additional drugs. That is the question we are asking and there is no data for those drugs. But, as Bob says, looking at the consistency of the data so far, that should inform your decision.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: If we vote yes on this, it does not say what the language might be. So that there could be intermediate language in different cases. So there could be some language that goes for everyone in the class, that this

class of drugs has been associated with or caused, whatever you want to say, and then there can be another sentence or statement, however, there is not sufficient evidence for this particular drug. I mean that would weaken it, it is in between a little bit, but the point is in voting on this, it doesn't say what the language would be, because that comes up in the fourth question.

DR. GOLDSTEIN: That is exactly right. We are taking each one of these in turn and we will deal with that next one.

Dr. Armenteros.

DR. ARMENTEROS: I think the concern I have with generalizing this to other drugs for which data has not been presented is that it implies we are making an extraordinary comment or statement without an extraordinary set of data to back that up, so that is just my concern.

DR. GOLDSTEIN: Again, I think that might go more in how this is worded. I guess you guys went through the exact same issue with the antidepressants. We can go to that and discuss that a little bit more in a bit.

DR. LAUGHREN: We had the exact same issue with the antidepressants. There, there was a great concern that

if we put the box on the current generation of antidepressants, clinicians would be driven back to using the older antidepressants in particular the tricyclics that are inherently more toxic, and nobody wanted that outcome.

I think that, in part, is what was driving that, but you have to think of the same issue here from a policy standpoint, what would clinicians do if you only had the box on the current generation of antiepileptics, would they be inclined to use older drugs that were developed years ago and for which you may not have as much safety data.

DR. GOLDSTEIN: Dr. Twyman.

DR. TWYMAN: Dr. Katz, I just want to clarify the definition of the AEDs. As a class, these compounds that have been analyzed have in common that indeed they have all been approved except for one for the adjunctive treatment of partial onset seizures, and I think divalproex has a broader claim for treatment of epilepsy

So, are you meaning to apply this to AEDs, as you pointed out, that are used for treatment of principally for generalized seizures and also the data set here basically included the ages from 5 and above, and at least one of the medications that is approved for generalized seizures is

often used for patients much younger than that, could you clarify what is this class definition?

DR. KATZ: Again, first of all, about the pediatrics, I don't think there are any drugs approved only in pediatrics. There are drugs approved for pediatric patients, some down to very young, but they are also all approved for adults I think.

It is a very simple operational definition. Anything that has an indication for epilepsy, any kind of seizure type, that is the proposal. You can discuss whether or not you want to parse out the few that don't have a partial seizure claim, but the proposal is any seizure type in approved indication.

DR. TWYMAN: To the missing data issue, I mean for the generalized seizure population, there is absolutely no data particularly for the compounds that are specific to generalized seizures, and there has been no data here presented for that.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: We don't have the language before us that is going to be written. All we are asked to do is say yes or no, we agree with the conclusion that this should

apply to all currently approved antiepileptic drugs.

We are not saying to the patient you are going to become suicidal if you take this drug. There is going to be some sort of language that indicates there is a risk involved with this drug, period.

If we had the specific language, it would be easier for us to vote. But I don't think we are telling people you are going to become suicidal if you take this drug at all.

So, I think this is an appropriate yes vote personally.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: From the FDA, can you give me some rough idea of how many other antiepileptic drugs there are other than these 11? Are there 3 more or 100 more?

MS. WARE: There are about 20.

DR. LEON: Total, 20 more?

MS. WARE: Roughly, if you are just talking generic names.

DR. PINE: Thirty-one or 20 total?

MS. WARE: Counting the 11 on the list, current working list there--would you like me to answer in the mike?

Sorry. Jackie Ware. I am a project manager in the Division of Neurology Products. The current working list, it is not a finalized list is about 43 drugs. They are not all-inclusive for dosage forms, but that includes just generic names, different generic names.

DR. JUNG: Can you list them for us?

MS. WARE: I can list part of them if that's okay. Like I said, it's not a complete list.

DR. JUNG: The point is that for those of us who trained 20 years ago, we all remember the antiepileptics that didn't work very well that we have moved away from. I think part of the concern here is that again we are recommending that we apply a black box label to drugs.

DR. GOLDSTEIN: No, we are not. That is later.

DR. JUNG: Let me back up. I think that if you look in the clinical setting, a patient or the parent of a patient is going to hear that there is a black box warning for a suicidal risk, and they are not going to differentiate the difference between this is going to cause you to become suicidal versus there is this risk. That is a concern I have.

I mean we tell our patients that drug X can make

them gain weight and they all refuse to take it.

DR. GOLDSTEIN: But the question being raised here is should it cover dilantin, should it cover phenytoin, should it cover phenobarbital, should it cover mephenytoin, whatever.

DR. JUNG: Yes, the other drugs, we all remember how well or not well those drugs worked.

DR. TEMPLE: But that is the question being raised in this one, should it apply to drugs other than the 11, whatever they are, Jackie will tell us, that weren't in the study.

DR. JUNG: It's a circular argument, right. We are going to try to cover these drugs even though we don't have data for it?

DR. TEMPLE: That is exactly what the question is. That is exactly what the question is, and the reason is the one Tom gave before, we didn't have any data for antidepressants on tricyclics, so what do you do? Leave them out? After all, if all the classes of antidepressants that were studied have this effect, why wouldn't another one? That is a question.

DR. JUNG: If we vote yes to those questions, that

means that we are making an assumption that we are going to try to change the behavior of the prescribing clinicians, that they should not be worried whether they are going to use an older drug versus a new drug.

DR. TEMPLE: I think the worry is that you would drive people toward older drugs inappropriately if you only identified the 11 drugs. That is where this concern comes from.

DR. PINE: I do think we are missing discussion of a very important point, that for the antidepressants there was a very specific realistic concern, that not only were there another class of medication where there was not data, there were considerable data to suggest that that class of antidepressant was dangerous. And so that there was a great deal of concern in the Committee about discouraging use of one group and driving people to the only other option that was known to be dangerous.

It was that specific fear that influenced that policy or that vote. So, as a psychiatrist, I would like to hear from the neurologists is there anything remotely like that for the antiepileptics. I am starting to hear that maybe there is. But the degree to which it is a legitimate

concern that people are going to drive parents or patients are going to want to take medications that the neurologists in the room are not going to want to use, then, this is a relevant issue.

DR. JUNG: That is exactly what we are doing by answering Question No. 1.

DR. PINE: We are trying to prevent that if we don't want that to happen. If we don't say anything, it could happen.

DR. GOODMAN: I just want to add something quickly to what Danny Pine just said, going back to the rationale for expanding the list to include the tricyclics.

In addition to safety concerns we had about the tricyclics, some of the earliest descriptions of an association between suicidality and administration of antidepressants was in the context of the administration of the tricyclic antidepressants.

I think going back to the early '60s, there was the description of the energizing phenomenon. It urged the clinician to be cautious in the early days to weeks of prescribing tricyclic antidepressant, that the person now became immobilized and they could act on their suicidality.

So there are other reasons, too, to implicate the tricyclics, and I am not clear that those obtain here for a drug like phenobarbital.

DR. TEMPLE: It is worth remembering that your answer to Question 2 I guess--you may need to tell me this is wrong--seemed to be that yes, we have no idea why this should be a common effect in all of the antiepileptic drugs, because we don't know of a mechanistic explanation for this, but we think the conclusions should apply to all 11 of them even though some of them didn't actually lean that way.

Following similar reasoning might lead you to conclude the same thing here. That is the question.

DR. GOODMAN: Where you have no data at all.

DR. TEMPLE: But you didn't have any data on two or three of those drugs either.

DR. GOLDSTEIN: Exactly.

Dr. Lu.

DR. LU: I think I just comment on Dr. Temple's comment. One thing that is different from Question 2 versus here is in Question 2 we actually had data and confidence interval which covers the estimate points, and here really we extrapolate something that--I mean personally I don't

have any idea about.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: Thanks. Dr. Temple made my point. I am usually not one to be slavish to do the same thing as I did earlier. But, earlier, we assumed that the results should apply even to the drugs for which there wasn't a point estimate greater than 1. So, it seems easier to me to extrapolate to areas where we don't have data to areas where we have data that seemed to suggest safety.

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: No.

DR. GOLDSTEIN: Dr. Potter.

DR. POTTER: Just a quick follow-up on the statistical question of confidence limits. For those drugs for which you don't have data, given the infrequency, the sparseness of the events in question, wouldn't you need huge sample sizes. So, even if you did have data, wouldn't it have been extraordinarily unlikely that the confidence limits there would be far enough to the good side to say they don't have--I mean what would it have to be?

Is there any statistical way in the world that you could convince yourself with the old drugs that they don't

share this? I don't think there is a measure that this group would accept from what I have heard.

DR. GOLDSTEIN: The other point to the question was is there concern about driving people to prescribe the older drugs. The older drugs aren't used anywhere as near as frequently for a whole variety of reasons.

Among them are the adverse side effect profile and the inability and for many of them to control seizures. So, it is again the law of unintended consequences, and I think everybody is quite aware of them.

Based on this signal that we said was real, and we are concerned about, does that mean that you want to drive people from the seizure medicines that they are on now, that may be adequately controlling their seizures.

We heard about the terrible down side that that would have--increased mortality, loss of jobs, whole bunches of bad stuff happens. So that is not where we are going here. But again by analogy, from what I understand, I wasn't part of that with the antidepressants, it is not a dissimilar argument.

As scientists, we like to have the data, we want it with tight confidence intervals, we want to make clear

decisions. This is way past that. Just to get an answer to how many AEDs.

DR. KATZ: How many additional AEDs are we talking about? Our count as best we can figure out is that there are 14 additional different AEDs approved, in addition to the 11, so 25 different chemicals, so additional 14.

DR. LU: Are they in the same group, like you have a classification of 3 mechanisms.

DR. KATZ: We haven't looked at them. I am sure there is some overlap, but a lot of them are old. I don't know what we know about their mechanisms, but we haven't looked at that. It includes barbiturates, includes fentanyl.

DR. CAPLAN: Dr. Gilman.

DR. GILMAN: Does it include bromides? I just wondered how far back it went. I find this as very difficult question because phenytoin is actually a very effective drug and I use it myself on patients frequently, especially phosphenytoins, a currently active and very good drug.

Is there any evidence and will we ever have evidence that it has suicidal risk associated with it? I

think the answer to that is no, we will never have evidence for it. So, I go back to our original conversation and the original data that we have here, which is that we have a number of medications that have different biochemical mechanisms of action and yet are antiepileptic drugs.

Therefore, by analogy, it might stand to reason that the earlier drugs may have a similar mechanism of action, may have a similar effect even though they have a different mechanism of action.

Consequently, I think it is perfectly reasonable that they should be included first, just from the purely logical perspective.

Second, these newer agents have done a great deal for patients. Even though we were once hoping for monotherapy, one drug for a seizure patient, that seems to elude us, and now we are back to treating with two or three or even four different medications to keep people seizure free. Epilepsy can be very difficult to control, of course.

I find myself torn, but on balance I think my vote is going to be yes, and the reason it is going to be yes is because there are just a few drugs that really we are talking about here. It may be 14 in the list, but, in fact,

it is not going to be 40, we are not going to go back to bromides, we never will do that. I am not old enough to experience what they were like, but they were apparently terrible things.

Phenobarbital is a very poor drug for chronic use, so we are really dealing with phenytoin as the practical one, and I just don't think it's a good idea to drive the clinicians or the patients and clinicians back into a single agent that was very effective.

It was actually a miraculous drug at the time. But we have so much better drugs now that on balance, even though there are no data, and we will not acquire data, I at least have, at least supporting this idea, logic, and the fact that there are other medications that have different biochemical mechanisms of action that lead to the same kind of adverse event liability.

So, my vote is going to be yes.

DR. GOLDSTEIN: Dr. Rizzo. Just to remind the Committee members, I should have said this more explicitly before, as we are discussing these things, please don't say how you would vote, just raise your points.

DR. RIZZO: Along the lines of guilt by

association and driving practice patterns, have we considered the possibility that by extending this warning to all antiepileptics, we might be driving patients to surgery or to vagal nerve stimulation? What are your thoughts on that?

DR. KATZ: Well, actually, we would like to hear your thoughts on it. This is the reason we are asking, and this is one of the reasons it is a tough question. We would be very interested to hear what you think. If you think that by doing this for all drugs, we are going to drive people to surgery inappropriately perhaps or vagal nerve, we don't know.

DR. GOLDSTEIN: I think that there are some data, as was mentioned by one of the public speakers, about surgery, and there is apparently an increased risk of suicidality after surgical procedures, as well. So I don't see, you know, if one understands the data correctly, then, I don't see where that should be operative.

Dr. Schultz, did you have your hand up?

DR. SCHULTZ: I am struggling a little bit. I understand the concern about you never want to drive practice back to phenytoin, but there was also a lot of

discussion from the neurologists earlier about patients often are noncompliant and blame everything on the medicines.

Are we going to drive stable patients off their phenytoin by virtue of a warning if people are equivocally compliant anyway, are we going to do more harm by driving stable patients off their older anticonvulsants?

DR. GOLDSTEIN: I guess part of that would be the way that this is worded among other things which we will deal with next.

Dr. Twyman.

DR. TWYMAN: I am just as little concerned about the labeling for the future for all drugs that you use to treat epilepsy, and so I just want one more stab at the classification.

There is at least one compound that very specifically targets absence epilepsy, for example, and has absolutely no activity in partial onset seizures. And so perhaps the science of the future may evolve that we have more specific therapies that target very specific subtypes of these seizures and cannot be reasonably classified as an agent that works on partial seizures and, in fact, probably

may not work in partial seizures.

So, I am just trying to make some distinction that this drug class, as a whole, appears to be--at least the day of the supports, this appears to be for those drugs a theft of impartial onset seizures.

The data is absolutely absent on conditions, say, like absence seizures and drugs that are used specifically to treat those and have no activity in partial seizures.

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: That is a fair point and you should take that into--that is why I raised it before--you should take that into consideration when you vote on this, that the proposal on the table is to include all drugs with an indication for any kind of seizure type.

If you think that that absence drugs, drugs specifically and only that are approved for absence should be excluded from this, then, we need to know that, but that is the proposal. We have no--it has been said many, many times there are a lot of questions that we are asking you that we don't really have specific data to answer, but we do need an answer.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: My comment was made already, I pass. Thanks.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: Like Dr. Schultz, I want to bring up the point that I am really very uncomfortable with this because the question is are we doing this in the best interests of the patients. And if, you know, as mentioned by the speakers before, the experts in epilepsy, irrespective of the type of treatment, be that surgery, be that medication, patients with epilepsy have much higher rates of depression and suicidal ideation so that again I am bringing us back to the question if we have good drugs, and if we have drugs that are working, we need to be very careful about scaring the patients into not taking these drugs.

I really think we need to give a lot of thought to that.

DR. GOLDSTEIN: Again, I think that is how this is going to be presented. I think you are absolutely right, and it is going to be an important thing for us to really discuss in great detail.

Dr. Jung.

DR. JUNG: I would like to point out, similar to what Dr. Rizzo said, but in a converse way, if we are going to drive people away from anticonvulsants towards surgery, the question is are we going to drive them away from medical therapy all together.

Those of us who treat patients with seizures know that there is a huge amount of denial out there. We spend a lot of our time fighting to get patients onto therapy in the first place, and I think we are going to scare them off. And if you think about the risk of sudden death associated with untreated epilepsy or treated epilepsy for that matter, I think we really need to think that through.

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: I am not sure if it directly affects the voting of this question, but I still want to emphasize my concern for the non-epilepsy, non-psychiatric population, that other category.

While I have sensitivity to the concern that we drive patients to phenytoin who have epilepsy, if we label these drugs and no phenytoin, I am concerned about the interpretation to application of a label to the class of AEDs for new agents and that there should be some--how there

is supposed to be some prospective determination again for new agents that come along that would easily have been fit into this group of 11 if we hadn't given the AED some sort of specific suicidal warning action, whatever that is determined to be.

And now for new applications for postherpetic neuralgia or pain, or something else, there is a specific avoidance of studying those medicines for epilepsy where they may be effective in order not to be able to be tarred with the AED label.

So, I think the action that is taken against the class of AEDs that currently exist, there is a need for some mechanism or sensitivity to making sure that future approvals sort of don't necessarily just go with the seizure indication as much as they do some sensitivity to similarity in class or action.

DR. GOLDSTEIN: Dr. Hudson.

DR. HUDSON: I guess I am not having as much angst considering most of the medications I use in my practice are potential life-threatening, so you are used to having a dialogue with the family and the patient and how they are tolerating it and weighing the risk and benefit. So I think

this offers the opportunity even if we extend it to all AEDs for dialogue with the patient and the family for enhanced awareness of the need to monitor and continued follow-up.

That at the very least is probably worthwhile so people can be aware. The label or whatever we state in Question 4, that is going to be the meat of the matter in my view.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: Related to Dr. Anderson's comment, I just want to clarify based on the question to Dr. Katz, my understanding is we have taken future agents off the table and we are not even considering that, and I would share the concerns that Dr. Anderson raised.

One thing I would suggest, though, and again I know this came up with the antidepressant data, one of the problems with the data are not just the small number of events, but there is a lot of problems with the outcome measures.

So, I think one of the thoughts going forward for future medicines is some systematic effort on behalf of the FDA--again, I don't think we need to talk about this today--but if some of the problems in the data in terms of what was

measured and how it was collected were fixed in future studies, it might be feasible to say something with more confidence about new agents that come along, if these concerns, and there is a whole host of other things that you might measure related to mechanism, if data were produced that would answer more definitively is there an association or how do we understand it in this medicine or not.

But the bottom line is let's keep the future off the table, because I think it is a very sticky wicket.

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: Right. I think we have taken that off the table although as I said before, and I agree, in the future we should be collecting better data, it is just that it is going to take I think probably as long time to figure out whether there is a signal with better collecting devices.

So, we will have to deal with the question of the anticonvulsant that is approved next week or next month or next year. We are going to have to deal with that, and we will. I don't know how we will, but I have a guess.

So, that just needs to be taken into consideration. But for purposes of this question, I think

we have decided to talk about those that are currently approved.

DR. GOLDSTEIN: Any other points of clarification? Questions? Okay. I think then that we are again ready.

The question on the table is: Does the Committee agree with the Agency's conclusion that the finding should apply to all currently approved chronically administered AEDs including those not part of the analyses?

[Voting by Committee members electronically.]

DR. WAPLES: For the record, for Question No. 3: Yes 15, No 5, Abstain 1.

DR. GOLDSTEIN: Very good. I think you are getting a feel that our unease is similar to your unease.

I think we start this way this time.

DR. SCHULTZ: Schultz. No.

DR. ANDERSON: Anderson. Yes.

DR. HUDSON: Hudson. Yes.

DR. LU: Lu. Yes.

DR. MALONE: Malone. Yes.

DR. RIZZO: Rizzo. No.

DR. WINOKUR: Winokur. Yes.

DR. LEON: Leon. Yes.

DR. WOOLSON: Woolson. Yes.

DR. JUNG: Jung. No.

DR. PINE: Pine. Yes.

DR. ROBINSON: Robinson. Yes.

DR. GOLDSTEIN: Goldstein. Yes.

DR. GOODMAN: Goodman. Yes.

DR. RUDNICKI: Rudnicki. Yes.

DR. GILMAN: Gilman. Yes.

DR. HENNESSY: Hennessy. Yes.

MS. GRIFFITH: I abstain. I felt as though we are in a trick box and we had walked ourselves into this very similarly to the antidepressant situation. I mean we are damned if we do or damned if we don't.

We truly don't want to discourage patients from taking their medication. At the same time if they are forced to take medications that are older, we don't know the consequences of that, and I don't feel like I have enough information.

DR. CAPLAN: Caplan. No.

DR. ARMENTEROS: Armenteros. No.

DR. DAY: Day. Yes, but close to abstain.

DR. GOLDSTEIN: Very good.

Does anybody who voted No just want to amplify anything else, because again, part of the whole exercise here is to make sure that the Agency has heard a full discussion and opinions?

I think we have had a good discussion, but I just want to make sure that everybody has had their chance.

Okay. Let's go on now to the last questions, and there are actually two questions. I think I would like to deal with the first one first, and then we can go on to the second depending upon the first.

The first question is: Does the Committee agree with the Agency's plan to require labeling changes for all AEDs, including a Boxed Warning and a Medication Guide? Then, if not, does the Committee want to offer guidance on other approaches to communicating this information?

I guess the discussion would cover both, but I would like to hold the vote separately if we could.

Dr. Malone.

DR. MALONE: I am not sure what the order of warnings are, but I guess black box is at the top. I am not sure how it goes then down.

DR. KATZ: The new labeling format combines what

used to be warnings and precautions. It used to be separate warnings and precautions sections in the old labels, so now there is a section for warning and precautions. It is one section. We place those which we think are most important first and then we just go down.

That is the next most severe, you know, that is the next most prominent place in labeling that you would put, and you could bold. I think you can still do that, bold the print for those warnings which we really think people ought to pay attention to.

DR. MALONE: Another question is can you get a Medication Guide only if you have a black box, or is that a separate issue?

DR. KATZ: That is separate.

DR. TEMPLE: It is separate and there are rules about what can lead to a Medication Guide. You can have a patient package insert that isn't called a Medication Guide. You do that for a lot of reasons.

But Medication Guides are put there for three reasons, one of which is that you really think the patient ought to participate in the risk-benefit judgment--the Medication Guide goes to the patient--or to participate in

the decision to use the drug, that is one.

Two, they can do something really important to avoid a problem. And then there is a third that isn't relevant to this, but that is what gets you a Medication Guide, something that they really need to think about, two, they can really help avoid a problem. That is not so different from the bases for putting things in a box.

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: A question. If you put a black box warning on a drug when there is not really any clear implication or clear evidence that there is a big problem, does that detract from other warnings for a drug, which are more likely. In other words, suppose you have this black box warning for Tegretol or carbamazepine, but suppose there are other side effects of carbamazepine that are much more likely to cause harm, how does the black box warning for suicidality interact with those other warnings that maybe are more important to get out for a drug?

DR. KATZ: Well, I guess if we thought there were other warnings for a drug that were more important than the warning we put in a boxed warning, we would put those in a boxed warning, and you can put more than one warning about

more than one adverse event in a box, and we have done that.

DR. RIZZO: So, it is not a special box just for suicidality, the box includes all of the stuff that can go wrong.

DR. KATZ: Let's say there were already a boxed warning, if that is what you are talking about for a drug, and now we wanted to add language about suicidality, it would be in the same box. Again, we would have to decide which one was a bigger issue, and we would order them accordingly, but there are numerous examples of drugs that have boxed warnings with multiple different type of adverse events described in that same box.

DR. RIZZO: I was just trying to think outside the box.

[Laughter.]

DR. GOLDSTEIN: Dr. Lu.

DR LU: I am just trying to clarify the question here. Yes means we want to put a box for the suicidal, or we want to--so, if you want to put the other warnings, it seems to me the discontinuation of treatment will be worse than just suicidal warning.

The warning here, I am not quite sure, because we

330

are asked to say if we agree with Agency's plan to require label changes. But what are the changes? If we say Yes, I mean what is the condition of Yes and No.

DR. KATZ: I am not sure exactly what you are asking. If you are asking if you vote Yes, does that mean you are committed to the language that we have proposed in the boxed warning. I would say no. I would just say do you think--maybe we can take this sort of piecemeal--for example, do you think there should be a boxed warming? Forget about for the moment what we proposed as language be included, because we can always obviously change the language.

We really, as a first step, want to know whether or not you think there should be a boxed warning, does this rise to the level, given all the considerations about unintended consequences, the actual numbers involved, do you think there should be a boxed warning. We will fool with the language.

DR. GOLDSTEIN: As I understand it, the alternative is to have language as part of the labeling, but it is not part of the boxed, you know, that black box thing. Again, physicians look at this black box and this is a big

331

deal. I mean this is a big deal.

So, when you put something in a black box, that is put there to bring attention to it and it carries a lot of baggage along with it, and we heard some of that.

So, an alternative given again all the discussions and hemming and hawing and iffing that we had is should there be or could there be a warning there, but it is not separated as one of these black box warnings.

So, that is the Part B here. So, the Part A of the question is should this be a separated black box warning with all that implies or can it have warning language or language, but not as part of that black box.

DR. JUNG: For all AEDs.

DR. GOLDSTEIN: For all AEDs, right. That is what we have said already. Dr. Malone.

DR. MALONE: I just have two things. Following psychiatric drugs now it seems a lot of them have black box warnings, and you start wondering about the effects of a black box, if that keeps happening.

But the second question is if they go into precautions, does that get some sort of publicity? I guess if you get a black box, there is a lot of publicity. Is

332

there anything like that if you just go into warnings and precautions?

DR. KATZ: There is no official connection between how a change in labeling is announced by the Agency and where it is in labeling. Typically, the higher up, you know, the more prominent it is in labeling, these are all related, the more important we think it is, and the more likely we are to make some sort of public announcement about it, but you can certainly put language in the warning and precaution section, not in a boxed warning, and still have some public announcement about it and publicity about it, whatever we think is appropriate.

You certain can mix and match that way.

DR. GOLDSTEIN: Just to make sure we are clear, could it also be part of a Medication Guide, and not part of a black box warning?

DR. KATZ: Certainly, you can have a Medication Guide to discuss a particular adverse event that is not described in a boxed warning. It would typically be somewhere in labeling relatively prominently.

By the way, I think again we ought to take this question piecemeal and first get your views about whether

333

there should be a boxed warning, and put Medication Guide into a separate question.

DR. GOLDSTEIN: I think that is exactly what I would like to do, and maybe we can do that.

Ms. Griffith.

MS. GRIFFITH: Judging from the public outcry the last time we did this, I can fairly well gather that we will have some hysterical reaction if we indeed vote for a black box.

But one of the questions that came up the last time around, and I am sorry to keep alluding to the antidepressant debate, but, Dr. Temple, I remember we had a conversation about informed consent.

It seemed to me that that accomplished a lot of the goals, you had a conversation about the risks and benefits amongst physicians and doctors at that time you thought it would be too cumbersome, and I am wondering now, knowing what we went through, wouldn't it be more advisable than jumping to the black box.

DR. TEMPLE: Can I ask about that? You mean should--instead of a box, should we ask for informed consent? Is that what you are saying? It is unusual to ask

for informed consent.

I believe a Medication Guide comes moderately close to that. it gives a document to the patient, it lists all this stuff, and the patient obviously has a choice of asking the physician, hey, what are you doing to me, and so on, and there is a sort of implicit consent, because they are, after all, taking the drug.

We haven't actually made people sign a consent form even when the drug has a limited distribution. They may sign something saying they have been given this piece of paper and have read it, which is not quite the same thing.

But enforcing that is very burdensome. I mean you have to have limited distribution, and you have to be sure the person gets it. That is a very restrictive thing to do.

DR. GOLDSTEIN: Dr. Caplan.

DR. CAPLAN: I would like to ask the Committee if they would consider either in terms of if we are talking about a Medication Guide or an informed consent, putting in language there of depression, so that if the clinicians would be considering or the patients, whatever, have depression and suicidal ideation, because in that way, I think we would really be doing a great service to this

population of patients be they the psychiatric or the epilepsy patients or the other patients that have very high rates of depression. That would be one step towards getting them help.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: I think that requiring informed consent would be much more draconian even than a black box warning or a Medication Guide. There are much more dangerous drugs that we have on the market that don't require that.

So, both for Med Guides and for black box warnings, I would be concerned, one, about unnecessarily scaring patients who need the drug, who are on the fence about whether or not to take it, and then, two, devaluing the currency.

If we keep issuing Med Guides and black box warnings for risks that are moderate and I will still say unproven for this one, then, it is tough to know what to believe in the black box. I won't say how I am going to vote, but in my view, this doesn't rise to the level of either black box warning or a Med Guide.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I am not even going to mention the word vote, but let me say I am very concerned as in the antidepressant story about the risk of unintended consequences and influencing practice which would discourage patients from taking their medications, number one.

Number two, I think there are two other very significant things to think about with these medications when we think about a black box. The decision on a black box, as I have thought about it, is a balancing of data on efficacy and data on harm.

People struggled a lot in the discussions about antidepressants, that it was not only that the data on harm were there, and everybody agreed with it much as we did today, but as Dr. Malone suggested, the date on efficacy were very weak. That is clearly not the case here.

The data on efficacy are unequivocal, and that further influences me. The last thing to say is that if we just think about the randomized controlled trial, I am very influenced by the fact that two-thirds of the trials had no events in them whatsoever and, while different trials had different patient numbers, we can safely say for the people who were studied in the data that we are basing our

conclusions on, at least half of them, this warning would be irrelevant to.

So, I am very concerned about unintended consequences, and it feels like taking a cannon to an issue where we don't really have a clear definitive idea about what is the most appropriate action to take.

DR. GOLDSTEIN: Dr. Leon.

DR. LEON: To follow up on what Dr. Pine said, I would word that differently. Two-thirds of the trials had no events reported. We don't know that in those--I had a couple other comments, though.

You said, Dr. Goldstein, that the black box carries, you, as a clinician, said the black box carries a lot of baggage. Could you elaborate?

DR. GOLDSTEIN: I think when there is a black box warning, I think it really might drive physicians to really question whether they need the drug to begin with or might affect on alternative choices as was mentioned before.

It really does carry a very negative connotation especially when it is something like this.

DR. LEON: I am not basing this on data, but I think with antidepressants, there was a belief that there

were at least some people who were getting antidepressants who didn't need them. That is a fair statement, I am not going to quantify that.

Could you say the same thing about antiepileptics?

DR. GOLDSTEIN: Well, again, this is a long, complicated story as to when one considers withdrawing antiepileptic drugs in particular circumstances in trials of patients off of drugs but in general, I think that patients who have epilepsy, which is by definition a chronic condition, require a chronic treatment.

DR. LEON: My last comment. I want to bring it up again, I asked earlier, but is there some way we can at least request that the black box, as with antidepressants, refers to the risk of untreated epilepsy, untreated pain, untreated bipolar disorder?

DR. KATZ: Certainly.

DR. GOLDSTEIN: The same could be done for a warning.

DR. KATZ: Absolutely.

DR. ROBINSON: I hate to bring back the antidepressants meeting, but the bottom line is like if you have a potentially fatal side effect, how frequently does

that have to happen that you feel like it needs to be prominently warned?

Ultimately, completed suicide is a fatal, you know, adverse event. That was one of the things that we sort of struggled with. I was more on the side of letting people know in the sense that you can have a dialogue.

It happens in psychiatry, as Dr. Malone brought up, a lot of drugs now have these black boxes, and so it is not that you can't get patients to take them, it is just that you have to have a dialogue with them.

That is the thing I think, you know, how we can get the best across that physicians have a dialogue with their patients, and I think one of the struggles is actually the FDA is not the best mechanism for that. It is actually the professional societies who really should be educating the clinicians about how do you present this, what is the data, how do you talk, you know, with the patients.

I have always found it very interesting that a lot of these FDA meetings about suicide, we have the presidents of very prominent professional organizations. Afterwards, it doesn't seem that they are doing a lot of the follow-up about the education of their members and that sort of thing.

I think that is the difficulty. In some ways we are here to sort of identify are there risks and how those can be presented in a label. But actually, we are not a practice organization.

DR. GOLDSTEIN: Dr. Goodman.

DR. GOODMAN: Just briefly trying to reconstruct my rationale for voting for the black box during use of antidepressants comparing it to a current issue before us--I will do it very quickly. I already mentioned we had weak efficacy, in the current condition we have good evidence for efficacy.

We were concerned about the paradox of misinterpreting emergence of suicidality as deterioration of the underlying condition as opposed to identifying as an iatrogenic effect. I think we may be more concerned in this case about overattribution to the drugs of emergence of effective symptoms of suicidality and the risk of discontinuation.

Another thing that hasn't been mentioned I don't think yet today was that we had non-pharmacological alternatives, not just the devices, but in some of the psychiatric indications, proven psychosocial interventions

such as cognitive behavioral therapy, and we wanted to make sure that patients were aware of those options.

I don't think we had that situation here, I am not aware of behavioral interventions. We also had a theory, in fact, we had more than one theory, for explaining the mechanisms that could explain this phenomenon.

Moreover, it fit with some of our clinical observations. I haven't heard any really plausible explanation other than some nonspecific ones today.

So, on balance, what drove me to make that decision in the face of the concern about unintended consequences is a different weighting today than I had in facing this issue before.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: I know we are just considering Yes or No, whether there should be the black box warning and then the Medication Guide, but I think a lot of people are having trouble deciding on this because they have a certain set of language in mind.

We have done comprehension studies on a couple of Medication Guides in my lab as to how people then understand this information, and one thing that I can tell you is that

if you say something in a Medication Guide--and we can talk about implications for the box--if you say it doubles the risk, the way people interpret that is more draconian than if you say that there was an increased risk approximately, say, 2 in 1,000 or 10,000, or 1, and so on.

So, the way you say something makes a difference, and if you say to lay persons it is going to double your risk, they don't understand the numerator or the denominator at all, and I would then vote No for. So, we can't do the wordsmithing of what is going to go into either of these if we vote for them.

But I think as we discuss each one, we can be recommending what to say and what not to say, and I have heard from a lot of the clinical people that it has to be balanced with the risk of not treating.

So, if those were somehow linkable in the same place, then, I think that people would be more likely to vote Yes for this.

DR. GOLDSTEIN: Dr. Armenteros.

DR. ARMENTEROS: Let's also not forget that unintended consequences may include, of course, a psychiatric population where the signal didn't seem to be as

strong as epileptic population.

The warning may impact all kind of practices for which some, at least in the psychiatric world, the data wasn't that phenomenal that we saw. You have to keep that in mind.

DR. GOLDSTEIN: Dr. Temple, and then I think we will try to bring this around.

DR. TEMPLE: It hasn't been discussed, but while thinking about this, I wondered if people could comment on whether they are influenced at all by the significantly larger effect in the European trials than in the domestic trials. I think that is worth telling us whether that influenced you or not.

DR. GOLDSTEIN: Has that influenced anyone? Would anybody like to respond to Dr. Temple?

[No response.]

DR. GOLDSTEIN: It doesn't sound like it made much difference.

I think there was one more comment. Dr. Gilman.

DR. GILMAN: I found this difficult because we don't know what the wording is going to say. If this were very well balanced, there is a danger in not taking drugs

for epilepsy and taking drugs for epilepsy carries a small percentage risk of suicidal thoughts. So you need to be on the alert for that. That would be fine. But it all depends on the language.

So, we are being asked Yes, No, black box, not black box without knowing what will go in there. So, we trust the FDA to be judicious and saying the right thing, do the right thing, in which case I would be a little more comfortable with that. But just voting Yes or No is difficult right now.

DR. GOLDSTEIN: Given that concern, I think we can probably at least vote on the black box separation and then talk the remainder of the time about what language might be recommended, black box or non-black box, and then I guess secondarily the issue of the Medication Guide, which I think is not quite as big an issue although it may be.

So, if there are any other burning things that haven't been discussed? I don't think so, so let's vote on No. 4, should there be a black box warning, and remember that doesn't mean that there isn't a warning, just that separate black box warning as opposed to a different type of warning, should there be a black box warning, Yes or No.

[Voting by Committee members electronically.]

DR. WAPLES: For the record, there is 4 Yes, 14 No, 3 Abstain for Question No. 4.

DR. GOLDSTEIN: Let's head this way this time. Dr. Day is First.

DR. DAY: Day. Abstain.

DR. ARMENTEROS: Armenteros. No.

DR. CAPLAN: Caplan. No.

MS. GRIFFITH: Griffith. No.

DR. HENNESSY: Hennessy. No.

DR. GILMAN: Gilman. Yes based upon our future discussion, which is a risk.

DR. RUDNICKI: Rudnicki. No.

DR. GOODMAN: Goodman. No, and I am not recanting any previous Yes.

DR. GOLDSTEIN: Goldstein. No.

DR. ROBINSON: Robinson. I abstained because I didn't think I could evaluate it without seeing the language.

DR. PINE: Pine. No.

DR. JUNG: Jung. No.

DR. WOOLSON: Woolson. Yes.

DR. LEON: Leon. Yes.
DR. WINOKUR: Winokur. No.
DR. RIZZO: Rizzo. No.
DR. MALONE: Malone. No.
DR. LU: Lu. Abstain.
DR. HUDSON: Hudson. Yes.
DR. ANDERSON: Anderson. No.
DR. SCHULTZ: Schultz. No.
DR. GOLDSTEIN: Interesting. The statisticians voted one way, the clinicians voted a different way. Very interesting.

I think you have got the view. Given that, let's go to the last thing next, which is: If not, since it was not, does the Committee want to offer guidance on other approaches to communicating this information?

Dr. Anderson.

DR. ANDERSON: I just wanted to echo the suggestion that was made actually in some of our material, as well as by Dr. Day, which is that I found the increase of 2 per 1,000 or 786 patients to harm a more meaningful and interpretable event for me than doubling the risks since I don't know what the denominator is either probably when I am

sitting there in the clinic with an individual.

So, that sort of language is more helpful for me and also to engage the patient in a discussion is sort of the magnitude of what we are talking about.

DR. GOLDSTEIN: Dr. Hennessy.

DR. HENNESSY: I agree with that, and I think that the degree of uncertainty around the information that we think we know ought to be present as well.

DR. GOLDSTEIN: And I think that would include the generalizations or the problems we have that we were struggling with, with the generalizations that we don't have data for many of these drugs and there is this concern, but there is also a lack of data for a lot of this.

Dr. Pine.

DR. PINE: I do think while I feel comfortable voting No for a black box, I do think there is a serious need to communicate this knowledge, because I think all of us would probably say that we were surprised to see the finding, and it sounds like you guys were surprised as well, and I think that reflects the fact that it is not an association that is frequently thought about.

Given that and given the potential concern, I do

think that you need to think of creative ways short of a black box, and a Med Guide I do think would be one to make sure that clinicians and patients are aware of the possibility so that should it arise, clinicians and patients know what to do with it.

DR. GOLDSTEIN: Dr. Rizzo.

DR. RIZZO: Would we envision a Medication Guide that just had general information about warning for suicidality in the whole class of antiepileptic drugs, or would it have that plus maybe some specific information about the individual drug related to suicidality whether there was no information or whether there was no clear indication that this particular drug caused extra harm?

DR. TEMPLE: As with our proposed labeling approach, I think at least at the moment we would probably or likely to have sort of generic nondrug-specific language in a Medication Guide.

DR. GOLDSTEIN: I think what the general gist is that the wording of this obviously needs to be very, very carefully considered, that there is a concern and we talked about drugs for partial complex seizures as opposed to all antiepileptic drugs, as well as the extrapolation to drugs

for which we have no data, and all of those issues need to be carefully included because that is the discussion that physicians are going to have.

What do we know and what do we not know about this whole area, and as was also said all of these conditions are associated with depression and potentially increased suicidality. So having that patient population aware of this alone, regardless of whether it's drug-related or not is an important thing to do.

Dr. Gilman.

DR. GILMAN: I would urge that this be prominent in language on the Medication Guide. In other words, calling attention to this as a problem would be the important thing to do. If we are not going to have a black box as the majority wishes, then, at least putting it in prominent, whatever kind of letters at the top of the Medication Guide would be helpful.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: I think there is a little bit of confusion here if you don't do a black box you jump down to Medication Guide. That is not it at all. There is two separate tracks. One is for the professionals. If you don't

do black box warning, we might discuss or decide we still want to have something in the professional labeling, but it would go in another section.

So, that would be in the warnings and precautions section, something of the sort, and I think that is what Dr. Goldstein was just addressing. I would like clarification from the FDA. I used to know all of the drugs with Medication Guides, and they have gotten so many now that I don't. But are there examples where there is a Medication Guide, which is issued for something specific, say, as Accutane and warnings about pregnancy and fetal harm.

Are there cases where there is a Medication Guide on an issue which does not also have a black box warning in the professional label?

DR. LAUGHREN: The ADHD drugs all have a Medication Guide regarding cardiovascular risk, but do not have a black box for that.

DR. DAY: And those are generally exceptions, most of them have both, is that correct? I mean most Medication Guides also have that issue addressed in a black box warning except for a few.

DR. TEMPLE: A lot of older boxes do not have

Medication Guides. More recently they tend to.

DR. DAY: That is why I was conditionalizing the other way. Given Medication Guide, most of those Medication Guides also have that issue addressed in the box.

DR. KATZ: There certainly are examples where we are currently working with sponsors to develop Medication Guides without the box warning in their label. Those aren't finalized, but there certainly are examples that we are working on.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: I seem to recall, you know, whatever, three or four years ago, when we first talked about Medication Guides you guys had a very different tone in terms of talking about them in that they were seen as not a very valuable thing.

I remember Dr. Temple in particular talking about how the fact that your experience is that pharmacists usually don't hand them out, patients usually don't read them, and I think today's discussion, it sounds like you are looking at Medication Guides differently as an important way to communicate to patients, which is refreshing, but maybe you might comment on that.

DR. TEMPLE: No, it is still getting them distributed is certainly still a problem that has not been solved. Our attempts to solve it in the past have been to try to get the sponsor to make unit of use packaging, at which point you get the Med Guide.

But we haven't done that uniformly. It remains to be seen I have to tell you whether our new authorities under FDAAA will make it more possible to get this done. I think that is entirely possible, but it is not a fully solved problem.

In some cases with the nonsteroidal anti-inflammatory drugs, we resorted to a common Med Guide for 10 or 15 drugs. That helped. It was more manageable for the pharmacy. But no, I don't think that problem is fully solved. But the idea that the patient gets it and participates is still very attractive. We just can't quite figure out how to get them distributed all the time.

DR. GOLDSTEIN: Dr. Day.

DR. DAY: One piece of evidence. There was a study conducted at Duke in two laboratories, and the Duke Clinical Research Institute, they tracked whether patients got the Medication Guide or not.

As you know, they are supposed to be with the prescription every time it is dispensed, not just the first time. I don't remember the exact data, but I think my colleagues found up in the 90s, 90 percent distribution, and the two drugs were Accutane and premarin.

We did the comprehension part of it and we found good things about it and that patients paid attention and understood a lot of it, and so on. So, I think they are taken seriously, and there is pretty good distribution and very good in some cases. I am not aware of other subsequent studies.

DR. TEMPLE: For example, oral contraceptives are almost always administered as unit of use packaging, so the thing can be attached to that. I think that is largely true of Accutane. So, when you have that, then, it goes out, no problem.

DR. GOLDSTEIN: Dr. Gilman.

DR. GILMAN: The message about the low risk, but nevertheless risk for suicide, should go not only to professionals, but also to patients. That is true for what the pharmacists hand out, but also on the web. There is lots of information about drugs on the web that should

contain this information in the proper language to patients.

DR. GOLDSTEIN: I think you have heard a lot about all of our concerns and issues, and hemming and hawing on the language. Obviously, that is something you are going to need to really think a lot and very carefully about.

The question that was for the secondary vote was should there be a Medication Guide, that is, something given to patients that describes this in the appropriate language.

I think we are up for a vote for that.

DR. LEON: I just want to follow up on Dr. Day's comment. In your study, what percentage of people would voluntarily read the Medication Guide? I understood from the way you said that, among those who read it, people comprehended.

DR. DAY: Let me clarify. These were people on the drug, and first of all, they were contacted by somebody else by phone as to whether they had read it and whether they had gotten it, and so on.

In our study, in my lab, people actually showed up and they were there, and we made them sit there and read it, and then we tested comprehension. But we did also ask them about how much, you know, what percentages they would have

read in everyday life, and so on, and so forth, and it's all pretty good.

Medication Guides are supposedly written in patient-friendly language. The structure is different, every little section has a question, what should I know before taking this drug, et cetera, so there are some patient-friendly things, not as high as I would like, but people do pay attention to them.

DR. GOLDSTEIN: Dr. Anderson.

DR. ANDERSON: This is a question for people to answer to help me decide on my vote. We were reticent with the black box because I think in some of our cases a concern for adverse consequences, because we would be scared as physicians by the black box, but sending suicidality in a patient guide that is going to be inserted that they get with their medicine at the pharmacist, that's okay.

So, I guess I would like to know whether people feel that there isn't the same risk of adverse consequence by sending a mailer basically that the patient gets separated from his encounter with the physician that uses the word suicidality, whatever the language is that specifies the risk.

DR. GOLDSTEIN: Dr. Pine.

DR. PINE: Speaking as a physician, my hope would be that what we decide, the purpose is to encourage discussion between the physician and the patient, that that is really what one wants to do, and getting the Med Guide in a way that facilitates that discussion about the risk for suicide would be a good thing.

Whether or not there is a Med Guide, I would hope that after the FDA communicates our discussions, it will become standard practice for all physicians to discuss the risk of suicidal ideation or suicidal behavior when somebody starts an anticonvulsant given that that is at least my desire anything that is going to make it more likely that that discussion were to happen, then that is a good thing.

My sense is that the Med Guide would have that effect while at the same time not discouraging--it would encourage the physician to discuss the issue without scaring them away from using the treatment.

DR. GOLDSTEIN: Dr. Twyman.

DR. TWYMAN: I just want to follow up a little bit on Dr. Temple's question about the X-North American data set, and since what we are talking about is basically

influencing helping better manage the risk-benefit discussion in the U.S. label and a U.S. population, is the use of the global data set appropriate here, or is it better to use the North American data set?

I presume the antidepressant data analysis did not show a distinction between regional differences, and in the X-North American data set appears to be driven principally by the events in suicidal ideation, which could be an ascertainment by other sort of cultural differences.

So, since the discussion is principally around the U.S. label and U.S. practice, is it appropriate to use global data or is it more appropriate to use U.S. data?

DR. KATZ: Well, we might look more closely at some analyses of the non-North American data, but I think that is certainly contributing to our conclusions about the data overall. We are not aware of any obvious reason why, for example, there should be a differential ascertainment bias between placebo and drug in other countries.

We often rely on--that is not to say it is not a real question. But we often rely on data, non-U.S. data to make regulatory decisions. It is not uncommon to have international trials for effectiveness that show a stronger

signal outside the U.S. and certainly sponsors don't object to that.

So, at the moment absent some other results of some other analyses we might do, I think we are likely to describe overall data.

DR. TEMPLE: Also, I want to see a 2 by 2 analysis that looks at both the epilepsy and other data by region and even though you all didn't care much about it, I do, so we are going to look at it more.

DR. GOLDSTEIN: We have to come to a vote on this last issue within the next minute and a half, but both of our patient representatives would like to get one more word in, so I am going to get that and then we will vote.

Ms. Griffith.

MS. GRIFFITH: I would suggest that if we have learned anything from the experience with the antidepressant drugs, that is, the black box, and this is to address Dr. Anderson's question, the black box became a term that was larger than life.

Patients knew what that meant. It caused tremendous alarm as opposed to a Med Guide, which has this warm fuzzy feeling. I have to say that that never caused

anyone any distress, so I am very comfortable with separating those two out.

DR. GOLDSTEIN: Dr. Jung.

DR. JUNG: I would like to point out for those of us who are still stuck on the idea of extrapolating the data that we had to all the anticonvulsants, it seems to me that when I am sitting in a room with my patient, I am going to struggle if there isn't any clarity here, whether if I am using a drug that is an anticonvulsant for non-epilepsy, am I going to be held to the same responsibility of having that discussion since I am still not sure I buy it, and moving forward, if I use phenytoin on my patient for epilepsy, or for trigeminal neuralgia, I really am stuck here.

I understand that there is this need to have this discussion with a patient. But I am really uncomfortable with the extrapolation of the data that we do have to data that we don't have. I realize that not all of my colleagues agree with me, but I have to put that out there.

DR. GOLDSTEIN: Again, that exact distinction could be part of the language here.

I think we need to come to a vote now. The question is: Should there be a Medication Guide, Yes or No?

[Voting by Committee members electronically.]

DR. WAPLES: For the record, for Question No. 5, there are 17 Yes, 4 No, 0 Abstain.

DR. GOLDSTEIN: The last time around.

DR. SCHULTZ: Schultz. Yes.

DR. ANDERSON: Anderson. Yes.

DR. HUDSON: Hudson. Yes.

DR. LU: Lu. Yes.

DR. MALONE: Malone. Yes.

DR. RIZZO: Rizzo. Yes.

DR. WINOKUR: Winokur. Yes.

DR. LEON: Leon. Yes.

DR. WOOLSON: Woolson. Yes.

DR. JUNG: Jung. No.

DR. PINE: Pine. Yes.

DR. ROBINSON: Robinson. Yes.

DR. GOLDSTEIN: Goldstein. Yes.

DR. GOODMAN: Goodman. No.

DR. RUDNICKI: Rudnicki. Yes.

DR. GILMAN: Gilman. Yes.

DR. HENNESSY: Hennessy. No.

MS. GRIFFITH: Griffith. Yes.

DR. ARMENTEROS: Armenteros. No.

DR. DAY: Day. Yes.

DR. GOLDSTEIN: Very good. I hope that the FDA has gotten what they wished out of this exercise. It was certainly an interesting and difficult discussion. My sweep second hand has come across 5:00 and we are adjourned.

[Meeting adjourned at 5:00 p.m.]