UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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January 27, 2011
9:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

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LORETTA WILSON
SARAH H. LISANBY, M.D.
PAMELA SULLIVAN, M.D.
JAN EASTGATE
VINCE BOEHM on behalf of LEONARD R. FRANK
LAURA J. FOCHTMANN, M.D.
BARBARA WINKLER
RICHARD WEINER, M.D., Ph.D.
ROBERT ROCA, M.D.
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OPEN PUBLIC SPEAKERS: (cont.)

JULIE K. HERSH
JOHN BREEDING, Ph.D.
ANITA HAGIN, RN, B.S.N.
AMY LUTZ
KENDRICK MOXON on behalf of EVELYN SCOGIN
JAN EASTGATE on behalf of DIAN'NA POSTHAUER
DOROTHY DUNDAS
DANIEL FISHER, M.D., Ph.D.
DANIEL FISHER, M.D., Ph.D., on behalf of CAROL JEAN REYNOLDS
LAUREN TENNEY, M.Phil., M.A., M.P.A.
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M E E T I N G

(9:00 a.m.)

DR. BROTT: I would like to call this meeting of the Neurological Devices Panel to order.

I'm Dr. Thomas G. Brott, the Chairperson of this Panel. I'm a neurologist who specializes in stroke and also Director of Research at Mayo Clinic in Florida.

At this meeting, the Panel will discuss and make recommendations regarding the possible reclassification of devices indicated for use in electroconvulsive therapy.

Before we begin, I would now like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and affiliation, and why don't we start with Dr. Eydelman.

DR. EYDELMAN: Good morning, and thank you everybody for making it here today. My name is Malvina Eydelman. I'm Director of the Division of Ophthalmic, Neurological and ENT Devices here at FDA.

DR. GOODMAN: Good morning. I'm Wayne Goodman. I'm a psychiatrist, Chair of the Department of Psychiatry at Mount Sinai School of Medicine in New York, and my expertise is in psychopharmacology and use of devices.

DR. KIM: Hi, I'm Scott Kim. I'm a psychiatrist and a bioethicist

from the University of Michigan.

DR. DUFF: My name is Kevin Duff. I'm a neuropsychologist in the Department of Neurology at the University of Utah, and I specialize in mild cognitive impairment and early dementia.

DR. PAULSEN: Hi, my name is Jane Paulsen. I'm a neuropsychologist and Professor of Neurology and Psychiatry at the University of Iowa.

MS. WOOD: I'm Geretta Wood. I'm the Director of the Advisory Committee staff for the Center for Devices and Radiological Health. The Designated Federal Officer, Dr. Olga Claudio, has been delayed in the weather this morning, so I will be filling in for her until her arrival. Thank you very much.

DR. GOOD: Good morning. I'm Dr. David Good. I'm a neurologist, Professor and Chair of Neurology at Penn State University in Hershey, Pennsylvania. My major interest is stroke and rehabilitation, neurorehabilitation.

DR. ROSS: Hi, I'm Chris Ross from Johns Hopkins. I'm a Professor of Psychiatry, also Professor of Neurology, Neuroscience, and Pharmacology. I do research in a variety of neurodegenerative diseases and also research in schizophrenia and affective disorder, and my clinical practice is mainly in geriatric psychiatry.

DR. ELLENBERG: Good morning. I'm Jonas Ellenberg,

Professor of Biostatistics and Associate Dean in the School of Medicine at the University of Pennsylvania. My interest is in mostly children's neurology, but I go with what's available.

MS. CARRAS: Good morning. I'm Michelle Carras. I'm the Patient Representative. I'm a graduate student in public health from Johns Hopkins Bloomberg School of Public Health, and I have bipolar disorder and I have several generations of family members who have mood disorder.

MS. STOKES McELVEEN: I'm Francine Stokes McElveen. I'm General Counsel, Coppin State University, a constituent institution of the University of Maryland Systems.

MR. MUELLER: Good morning. My name is David Mueller. I'm the official Industry Representative. I have a consulting firm in medical device regulatory affairs and many years of experience in the field.

DR. BROTT: Thank you. We may also have some individuals on the telephone. If you can hear me and introduce yourselves, please do so at this time.

MS. WOOD: Okay. We will get a list of who is on the telephone and provide that to you later in the meeting.

Good morning, everyone. We appreciate you making the effort to be here in the inclement weather, and we welcome you to this meeting of the Neurological Devices Panel.

I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees 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 this Panel's compliance with Federal ethics and conflict of interest laws are 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.

The FDA has determined that members and consultants of this Panel 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 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 Food, Drug and Cosmetic 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, members and consultants of this Panel who are special Government employees 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 purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations regarding the possible reclassification of devices indicated for use in electroconvulsive therapy.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Sections 208 and 712 of the Food, Drug and Cosmetic Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

David Mueller is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Mueller and Associates Consulting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda

for which a 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 participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Drs. Richard Meisch, Andrew Winokur, Wayne Goodman, Christopher Ross, and Ms. Michelle Carras have been appointed as temporary non-voting members of the Neurological Devices Panel for the duration of the meeting on January 27 and 28, 2011.

For the record, Dr. Ross is a consultant to the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug Evaluation and Research, CDER. Ms. Carras, the Patient Representative, Drs. Winokur and Goodman are consultants to the Psychopharmacologic Advisory Committee in CDER, and Dr. Meisch is a consultant to the Drug Safety and Risk Management Advisory Committee in CDER. These special Government employees have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

These appointments were authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs on January 25, 2011.

Thank you.

Before I turn the meeting back over to Dr. Brott, I would like to

make a few general announcements

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, 1378 Cape Saint Claire Road, Annapolis, Maryland 21409. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the podiums. The press contact for today's meeting is Sandy Walsh. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing sessions today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

Dr. Brott.

DR. BROTT: Thank you, Ms. Wood. We will now hear the reclassification discussion from the FDA. At the conclusion of this presentation, there will be time for questions from the Panel members.

At this time, we will hear the FDA speaker, Ms. Shulman.

MS. SHULMAN: Good morning. My name is Marjorie

Shulman. I'm with the Program Operations Staff in the Office of Device Evaluation, and I'm going to give a little talk on device classification and reclassification procedures.

So, basically, the Federal Food, Drug and Cosmetic Act divided the arena of medical devices into one of two groups, either pre-amendment devices or post-amendment devices. Pre-amendment devices were those devices on the market prior to May 28, 1976, the enactment of the Medical Device Amendments.

Classification of pre-amendment devices. They are classified after FDA has received a recommendation from a device classification panel such as yourself, published the Panel's recommendation for comment along with a proposed regulation classifying the device, and then published a final regulation classifying the device.

FDA may reclassify pre-amendment devices in a proceeding that parallels the initial classification proceeding and based upon new information respecting a device, either on FDA's own initiative or upon the petition of an interested person.

Post-amendment devices are automatically classified into Class III, and these devices remain in Class III and require premarket approval unless and until the device is reclassified into either Class I or II, the FDA issues a substantial equivalence determination, or the device is classified into Class I or Class II via the evaluation of automatic Class III designation,

also known as de novo review.

Reclassification of post-amendment devices may be initiated either by FDA or the industry, and FDA may, for good cause shown, refer the petition to a device classification panel. The panel should make a recommendation to the Food and Drug Administration respecting the approval or denial of the petition.

There are three device classes, and basically a device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness. Class I is general controls. Class II is general and special controls, and Class III is premarket approval.

Class I includes devices for which any combination of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Some examples of general controls include prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the device types, record keeping, repair, replacement, refund, and banned devices.

Class II is for devices that cannot be classified in Class I, the general controls, because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such device and for which there is sufficient information to establish special controls to provide such assurance. Special controls include, for example, performance standards, postmarket surveillance, patient registries,

dissemination of guidances or guidelines, tracking requirements, and then recommendations and other appropriate actions.

Class III is for devices which insufficient information exists to determine that the general controls of Class I and the special controls of Class II are sufficient to provide reasonable assurance of safety and effectiveness of the device and the devices are life sustaining and/or life supporting; there is a substantial importance in preventing impairment of human health; or present a potential or unreasonable risk of illness or injury.

I also want to talk a little bit about restricted devices which can be a special control under the provisions of Section 520(e) of the Federal Food, Drug and Cosmetic Act. The Food and Drug Administration is authorized by regulation to restrict the sale, distribution, or use of a device if because of its potentiality for harmful effect or the collateral measures necessary to its use, FDA determines there cannot otherwise be reasonable assurance of the safety and effectiveness.

A restricted device can only be sold, distributed, or used either upon the written or oral authorization by a licensed practitioner or under such other conditions specified by the regulation. If the device is restricted for use by persons with specific training or experience in its use or by persons in certain facilities, the FDA must determine that such restriction is required for the safe and effective use of the device.

Devices such as cardiac pacemakers and heart valves require a

practitioner's authorization. Hearing aids, on the other hand, are restricted by regulation which limits their sale to persons who have obtained a medical evaluation of their hearing loss by a physician within six months prior to the sale of the hearing aid. The labeling of the hearing aids must provide information on their use and maintenance.

That is all I have. Thank you.

DR. BROTT: Thank you, Ms. Shulman.

LCDR CUNNINGHAM: Good morning. I'm Lieutenant Commander Brad Cunningham, Branch Chief of Ophthalmic Lasers, Neurostimulators and Diagnostic Devices. I will be presenting a brief background of ECT use and regulatory history and considerations.

Electroconvulsive therapy, or ECT, is a therapeutic application of electricity to the scalp for the purpose of inducing a seizure. The first human use of electroconvulsive therapy dates back to 1938 done by two Italian physicians, Cerletti and Bini. The earliest ECT devices used 125 volts, 50 hertz line current, available from the wall socket, modified only by a simple mechanical timing mechanism based on a metronome. The choice of the sine wave is likely based on convenience. The idea of ECT was originally based on the theory of biological antagonism, the theory that an opposing relationship existed between seizures and psychosis, or more generally, psychiatric symptoms.

During the 1940s and 1950s, ECT gained in usage primarily due

to a lack of effective alternative treatments. During the 1960s through 1980s, ECT use declined with the increased availability of viable alternatives to treat psychiatric disorders as well as increasing concern with ECT misuse and ECT-associated adverse events. However, during the 1990s through the present, it is estimated that ECT use is on the rise again, which is thought to be due to the developments in the use of general anesthesia and modifications in treatment delivery that may be associated with addressing some of the previously seen adverse events to reduce their occurrence. Today our best estimates of ECT treatment indicate that more than 100,000 patients receive ECT annually in the United States.

Since the first ECT procedure, developments in technology and treatment procedure have taken place to address issues of safety and effectiveness. Technology developments include changes in a waveform for electrical stimulus and alterations in energy dosing. The treatment procedure has incorporated variations in electrode placement, the use of general anesthesia, including modern medical monitoring and management, and EEG monitoring of seizure activity.

As shown here, this is a basic schematic of an ECT device. The basic characteristics of an ECT device include a power switch, an output for the stimulus electrodes, an input for monitoring EEG activity, typically two channels, left and right, a display to monitor EEG activity, as well as printing function that can record stimulus application and EEG activity. The display

may also provide information regarding stimulus intensity, stimulus duration, pulse width frequency, and impedance. In addition, controls are present to set specific treatment parameters such as stimulus intensity, duration of pulse width, and frequency. There's also an administration button that's pressed to apply the stimulus.

ECT is regulated by the FDA, as defined under the Code of Federal Regulations, Chapter 21, Part 882.5940. The regulations define ECT as an electroconvulsive therapy device used to treat severe psychiatric disturbances, for example, severe depression, by inducing in the patient a major motor seizure by applying a brief, intense electric current to the patient's head.

Pre-amendment devices are devices that were on the market prior to May 1976 when the Medical Devices Amendments took effect. ECT devices are one of the remaining pre-amendment device types. As you heard from Ms. Shulman's presentation, ECT and other pre-amendment devices are currently classified as Class III. Because FDA did not establish a requirement for premarket approval at the time of classification, some pre-amendment devices classified in the Class III have been regulated through the premarket notification, 510(k) pathway, which is typically done for Class II devices.

There have been nine applications submitted and cleared for ECT devices with the following indications for use: depression, both unipolar

and bipolar; schizophrenia; bipolar manic and mixed states; schizoaffective disorder; schizophreniform disorder; and catatonia.

Section 515(i) of the Safe Medical Devices Act of 1990 directed FDA to either revise a classification of certain pre-amendment devices in a Class I or II or to require a device to remain in Class III. For devices remaining in Class III, to establish a schedule for the promulgation of a rule requiring submission of PMAs rather than for 510(k) submissions.

In January 2009, the Government Accounting Office, GAO, recommended that FDA take steps to issue regulations for Class III device types currently allowed to enter the market through the 510(k) process, including ECT devices, by requiring PMAs or reclassifying them to a lower class. In response to this need for final classification, that is, to maintain Class III designation required PMAs or to down-classify to Class II and regulate ECT devices through the 510(k) program, and we initiated the reclassification process under Section 515(i) of the Federal Food, Drug and Cosmetic Act.

This involved opening two dockets, one for public comment and one for manufacturer comments. We received 3,045 responses from the public docket and 2 responses from the manufacturers' docket. The FDA review team has conducted a comprehensive review of both dockets. Information from both public and manufacturer dockets, combined with adverse event reports from the FDA database, as well as a review of the

literature conducted by FDA, comprise the analysis done for the 515(i) reclassification process. Today's public panel meeting is being held to report the findings of these analyses and to seek guidance from a panel of experts on a reclassification of ECT devices.

I would like to acknowledge the members of the ECT review team shown here on this slide for their extensive work and contributions to this project: LCDR Melissa Burns; Dr. Como; myself, LCDR Brad Cunningham; Dr. Georgiopoulos; Dr. Komiyama; Dr. Krauthamer; Dr. Krulewitch; Dr. Park; Dr. Schroeder; Ms. Shulman; and Dr. Soldani.

The goal of today's Panel is to obtain feedback regarding reclassification of ECT devices. Specifically, FDA is seeking input on whether ECT devices remain Class III devices and require premarket approval applications, or to be reclassified to Class II and undergo premarket notification, 510(k) review, for marketing in the United States.

We look forward to a constructive two-day meeting including comments from an Open Public Hearing and deliberations and recommendations from the expert Advisory Panel. Thank you.

DR. BROTT: Thank you, Lieutenant Commander Cunningham. Do we have another speaker from the FDA?

MS. SHULMAN: This concludes the morning's presentation from the FDA.

DR. BROTT: I'd like to thank the FDA speakers. Does anyone

on the Panel have a question for the speakers? You may also ask questions later.

We will now take a short 15-minute break. Panel members, please do not discuss -- a question?

DR. ELLENBERG: Just a quick one, Mr. Chairman. Is there an equivalent of off-label use in say Class III for devices? Is that concept -- I'm sorry. Is there an equivalent of off-label use for Class III devices?

MS. EYDELMAN: Off-label use means --

DR. BROTT: Excuse me. When you speak, could you please introduce yourselves before you initiate your comments?

DR. ELLENBERG: This is Jonas Ellenberg. Is there an equivalent of using the device for something for which it is not authorized in Class III devices?

MS. EYDELMAN: Malvina Eydelman, FDA. FDA only regulates devices according to the label. In other words, we regulate the device and we write the label in accordance to our recommendations and our guidance. It is up to the practitioner to follow the labeling. Off-label use implies that the practitioner is not following the label. So, hence, the practitioner cannot follow what FDA recommends for any device regardless of what class is it.

DR. ELLENBERG: Is it not correct that the FDA does not regulate the practice of medicine?

MS. EYDELMAN: Correct, FDA does not regulate the practice

of medicine. So, hence, we write the label and recommendation, but our authority does not follow, does not cover the --

DR. ELLENBERG: So it's incumbent -- sorry. Jonas Ellenberg again. So it's equivalent to the drug side? You don't regulate the use of the drug. You just say how it should be used with a particular label and indication.

MS. EYDELMAN: Just like drugs, we write labels with our recommendation.

DR. ELLENBERG: Thank you. Understood.

DR. BROTT: Dr. Ross.

DR. ROSS: Chris Ross from Johns Hopkins. Maybe this is going to be gone into in more detail later, but I just would like to ask if at some point there could be clarification of the practical implications of changing the classification. For instance, would there need to be certification of the person administering the ECT? What kinds of regulations or guidelines or practical changes would come from changing the classification?

DR. BROTT: I think we will get into that later. Ms. Shulman, would you like to make just a brief response to that question?

MS. SHULMAN: Okay. I'm going to defer to Dr. Eydelman.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Yes, hi. Dr. Eydelman. This afternoon we will have an extensive FDA presentation during which we will highlight the risk

factors and the potential mitigating factors, and I think that will address the question raised.

DR. BROTT: Very good. Thank you. It seems that we've been going at such a clip here since we started. We won't need the break, at least not for now. So we'll take the break a little bit later, and we can proceed to the Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda. Dr. Claudio will now -- excuse me, Ms. Wood will now read the Open Public Hearing disclosure process statement.

MS. WOOD: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at an Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the Open Public Hearing or industry speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement

to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I will now go over the process to ensure a smooth transition from one speaker to the next. You will have five minutes for your remarks. When you begin, the green light will appear on the podium timer. A yellow light will appear when you have one minute remaining. At the end of five minutes, a red light will appear and your microphone will go off. Your presentation should be completed. Since we have a number of speakers, it is very important to adhere to the five-minute time limit. As each speaker concludes their remarks, Ms. AnnMarie Williams will guide the next speaker to the podium.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the Open Public Hearing. If recognized by the Chair, please approach the podium to answer questions. I would like to remind public observers at this meeting, that while the meeting is open for public observations, public attendees may not participate except at the specific request of the Panel Chair.

DR. BROTT: The first speaker is Kendrick Moxon.

MR. MOXON: Good morning. I'm an attorney, and I've been involved in considerable litigation over the effects of ECT including litigation with MECTA Corporation. The litigation is over, and I have no conflict in

speaking to you today.

I had intended to speak about MECTA's failure to provide known evidence of grave harms that this device has caused, but after reviewing the FDA's Executive Summary, it's clear that this process has gone off the rails, and that this committee has been placed in an untenable position.

In 1976, the FDA recognized that ECT was dangerous and placed shock devices in Class III with the expectation that there would be a rapid evaluation of the safety and efficacy. In 1978, a survey of shock practitioners by the APA found 41 percent of them agreed that ECT caused brain damage, and 14 percent that ECT should be stopped. The FDA ignored that and in the following decade did no evaluation whatsoever.

In 1990, Congress ordered the FDA to revise the classifications of these grandfathered devices, the pre-amendment devices, or immediately require the submission of PMAs, but the FDA did neither.

Nineteen years later, we're here again. The FDA has required the manufacturers to submit evidence of safety and efficacy, but the manufacturers left it up to the FDA to prove what they could not. The FDA's Executive Summary, improperly supervised by an advocate of ECT in the FDA, identified over 1200 articles and studies on ECT but disregarded all but 68 of them because the studies and reports were not from randomized control trials. They disregarded 50 years of studies and reports because the

studies were not formulated with a research technique that was almost never used when most of the studies were done.

I've looked at some of the studies done by the Panel members that were identified and a very, very small percentage of them are randomized control trials. I hardly think that means those studies were worthless.

But the FDA also had a MAUDE database for professionals and manufacturers to report adverse effects, but according to the Summary, it disregarded that information. It didn't use it. The FDA opened a docket for the public to comment. It received 3,000 comments, and 78 percent of those comments were against reclassification. Only 14 percent called for reclassification, yet the FDA's summary indicated that it disregarded all of those comments. They were not from a randomized control trial. It wasn't part of the Summary that you've received.

The open docket made the public believe that their voices would be heard, but that was just false. The FDA essentially betrayed them by ignoring their statements. They didn't give them to you.

The FDA also concluded there was no evidence of brain damage because the limited studies that it considered didn't say that there was any brain damage, but honestly, there are hundreds and hundreds of studies indicating brain damage that they disregarded, and you don't need a randomized control trial to know that shooting 400 volts through a brain will

cause some damage. The conclusion is untenable and irresponsible.

While eschewing all this evidence, the FDA nevertheless asked this committee to assume first that the devices are effective. Now, this is astounding because even in consideration of the few studies that the FDA deemed worthy of consideration, the Executive Summary concluded, "Evidence for the effectiveness of ECT exists only for acute effects after ECT." Only. "ECT is probably more effective than placebo." Probably. And, "Little evidence exists supporting the long-term effectiveness of ECT." And, "Gains in efficacy are achieved only at the expense of increased risk of cognitive effects."

In other words, the studies they disregarded from the 1940s, 1950s, and 1960s, that all acknowledged that the "therapeutic effect of ECT was brain damage and memory loss." That was the therapeutic effect for the first three decades.

The Summary also states that at one month or longer, "There is no evidence that ECT is superior to sham." I hope you all read that because if except for immediately after the debilitating shock, ECT's effectiveness is no better than a sham or placebo --

MS. WOOD: Sir, you have 30 seconds to conclude your remarks.

MR. MOXON: -- and there's no evidence of any benefit thereafter, what are we doing here? Why are we here? Because the FDA

has now told you it's effective, and they've asked you not one single question on the questions submitted to you concerning effectiveness, not one single question.

You should not be a party to destroying minds with this dangerous device when there's no evidence that it has any benefit. You should not permit --

DR. BROTT: Thank you. The next speaker will be either Pamela Sullivan or Charles Kellner.

DR. KELLNER: Good morning. My name is Charles Kellner. I am a board certified psychiatrist and President of the International Society for ECT and Neurostimulation, ISEN.

MS. WOOD: Excuse me. You're speaking for Dr. Sullivan, and Dr. Sullivan just showed up.

DR. KELLNER: That's okay. I can go ahead.

MS. WOOD: Well, I think she wants to speak.

DR. SULLIVAN: Can we go to the next speaker?

MS. WOOD: Yes.

DR. BROTT: Yes. The next speaker will be Loretta Wilson. Could Loretta Wilson step to the microphone?

MS. WILSON: Good morning. My name is Loretta Wilson from Flushing, Michigan. I am 69, widowed, mother of 5, grandmother of 7, and great-grandma to my new baby girl, Sophie.

To begin, when you hear the world rainbow, what do you see? Well, in photography, when an image is placed on the CF card, it then becomes available to use that any time by the photographer. It is very important to preserve the image in its original state. The photographer can work from the original and be very creative and the variations are unlimited. Backgrounds can be changed, imperfections can be removed, and the photographer has the option of erasing undesirable images from the CF card. Formatting the CF card destroys all pertinent information. Many stores advertise that erased images can be recovered, but recovery is not guaranteed.

On the flip side of the coin, since psychiatrists are unable to detect individual memory cells, they simply aim the electroshock device and shoot. In a split second, irreversible damage is done. Since no technology exists for transferring memory cells onto a backup system prior to the electroshock, the originals are destroyed and can never be retrieved.

Destroyed memories have altered my life for the remainder of my life. Furthermore, memory loss is documented numerous times in my medical record as memory deficits, noted apparent, substantial. Pain is also documented multiple times after receiving electroshock. When electroshock is administered, it produces a grand mal seizure. In the aftermath, the individual appears zombie-like, as witnessed time after time by my family members and friends.

In addition, if grand mal seizures are such good therapy, producing no ill effect, why not leave epileptics alone and allow them to be therapeuticized to the max?

Consider this, 48 of the 50 United States of America have made it a felony to intentionally harm an animal. Should the human brain be treated with less dignity?

For me, huge amounts of memory were castrated, and I have no recourse in a court of law because the two-year statute of the limitations has long passed. I ask, how many does it take to change a light bulb? How many times must we speak about the irreversible effects of electroshock?

This highly controversial procedure is and will continue to be dangerous. Experience speaks volumes. Most people are unaware that memories are priceless until they are unable to access them. Personally, I believe all the use of electroshock devices should be banned.

Will this trauma be allowed to continue? Will the FDA yield to the manufacturers in spite of the lack of conclusive evidence on their part, or will the FDA stand by its first decision? The device is dangerous. Decades have passed, and the electroshock device continues to cause grave harm. As a nation, we have come so far. Shall we stoop so low as to allow the electroshock device be reclassified to less than dangerous? If the device is reclassified to anything less than dangerous, God help us all. No one is exempt from an emotional upheaval, and you or someone you know may be

the next one on the table.

In conclusion, unlike a beautiful rainbow, my life is faded with lots of black holes which represent the memories that were destroyed through the administration of electroshock. You have an awesome responsibility. A wrong decision now will affect countless thousands of people around the world. Yes, around the world because concern about reclassification of the electroshock device is international.

With that, I implore you, do not reclassify the electroshock device. It is imperative. You must say no. Proof of damage by electroshock has surpassed just being substantiated. Claims of safety and effectiveness are but mere speculation. Thank you.

DR. BROTT: Thank you. Dr. Sarah Lisanby.

DR. LISANBY: Good morning, and thank you for this opportunity to give testimony on this important topic. My name is Sarah Lisanby. I'm a medical doctor, a board certified psychiatrist and ECT practitioner and researcher, the Chair of the Department of Psychiatry at Duke University and the Chair of the American Psychiatric Association Task Force on ECT.

The APA reimbursed my travel to come to this meeting.

I'm here to deliver one critical point. Depression kills while ECT saves lives. ECT is the most effective and rapidly acting treatment for severe depression available today. Scientific evidence and peer-reviewed

medical literature supports the safety and efficacy of ECT. The number of publications on ECT exceeds 10,000 in the U.S. National Library of Medicine. The consistent finding is that ECT is unparalleled in efficacy in a range of serious conditions including major depressive disorder, bipolar disorder, catatonia, psychotic depression, medication resistant schizophrenia, and other severely disabling conditions, many of which are unresponsive to all other treatments.

ECT works even when psychotherapy or medications fail, and studies report that up 80 to 90 percent of people experience a complete recovery. ECT is an indispensable part of mainstream medicine. Training and the indications and uses of ECT is a required part of psychiatry residency. ECT is an essential part of the APA practice guidelines on the treatment of depression.

We still use ECT today because no approved treatment has yet been able to replace it. I also do research on new forms of brain stimulation, and while promising, none has yet replaced ECT.

The APA Task Force on ECT supports reclassification because large-scale controlled clinical trials in hundreds of patients, sponsored by the National Institutes of Health, have repeatedly demonstrated the efficacy of ECT. ECT has evolved dramatically over the years. In stark contrast to portrayals in the movies, ECT is performed under general anesthesia in a medical environment by physicians and nurses. Informed consent is an

important part of the process. The electrical parameters have been refined through decades of careful study, and the dosage is individually tailored to improve safety.

The enhanced safety profile merits Class II designation. It is my position and the official position of the APA that ECT is a safe and effective evidence-based medical treatment. ECT is endorsed by the APA when administered by properly qualified psychiatrists for appropriately selected patients.

Medication resistance is a serious problem. The National Institute of Mental Health funded STAR*D trial, noted that approximately 60 percent of the patients failed to respond after 2 treatments, and about 1/3 failed to respond even after 4 medications. If we assume that a third of the estimated 14 million Americans diagnosed with depression per year are treatment resistant, that yields an estimated 4.6 million Americans with treatment-resistant depression. The most effective approved treatment for these people is ECT.

When ECT goes untreated or when it is ineffectively treated, it can cause extreme suffering and even death by suicide. Suicide is a leading public health problem which accounted for nearly 35,000 deaths in the U.S. in 2007. ECT is rapidly effective against suicidal impulses. Without ECT, suicidal patients would have few effective options left.

Let's not lose sight here of the key stakeholders in this

discussion. If ECT were to disappear tomorrow, it's not the medical establishment that would suffer. Indeed, a comparatively small number of psychiatrists administer ECT. If ECT were to disappear, it's not the economy that would suffer. The two companies that make ECT devices are small and not publicly traded.

If ECT were to disappear tomorrow, those who are suffering already and who have no effective alternatives are precisely the ones who would suffer the most. Their families, their children, their loved ones, their friends, and their communities would suffer. Given the prevalence of depression, it is likely that everyone in this room knows someone who has been affected.

Aside from my professional roles, I'm also the family member of a person whose life was saved by ECT. This dual perspective puts me in an excellent position to speak to the gravity of the discussion that faces you today.

People whose lives have been affected by severe treatment-resistant depression deserve the best that medical science has to offer, and today that is ECT. Until a safe alternative that matches or exceeds the therapeutic spectrum of ECT comes along, threatening or restricting its availability would only --

MS. WOOD: Thirty seconds, please.

DR. LISANBY: -- serve to take away the last hope from those

who are already suffering from hopelessness. Without this safety net of ECT, we as physicians will only be able to stand by helplessly in the face of suffering, knowing that an effective treatment was removed from the medical toolbox.

Thank you for your attention, and the references to my comments are found in your packet.

DR. BROTT: Jan Eastgate. Excuse me. We're back to Pamela Sullivan.

DR. SULLIVAN: Yes, that's correct. Good morning. My name is Dr. Pamela Sullivan. I am a practicing psychiatrist and an officer of the International Society for ECT and Neurostimulation. ISEN is a professional society of over 200 ECT practitioners dedicated to promoting best practices in ECT. Our members have a vast amount of clinical experience in providing ECT. We have also contributed much of the research evidence base demonstrating the efficacy and safety of ECT. As a professional organization, representing psychiatric physicians, nurses, and other ECT clinicians, we urge the FDA to reclassify ECT devices as Class II devices.

ECT is an important lifesaving treatment that is a standard part of contemporary medical practice. When the clinical and scientific evidence is fairly considered, ECT is shown to be remarkably safe and effective.

Modern ECT is a highly developed procedure carried out by a team of medical practitioners with specialty training. ECT physicians must

be credentialed by their institutions to perform the procedure. Anesthesiologists who are part of the ECT team must also be credentialed to provide the anesthesia. Modern standards for anesthesia delivery apply to ECT just as they do for any other medical or surgical procedure.

ECT is typically prescribed for severely, psychiatrically ill patients for whom other forms of treatment, such as antidepressants and antipsychotic medications and psychotherapy, have not been effective or are poorly tolerated. It is also prescribed when a patient is so ill that rapid definitive treatment is urgently needed. Because of this, it is often lifesaving in patients who are suicidal or physically debilitated because of depression. ECT is an important treatment option for elderly patients. Depression in the elderly may be particularly severe and may not respond as well to medications. While ECT is very effective across all age groups, recent research shows especially favorable response in the elderly.

The medical risks of ECT have been carefully studied. These risks include the effects on memory, which are generally modest and acceptable, particularly when one considers how sick ECT patients typically are and how helpful the treatment is. The risks of severe, untreated depression including suicide are significantly greater than the risks of ECT. In other words, the risk/benefit ratio, a way of considering the advisability of any medical procedure, is overwhelmingly in favor of ECT in the severely ill patients for whom ECT is an option.

Modern ECT techniques, including the use of right unilateral, non-dominant hemispheric electrode placement and brief and ultrabrief pulse stimuli, have substantially reduced the cognitive side effects of ECT. After extensive study, researchers have found no evidence that ECT causes any damage to the brain. The memory effects of ECT are explained in detail to all patients in the informed consent process before the treatment is initiated and mostly limited to patchy gaps in memory for some events in the weeks to months before the treatment course and during the treatment series.

ECT has been subject to more scrutiny than almost any other procedure in medicine. Referral for ECT is already very restricted largely because of the inaccurate negative image of the treatment promulgated in the media, which is disturbing to patients and even some medical practitioners. To further inappropriately limit the availability of ECT as a treatment option would have devastating effects on thousands of our most ill psychiatric patients.

We believe access to ECT should be greater, not less, for appropriately selected patients. ECT relieves suffering and prevents loss of life by suicide and medical complications of untreated depression. Like many medical procedures for severe illness, it does have its side effects and risks. When the evidence is examined thoroughly and objectively, as the FDA is now doing, it becomes clear that ECT as practiced in the United States

today is a safe and vital treatment option for severely ill psychiatric patients.

The ISEN expresses its strong support for the reclassification of ECT devices to Class II. Thank you.

DR. BROTT: Thank you. Can Jan Eastgate come to the microphone.

MS. EASTGATE: Good morning. I'm the President of the Citizens Commission on Human Rights. It's a psychiatric watchdog group, and for 42 years, we've worked with consumers who fought for their inherent right to be informed about the harmful effects of ECT, and yet today the FDA is essentially asking you to ignore them.

The Exec Summary provided the public only two days ago a policy the FDA needs to change, and the questions being asked of you make a mockery of what Congress and the GAO intended when it told the FDA to do its job regarding Class III devices.

In fact, it appears from reading the Summary, the FDA has already made a decision to reclassify, and this hearing is just lip service to the public. They are leaving it up to you to be the fall guys to take the responsibility for the harm such a decision will cause. You are being asked to figure out how to mitigate the damage ECT causes by recommending controls to monitor or reduce the risks, and then while more than 70 percent of respondents oppose reclassification because of the damaging effects of ECT, you're to consider how to expand it.

The FDA relies largely on randomized controlled trials despite earlier criticisms of its reliance on these for establishing safety of Avandia. They ignored other evidence of serious heart risk associated with the drug. Seriously with 60,000 Americans suffering heart attacks from this drug, would you be sitting here today considering how to expand Avandia's use by mitigating its risks?

MECTA and Somatics seems to have had the opportunity to prove safety and efficacy but failed to do so despite a potential $30 million made in sales.

In the recent *New York Times* article about today's hearing, Dr. Matthew Rudorfer of NIMH had the audacity to call these companies mere "mom and pop" operations. Therefore, they shouldn't be expected to conduct expensive clinical trials. This comes from the same man that opposed the FDA placing a black box warning on SSRI antidepressants. Essentially NIMH expects the profits of the shock makers to take precedence over the safety of patients.

The APA parrots this in its submission. This is an industry that has benefited more than $28 billion over the past 3 decades from ECT. Yet never, it seems, has it demanded that MECTA and Somatics conduct the necessary studies.

The APA claims it is no more dangerous than minor surgery under general anesthesia and, for some patients, maybe less dangerous than

treatment with medication. This includes antidepressants that the APA also opposed carrying a black box warning. Arguably, a premarket approval was ignored because evidence already exists to show the device does not meet required standards, opening the door to massive lawsuits against the manufacturers as we have seen against pharmaceutical companies that covered up the risks of psychoactive drugs and Avandia. This and conflicts of interest are likely reasons for preventing ECT device safety studies.

MECTA's submission to the FDA cites 18 studies by Harold Sackeim, 13 by Dr. Richard Weiner, and 8 by Dr. Andrew Krystal, all of whom have conflicts of interest with MECTA. Dr. Sarah Lisanby, who sat on this Advisory Panel in October and now we've heard is being FDA paid to appear here today, has done MECTA studies as well. I'd be interested to know why she didn't demand MECTA conduct safety studies. Dr. Lawrence Park apparently co-wrote the Executive Summary. In his APA conflicts disclosure, he says that he has affiliations with Abbott Labs, which makes Quelicin chloride which is a muscle relaxant used in ECT. This Summary is so egregious that full transparency is needed, and the FDA must provide a disclosure of all conflicts of interest for each of the studies and the rating scales it relied upon.

Whether you mask ECT with anesthetic and muscle relaxants or add controls to try and mitigate the risk, the bottom line is that thousands of patients report that ECT causes harm. The electroshock

destroys lives. The FDA has received 151 MAUDE reports for ECT since 1996, roughly 10 a year.

It took public and Senate Finance Committee pressure to obtain legislative changes forcing the FDA to educate consumers of their right to report adverse drug reactions. Government officials cited a survey that said 86 percent of consumers were completely unaware of their right to report.

MS. WOOD: Thirty seconds remain.

MS. EASTGATE: CCHR Italy recently interviewed the daughter of Dr. Hugo Cerletti. She is emphatic her father recognized the damage electroshock caused and researched alternatives. She said he was appalled to find ECT was primarily being used to enrich the pockets of those administering it. The Panel should take heed of Cerletti and the first victim that said, "Not another one. It's deadly." The ECT device must never --

DR. BROTT: The next scheduled speaker is Leonard Frank, and I think we have Vince Bloom [sic] speaking in his behalf.

MR. BOEHM: My name is Vince Boehm, B O E H M.

DR. BROTT: Thank you.

MR. BOEHM: Good afternoon, good morning. I'm a pinch hitter. I'm going to read into the record the statement of a person that was stranded at an airport yesterday and couldn't make it. In addition to that, there are others, Dr. John Breeding, Carol Jean Reynolds, Dian'na Posthauer.

I'm going to read the statement of Leonard Roy Frank.

Mr. Frank's statement begins that, My name is Leonard Roy Frank. I am 78 years old, live in San Francisco, and have been active in the struggle against electroshock for almost 40 years. I'm here today to urge the FDA's Medical Devices Advisory Panel to recommend that electroshock devices not be reclassified from the high risk to low risk category because these instruments of infamy can and often do tremendous harm.

In 1963, I was forced to endure 85 shock procedures, that's 50 insulin comas and 35 electroshocks. As a result, my memory for the preceding three years was obliterated. In addition, my high school and college educations were effectively destroyed. Every part of me, spiritual, intellectual, emotional, and physical, was less than what it would have been. I believe I never recovered fully from these repeated brain assaults. They rendered my life since then considerably less abundant.

A brain is a terrible thing to waste, to damage, and brain damage is electroshock's bottom line. The surest indicator of brain damage is memory loss, which is practically universal among the survivors, but psychiatrists deny that electroshock causes brain damage.

The American Psychiatric Association's Task Force report "Practice of Electroconvulsive Therapy," 2001, the most authoritative text on the subject, stated that, "In light of the accumulated body of data dealing with structural defects of ECT, brain damage should not be included in the

ECT consent form as a potential risk of treatment."

This is one of modern psychiatry's biggest lies. The scientific evidence contradicts this claim. The best example that I am aware of is a 1957 report by psychiatrist David Impastato, a leading electroshock proponent. In the largest and most detailed review of electroshock-related tests ever published, Impastato studies 254 deaths, all but 40 from previously published reports, and found that 66 patients died of cerebral causes. In other words, they died of electroshock-caused brain damage.

Electroshock psychiatrists have had more than 70 years to prove that their procedure is safe and effective, and they haven't been able to. During that time, with no more scientific justification, more than 7 million people in the United States have been electroshocked. Even today, more than 100,000 people a year in this country are being electroshocked.

Now is the time to call the psychiatric profession to account for its cruelty and criminality, and the Food and Drug Administration is the place to begin. I say criminality because electroshock is rarely, if ever, administered with a genuine informed consent. The absence of brain damage risk from the consent form alone makes the current electroshock procedure entirely fraudulent.

If the law considers touching another person without their consent an assault, then the law should regard administering electroshock with an electroshock device to another person's brain without --

MS. WOOD: Thirty seconds.

MR. BOEHM: -- as a far more serious form of assault. As a destroyer of beliefs, memories, and ideas, electroshock violates these hallmarks of American liberty, freedom of conscience and freedom of belief, freedom of thought, freedom of religion, freedom of speech. There's no place for electroshock in a free society, and no society where it is sanctioned or tolerated is justified to call itself free.

If the body is --

MS. WOOD: Sir, your time has ended. Thank you very much.

DR. BROTT: Barbara Winkler.

DR. FOCHTMANN: My name is Laura Fochtmann.

DR. BROTT: Okay, fine.

DR. FOCHTMANN: I believe I was the next person.

DR. BROTT: Yeah.

DR. FOCHTMANN: My name is Laura Fochtmann. I appreciate the opportunity to give testimony to the Panel today. I'm a board certified psychiatrist, a professor in the Department of Psychiatry and Behavioral Science and Director of the ECT Service at Stony Brook University Medical Center. I am also a member of the American Psychiatric Association Task Force on ECT, and I serve as the medical editor for the APA Practice Guidelines. My department is reimbursed by the APA for my guideline-related work, and my travel expenses today are also reimbursed by APA. I

have no relationships with industry.

My interest in ECT dates back to my days as a medical student over 30 years ago, and I can still picture one of my patients, an emaciated woman who spent countless hours sitting at the edge of her bed staring into space. When the attending physician mentioned the possibility of ECT, I will admit to having some in trepidation, but I quickly saw that ECT bore no resemblance to its movie portrayals, and just a week after her first ECT, my despondent patient was playing cards and joking with the others on the unit.

This experience and others like it crystallized my interest in becoming a psychiatrist. It showed me the impact of serious psychiatric illness, on our thinking, our feeling, and our abilities to do the things that we want to do. It also showed me how psychiatric treatment such as ECT could allow individuals to function again and experience the positive things in life.

I've subsequently seen many patients whose symptoms have not responded to other treatments but have responded to ECT, and without ECT, some of these individuals would have had much longer periods of suffering, sometimes ending in death due to poor food intake, prolonged immobility, or suicide. If ECT were not available, it would be tragic for many individuals and for those who care about them.

One of the key issues of this hearing relates to the efficacy of ECT. In my work as medical editor of the Practice Guidelines, I do systematic reviews and develop practice guideline recommendations for the treatment

of psychiatric disorders, and through this work I have reviewed the evidence of ECT efficacy that come from meta-analyses, studies of different ECT techniques, post-ECT continuation treatments, or concomitant ECT and medication.

The speed and rate of symptom response and episode remission in these studies are particularly impressive since enrolled patients have severe symptoms or treatment-resistant episodes. The findings from older studies and meta-analyses of ECT as compared to sham ECT also show the efficacy of ECT, and I think these latter data are sufficiently strong that it would be ethnically difficult to justify additional studies of the sort that are typically needed for premarket approval.

As with any treatment for a severe medical illness, ECT does not always work, and it can be associated with side effects which are sometimes significant. However, when administered by appropriately trained and privileged psychiatrists and anesthesiologists, ECT is a generally safe treatment. For a substantial number of patients, the benefits of ECT clearly outweigh the disadvantages, and as part of the informed consent process, we describe these anticipated benefits and risks of ECT, compare them to other treatment options, and review the steps of the anesthetic and ECT procedure.

Our goal is for the patient, and his or her involved family members, to think about the available options and make a collaborative

decision based on his or her own circumstances and treatment preferences. In fact, as mental health consumers have become more educated about treatment options, we have seen increasing numbers of requests for ECT from patients who want relief from their intractable symptoms. And, thus, even though some people have strong negative opinions about ECT, others very much want ECT and feel positively about it as a treatment.

In closing, let me reiterate, psychiatric illnesses can be associated with extremely severe symptoms and can have very poor outcomes without effective treatment. ECT is an effective and important treatment option which can be particularly crucial for those with depressive or manic episodes, catatonia, or psychosis that is severe and life-threatening or unresponsive to other treatments. Future research will allow refinement in ECT technique that will enhance benefits and reduce side effects of ECT, but this should not take away from the fact that the efficacy and overall safety of ECT are already clear.

Thank you again for allowing me to speak with you today. I'm happy to answer any questions.

MS. WINKLER: I'm Barbara Winkler.

DR. BROTT: Thank you.

MS. WINKLER: My name is Barbara Winkler, and I am 49, almost 69. I was born in 1961. My diagnosis is bipolar, and I'm also a recovering alcoholic. I was financially supported here by my husband who

works very hard to put up with me and paid for the ticket for me and us to come here all the way from the state of Washington.

I can't ramble off all this technical stuff, but I can say that I want the FDA to really take a look at the harm these shock treatments have caused and do some new research before they reclassify it. New studies need to be done. I haven't heard, you know, too many issues or people talking about the cognitive problems, but I have cognitive problems, and until there's a way to know how many treatments are being done and who's monitoring all these psychiatrists around the country -- I had over 80 shock treatments and, yes, they called them maintenance treatments, but I don't remember my wedding day. I don't remember putting the ring on my finger.

I'm also a college graduate with a bachelor's in science from Grand Canyon University in Phoenix, Arizona, and I don't remember any of that. I do remember my anatomy and physiology class and unzipping a cadaver and little bits and pieces, but I don't remember details. I also was a professional athlete. I competed in the Hawaiian Ironman and finished. I don't remember finishing, but I know I have a metal that says I did. I have boxes of trophies that I tell my husband to go ahead and put in the attic because when I open those boxes and pull out a trophy and it has my name on it, I don't know who that person is. I know it's mine, but there's a separation between that person because I don't have the feelings or remember the feelings or the events or the traveling I did when I was

sponsored as an athlete. So I really think there's need to be some research done on the cognitive effects and the long-term effects that ECT can have not only on the past memories or the memories around the shock treatments, but even new things today.

We've lived in the same house, and I still will come home, and -- you can laugh because it was kind of funny, but it wasn't -- I used the car little button that you press to lock your truck and was talking to my sister on the cell phone and was trying to open the front door with the little remote. You know, I can kind of laugh at myself now, but it's really not funny -- or using my dad's house key who's 89 to try to open my car door or trying to learn information, trying to learn new numbers, trying to go to college, trying to be a productive citizen. I'm on Social Security Disability. That's probably costing us all right now since 1999, probably 80 to 100 thousand dollars. While I hear there's not enough money to do new research, well, so we're just going to make a bunch more people developmentally disabled by giving them more shock treatments before we really know what we're unleashing?

I remember reading something about Ernest Hemingway, and it goes back to when they did shock treatments a long time ago. Well, he was born in 1961 -- or he committed suicide in 1961, and that's when I was born. He said something to the effect that he couldn't remember anything and he couldn't do what he loved to do, so he took his life.

You say that ECT doesn't cause problems. It just burns people, and you don't get burns from the electrodes and you don't break bones? Well, I'd almost rather have broken bones and burns on my body than be mentally unable to learn new material.

So all I can say is take caution. You know, there needs to be some kind of legislation out there for each state to monitor how many of these treatments that the doctors give. In my case, Medicare paid for it. Oh, so Medicare pays for it. So the doctor just signs off on it, and they keep doing more and more and more. There needs to be some parameters with these treatments.

And my mouth is really drying out. So you don't need to ring the bell for me. I'm just going to leave. But thank you, and please spend some time before you make a rash decision. Thanks.

DR. BROTT: Dr. Weiner. Is Dr. Weiner here?

DR. WEINER: Thank you for the opportunity to speak today. My name is Richard Weiner, and I'm here to speak for reclassification of ECT devices to Class II. I'm a board certified psychiatrist with undergraduate or graduate degrees in electrical engineering, systems engineering, and neurophysiology. I presently hold a position as Professor of Psychiatry at the Duke University School of Medicine. For the past three decades, I've undertaken a considerable amount of research dealing with various aspects of making ECT safer and more effective. Over this time period, I have also

represented the American Psychiatric Association in regard to FDA classification of ECT devices on multiple occasions, including testimony at earlier public hearings on the topic.

Many in this room may not be aware that the most recent FDA proposed rule regarding ECT devices was actually a notice of intent published in 1990 in the Federal Register, stating FDA's plan to reclassify ECT devices to Class II based on information provided by an earlier petition by APA, a subsequent Advisory Panel hearing, and a comprehensive FDA review at the time.

Today and tomorrow, this Advisory Panel has the task of deciding whether to recommend that FDA allow that intent to finally come to fruition. In this regard, it is worthwhile to focus upon whether the body of data over the intervening 20 years, in particular, what has been reported in the relevant peer-reviewed scientific literature, further supports such reclassification. Specifically, do such findings support the efficacy and safety of ECT itself, and are these findings applicable to contemporary U.S. ECT devices since FDA's mandate is to regulate medical devices rather than medical practice?

Since 1990, there have been major advances in both ECT practice and ECT instrumentation, as has and will be pointed out by others of today's speakers. These developments provide further compelling evidence that ECT can be delivered in a safe and effective fashion.

Specifically, for major depressive episodes, recent large NIMH-sponsored, multicenter trials, using contemporary U.S. ECT devices, have demonstrated that modern, evidence-based ECT technique is associated with response and remission rates that are substantially greater and more rapidly achieved than that reported elsewhere in the literature for any other form of antidepressant treatment, be it medications, psychotherapy, or more recently transcranial magnet stimulation. These studies have also provided the largest and most rigorously defined body of data concerning ECT side effects, most notably memory deficits, and have also elicited information on important functional indices such as quality of life, which not surprisingly improves following ECT.

With respect to memory deficits, such data are consistent with earlier findings that anterograde amnesia and retrograde amnesia, particularly for recent events, can be persistent. It should, however, be noted that the most recent APA recommendations on ECT practice clearly spell out the need to include the possibility of persistent retrograde amnesia in the informed consent process with ECT to ensure that all individuals for whom ECT is recommended receive this information.

I would also like to point out that recent multicenter trials have investigated the safety and efficacy of maintenance ECT, i.e., the use of single ECT treatments spread out over time to decrease the likelihood and severity of relapse. These data reveal that maintenance ECT is, indeed,

effective and further that there is no evidence of memory impairment associated with such widely spaced out treatments.

One last point I would like to make is that the benefits and risks of any treatment are relative as opposed to absolute. By this I mean that the truly relevant consideration is whether providing a given treatment is more effective and safe than not using the treatment. For ECT, it is often the case that its more rapid and substantial benefit obviates the considerable morbidity and mortality of the underlying mental disorder remaining untreated. Individuals in the throes of a severe depressive episode are not just depressed. A compelling body of data indicate that they are also at significantly elevated risk not only of suicide, but medical debilitation and death from a wide variety of causes.

MS. WOOD: Thirty seconds.

DR. WEINER: This is particularly the case for the elderly where one study showed a significantly greater multiyear survival rate for individuals who received ECT for treatment of major depression than those who did not.

In closing, the evidence that present U.S. ECT devices are associated with a reasonable level of efficacy and safety is compelling, not on the basis of opinion or empirical observation but on the basis of hard scientific evidence. As such, present U.S. ECT devices meet established FDA criteria for Class II designation and I --

DR. BROTT: Dr. Robert Roca.

DR. ROCA: Thank you for this opportunity to speak. I'm Dr. Robert Roca. I've no relationship to industry of any sort. I'm a board certified psychiatrist, board certified internist, and I'm in the active practice of geriatric psychiatry. I'm also the Medical Director at Sheppard Pratt Health System in Baltimore, and in that role, I have responsibility for the safety and quality of care for a very large mental healthcare system.

We perform thousands of ECTs yearly. So I'm acquainted with all the issues that have been raised today, primarily on persons who come in as outpatients, and I want to make three points today.

The first is that ECT works. It's one of the most dramatically effective treatments in medicine. Others have presented the empirical data showing that ECT helps in a variety of conditions and is the single most effective treatment for severe depression, particularly when depression is accompanied by delusions. It's unquestionably more reliable and effective than talk therapy for these kinds of depressions and more effective than medications.

But let me recount a few anecdotes. A woman I treated recently in her 80s, she was curled up in a ball, in a fetal position, in a local medical facility, requiring total nursing care and a feeding tube because she was not willing to eat. She could barely be persuaded to speak, but when she did speak, she expressed the conviction that there was no hope for her.

Everything was over. She had once had a good response to ECT. So her family begged her medical team to transfer her to our hospital. They did that. They then begged us to do ECT, and the patient agreed although she didn't expect any benefit from it. After about three treatments, she was out of bed. She was walking. She was wanting to eat. She was much clearer and more accessible than she had been when profoundly depressed. She went on to return to the assisted living facility from which she had originally been referred.

Another story, a retired machinist, who is in his 70s now, develops recurrent depression characterized by this terrible distress every morning accompanied by a strong wish to die. The only thing that's kept him from suicide is a very devoted family and the experience that the distress gets substantially better later in the day. Medicines haven't worked. Family support, which is abundant, has not helped, but his symptoms are eliminated dramatically and immediately by one or two ECTs, and he's had this over the years on three or four occasions.

A 95-year-old woman, the mother of two doting sons who are both physicians, gets a weekly treatment as an outpatient because if she doesn't have timely treatments at about this frequency, she becomes frantic, ruminative, and disorganized to the point of becoming disabled. She's someone who could not tolerate medicines of any kind because they made her drowsy and prone to fall. ECT clearly renders her more functional

and engaging. It does not, in her case, produce any clouding or impairment.

And then finally, an elderly cantor, who has a ruminative, disabling depression characterized by profound feelings of worthlessness and paralyzing anxiety, has been unresponsive to medication and psychotherapy over the years. ECT was found to be the only thing that helps him, and with the strong encouragement of this daughters, he has ECT about every two weeks. This allows him to remain integrally involved with his family and with his synagogue where he continues to be respected as a cantor.

I could go on with these kinds of stories, but suffice it to say that I've seen ECT help people again and again. I don't personally have any doubt that it works.

Now, these stories also serve to make my second point, that ECT as it's provided today is well tolerated by most people, even very elderly people. We know that the main acute risks are those associated with the anesthesia, not with the procedure itself or with the machine. There's always an anesthesiologist present. There's always a psychiatrist who has special training present. The patient is very closely monitored.

In the decades over which we've given tens of thousands of treatments, we've never had a complication as serious as a death. The main worry is the effect on memory, of course, and, in fact, this effect is highly variable. Some have very little or none. Others clearly have more, but this is

always part of the consent discussion, and patients decide for themselves if relief of the depression is worth the risk of memory difficulty, which truthfully it is usually minor and temporary if it occurs.

The final point to emphasize is another truth that was apparent from my stories. ECT is sometimes the only thing that works. It's the only thing that keeps people well in some cases, and it can be literally lifesaving. I've already mentioned several cases in which people who were experiencing agonizing symptoms and profound disability were literally brought back to life by ECT.

MS. WOOD: Thirty seconds remaining.

DR. ROCA: This is not rare or exceptional. It's something that you have to witness to fully appreciate. I can't say I can think of an instance in which I regret having ordered it, but I know of instances in which ECT was withheld and the patients went on to die. These are people who didn't need to die. They had a treatable illness for which we have a very effective treatment and to which they were denied access. Some people say it's --

DR. BROTT: Dr. Narrow is on our list as the next speaker.

DR. NARROW: My name is William Narrow. I've been a board certified psychiatrist for 20 years and currently serve as the Associate Director for the Division of Research at the American Psychiatric Association. Thank you all for the opportunity to speak on behalf of the APA regarding the safety and efficacy of electroconvulsive therapy and to address FDA's

classification of medical devices used for ECT.

Before I begin my remarks, let me say that neither I nor the American Psychiatric Association is involved in the manufacture or sale of ECT devices.

ECT is an important treatment option for psychiatrists. It is most often used to treat psychiatric illness in three situations: when rapid, definitive treatment is needed to prevent harm to the patient, when other treatment options present unacceptable risks, or when a patient has a previous history of poor medication response or a good response to ECT.

ECT is most often used to treat severe symptoms of three mental disorders, major depressive disorder, schizophrenia, and bipolar disorder. All of these disorders can be manifested in life-threatening ways, including profound and intractable suicidal intent, catatonia that can lead to complications such dehydration, starvation, and venous thrombosis, and manic episodes that can lead to lack of self care, destructive behavior, and physical exhaustion.

The availability of ECT assures rapid, safe, and effective treatment for the manifestations of severe mental disorders. In many cases, it is lifesaving. A large body of evidence published in peer-reviewed medical journals has documented the safety and efficacy of ECT.

Much of the public stigma attached to ECT is based on lurid media depictions of early treatments in which high doses of electricity were

administered without anesthesia for any number of psychiatric problems or simply for punishment. Modern ECT is nothing like these portrayals.

The American Psychiatric Association has developed recommendations for ECT treatments, training, and privileging. These recommendations state that ECT should be administered by a team of trained health professionals with experience in ECT administration, including a trained ECT psychiatrist, an anesthesia provider, and one or more nurses. The electrical stimulus is given while the patient is under light general anesthesia with muscle relaxation. The seizure, initiated by the electrical stimulus, is monitored by EEG. After the procedure, the patient is monitored by a registered nurse as is done for any procedure involving general anesthesia. Although ECT causes side effects, it uses electrical currents given in a controlled setting to achieve the most benefit with the fewest possible risks.

ECT is not a treatment that should be lightly considered, and the patient and physician must discuss all options available before deciding on any treatment. The APA recommends a rigorous informed consent procedure for ECT. The patient and his or her family are informed about the procedure through in-person discussions, written material, and any supplementary means available before giving consent. Risks, benefits, and the voluntary nature of treatment are explained. If the patient is unable to give informed consent, state and local laws governing consent to treatment

are followed. Detailed sample patient information and consent forms have been developed by the APA.

As noted in our written comments submitted to the FDA in 2010, the APA strongly supports the reclassification of ECT devices to Class II with special controls. Should the ECT move forward with such a reclassification, manufacturers should be asked to disseminate science-based guidelines similar to those developed by the APA. If the FDA does decide to promulgate controls involving postmarket surveillance, the controls should only be those to ensure the safety of the device. The APA has particular concerns regarding patient registries based on the potential for re-identification and breaches of privacy by third parties.

Thank you for allowing me to speak to the FDA Panel today. I'm happy to answer any questions you may have. As a psychiatrist and a researcher, I consider ECT an important treatment option for patients who are not responding to other therapies or whose lives are at risk. Thank you.

DR. BROTT: I'd like to thank the participants in the Open Public Hearing to this point. We will now take a 10 minute break. I would ask that the speakers be available for questions. We're holding the questions until all the scheduled speakers have had an opportunity to speak.

Before we break away, Dr. Ross.

DR. ROSS: Just a quick question. I was just wondering if we got any submissions from any of the patient organizations like NAMI or

NORASID (ph.) or other advocacy groups?

DR. BROTT: I'll direct that question to Dr. Eydelman.

DR. EYDELMAN: I'm not sure if you're commenting on the submissions to the public docket or written comments to this Panel, but those are publicly available from my website.

DR. ROSS: Chris Ross again. Let me try and clarify that. I was just wondering if you got any submissions for those organizations to have representatives to speak here, and if so -- actually that's my question.

DR. EYDELMAN: Each speaker for the Open Public Hearing will identify which organization, if any, they are associated with.

DR. BROTT: What I'm hearing, I guess, what is the process whereby we have the schedule that we have today?

MS. WOOD: I can comment on that. The FR published with a deadline to request time to speak in the Open Public Hearing. There was a docket open for public comment. Each of you should have received a CD also with those docket comments on it for your review before you attended the meeting today. And so any organization that wanted to comment or any individual that wished to comment could do so on the public docket. So you should have that information available to you, Dr. Ross.

DR. BROTT: Does that answer your question, Dr. Ross?

DR. ROSS: No.

DR. BROTT: With that, we will break for 10 minutes.

(Off the record.)

(On the record.)

DR. BROTT: Before we get started, Dr. Claudio is the Designated Federal Officer for this hearing and has a couple of comments.

DR. CLAUDIO: Good morning. I would like to remember [sic] the people from the public and from the press that they cannot come beyond the podium or towards the podium unless they're recognized by the Chair.

Dr. Ross is not here. Do we have all the Panelists?

DR. BROTT: Dr. Ross is not here. We'll wait just a moment before we really get started.

We're waiting for Dr. Ross. This is just a reminder that the Panel members should not be speaking with the public and the press until the end of these deliberations, and we will -- I think we, even though, Dr. -- well, I guess we better wait. Could someone check on Dr. Ross?

DR. CLAUDIO: I would also like to, while we wait for Dr. Ross, I would also like to read into the record the people that we have either on webcast or on the phone, and we have Dr. Stebbins, Dr. Anderson, Dr. Winokur, Dr. Peavy, Dr. McDonald, Dr. Gordon, and Dr. Domino. Hopefully they will be here tomorrow present, but at the moment, because of the inclement weather, they're either on the webcast or on the phone.

DR. BROTT: We will get started. We've had some speakers

come in late for good reason, and so we will go back to Julie Hersh. Is she here?

MS. HERSH: Do I get a timer, or do I just start going?

DR. BROTT: Yes, you didn't hear the procedure. You have five minutes.

MS. HERSH: Okay.

DR. BROTT: At four minutes you'll see an amber light, and at five minutes your microphone will go off.

MS. HERSH: Starting now.

MS. CLAUDIO: Yes.

MS. HERSH: Hi. I'm Julie Hersh, and I am an ECT patient, and I'm part of the silent majority of those who have greatly benefited from ECT.

In 2001, after nine months of debilitating clinical depression and three suicide attempts, I did ECT at the insistence of my psychiatrist and my husband. The results for me were miraculous. I can remember the day after my first treatment, opening up my journal and looking at the page and thinking, who is this person? I just felt so completely differently from the point that I wanted to die to suddenly my life became real again. I was able to return to my life as a mother of a five- and seven-year-old, an active volunteer in the community, and a wife almost immediately. I had some short-term memory issues the two weeks before and the two weeks after ECT, but within a few weeks after that, my short-term memory was

completely recovered, and I function very well.

At the pleading of my psychiatrist not to in 2005, I went off medication, and I relapsed in 2007 again and got to the point where I had to do ECT again, and again, the results were very positive for me.

In the almost decade since my last suicide attempt, I have raised my children. They're 14 and 16 years old. I've written a book. I've been president of the Dallas Children's Theater, raised millions of dollars in fundraising for my community, and I'm on the board of the Dallas Theater Center and UT Southwestern Medical Board. Without ECT, I would be dead.

ECT is an assessment of risk. Not everyone should do ECT. It's a very serious procedure, but for people like me, ECT is a risk worth taking. I would urge you to make this procedure available for more people. It saved my life. Thank you.

DR. BROTT: Our next --

MS. HERSH: Can I say a few things more since I have 2 1/2 minutes --

DR. BROTT: Yes.

MS. HERSH: -- please? Okay. And since I have written this book and I have been speaking, the book was published in April, and I've done about 80 speaking engagements since then. I've helped two other people who are in a debilitated state of depression, one woman who seemed exactly as I did in 2001, and I encouraged her to see my psychiatrist.

I had never met this woman before. She was hidden in her room, afraid to talk to me, but I came to her house on her husband's pleas. She finally talked to me, snuck out of the room and spoke to me for about an hour, and she said that that was the most she had talked to someone in over three months. She did ECT. I didn't see her.

About six months later, a woman came up to me at the gym I work out in, and she said, "Julie, hi. How are you doing?" And I looked at her and I said, "I don't think I know you." And she said her name, and I realized then who it was. This was a person completely transformed, a person who was alive and invigorated about life. Six months earlier, she had told me that she was eyeing a bottle of pills. She wanted to take her life. She felt like she was useless and no good for the world even though she had two wonderful children and a husband who loved her dearly.

I have another example of a very good friend that I helped who was exceedingly depressed and had come under the impression that he had done some dramatically things wrong to his family which he hadn't. His wife was very skeptical about ECT. She talked with me, read my book. He did ECT, and again he's fully functional. I had coffee with him about a week ago, and he is reengaged and reinvigorated about life.

So, unfortunately, most of the people like me wouldn't go through snow and sleet and bribe a taxi guy to get here today, but ECT is a fabulous tool, and again I really urge you not to restrict it from the people

who get benefit from it. Thank you very much.

DR. BROTT: Is Dr. John Breeding here?

DR. BREEDING: My name is John Breeding. I slept in the Charlotte Airport last night, so I'm a little frazzled, but I'm grateful to be here, and I appreciate your flexibility. I left two friends of mine, electroshock survivors in Texas, in tears in the airport because they couldn't get here on a plane, but fortunately somebody's going to read their testimony to you.

My name is John Breeding. I've been a Texas psychologist for almost 30 years, and I'm a founding member of the Coalition for the Abolition of Electroshock in Texas. I've been active for 20 years in efforts to abolish or at least limit the use of electroshock because of its severe danger and lack of efficacy. Although we narrowly failed to accomplish a total ban on electroshock in Texas, the procedure is banned for children under age 16 and extra safeguards are in place for the elderly. In Texas at least, we know that electroshock is dangerous, and electroshock machines are very dangerous. So, of course, I'm strongly against the reclassification of the machines.

Two very experienced neurologists submitted written testimony but could not be here today. Dr. John Friedberg is the author of *Shock Treatment is Not Good for Your Brain*. Here's what he said. "The intentional induction of convulsions should be abolished. In my entire

career, I never met an epileptic who benefited from their seizures. I never had a patient tell me a seizure leaves them feeling happier. ECT causes memory loss in all cases, dramatic damage in some."

I completely agree with Dr. Friedberg. I've seen the research showing brain damage and memory loss, and I've sat with the victims of electroshock. I've witnessed their profound losses and disabilities. I personally know at least three people who have permanent seizure disorders now as a result of electroshock, including Diana Loper (ph.) who is one of the women I left in Charlotte. I know many more who are unable to work and on permanent disability. The other woman I left there, Evelyn Scogin, is unable to work as a teacher because of her disabilities.

As a psychologist, I appreciate also what Dr. Fred Bowman had to say. "Throughout the more than three decades of my neurological practice, I have encountered patients treated with ECT who had permanent erasures of their memory. Psychiatrists may wish to call ECT therapeutic, but it never achieves anything but to diminish adaptability in the broadest sense and cannot be called therapeutic or medically justifiable."

That my own mental health profession systematically inflicts brain damage is a shame and a disgrace, that women like Evelyn Scogin and Diana Loper strove to get here today is an incredible testament to their resilient spirit.

Anyone who is serious about evaluating electroshock needs to

read this book, *Doctors of Deception, What They Don't Want You To Know about Shock Treatment*, by researcher and electroshock survivor, Linda Andre. It's the best up-to-date document on shock and makes it clear that the reason we're even having this conversation today is a victory of public relations over science.

The science is clear about the basic questions of risk and benefit. Electroshock is not safe. It is extremely dangerous. It always causes brain damage. The most obvious evidence of this is memory loss. It sometimes causes death. While the American Psychiatric Association argues that electroshock deaths are rare, one study published in 1993 reported 10 deaths among 37 patients 80 and older who underwent electroshock. In the mid 1990s, the Texas Department of Mental Health and Retardation reported 21 deaths among an estimated 2,000 patients who were electroshocked. In Texas, we're clear that these machines are dangerous.

The electroshock machine industry has consistently ignored FDA requirements for evidence on the safety and efficacy of their machines. I suppose it is a political question as to why your agency has consistently refused to apply the law and hold the industry accountable. For now, I urge you to do the right thing and leave these brain-damaging machines in the high risk category. Thank you.

DR. BROTT: Next we have Anita Hagin.

MS. HAGIN: Thank you for this opportunity to speak to the

Panel. I'm a psychiatric nurse at Sheppard Pratt Health System, and I came on my day off to express my concern about this issue.

For over 20 years, I have been a registered nurse working with patients receiving ECT. It has been a career of helping people. I can say that I look forward to going to work each day and having the privilege of helping someone battling depression get relief from their symptoms when medications have proven ineffective.

ECT is a treatment that has been proven effective in treating depression. To see a patient who was mute, despondent, suicidal, or psychotic come into the room with a smile and say, "I'm doing better," there's professional and personal satisfaction in being part of that. Patients have said to me that ECT has given them their life back.

I come here to speak as an advocate for the patient receiving ECT. Patients receiving ECT have treatment-resistant depression and are often suicidal. The decision to receive ECT comes after much deliberation and thought, to say nothing of the many medication trials they have undergone. The decision by the psychiatrists to refer their patient also comes after prescribing multiple medications in varying doses only to find that their patient continues to suffer and are suicidal. So you see, the decision to receive ECT or prescribe ECT is a seriously considered treatment choice. Ultimately, the decision to receive ECT is made by the patient and the family alone.

There are many cases where ECT has been the only treatment that has worked for patients and improved their quality of life. I have two examples.

Mr. S, an inpatient on the geriatric unit, was suffering from a severe depression. He had stopped eating and was being fed by a gastrostomy tube. His family sought help for treatment for Mr. S. He is someone's husband, father, and grandfather. Medications were not working. He received a course of ECT, and within weeks, he was eating again. We see him now, and he works alongside his son on the family farm. ECT saved his life. What would have happened to Mr. S if ECT was not available to him?

I have seen many patients with similar stories. I see dramatic improvement in moods that are just short of miraculous.

There's a mother with two children who was suffering from psychotic depression. I see the fear in her eyes and the tears in the eyes of her husband as she struggles with depression and paranoia that makes it impossible for her to be a wife and mother. Within three treatments, she is smiling, greeting the staff, the paranoia is gone, and the depression is lifting. Only ECT can bring about this type of change.

I believe that I save lives every day. Therefore, it is important to classify the ECT equipment so that it would not interfere with the opportunity for patients who need this lifesaving treatment to receive it. I

ask you to be an advocate along with me for the depressed patients, those patients who need this treatment and without it would continue to suffer with severe and debilitating depression.

I also brought a little card from one of our patients that she sent at Christmastime. "I would like to thank everyone in the ECT Suite who helped me get back to being Sarah again. Everyone in my family always talks about how great it is to have me back. I will never get tired of hearing this. My mom says it's a miracle, and sometimes it brings tears to her eyes. These tears are no longer of worry or sadness but of joy. I finally see how great I am and how great I can be. With all your encouragement and care, I've gotten back to work, I've gotten back to doing the things I love, and most importantly I've gotten back to me. Yesterday was great. I look forward to tomorrow, and my future will be even better." Thank you.

DR. BROTT: I think the next speaker we have is Amy Lutz.

MS. LUTZ: Thank you, members of the Panel. My name is Amy Lutz, and my son, Jonah, suffers from autism and rapid cycling bipolar disorder. Until last March, he was plagued by frequent, unpredictable, and violent rages during which he would pound himself in the face like this until he looked like this. I'm showing you these pictures because I need you to understand the state of crisis we lived in for the better part of a decade, and even worse than what he would do to himself was what Jonah would do to others when he was in one of these states. He broke a teacher's nose when

he was 6 years old, and by the time he was 10, when those pictures were taken, his almost daily attacks left me, his teachers, and his aides bruised, scratched, and bitten.

We tried everything to control Jonah' aggression, including almost every alternative treatment ever popularized by the autism community: gluten and casein free diets, vitamin cocktails, B_{12} injections, auditory integration training, hyperbaric oxygen therapy. When none of these helped, we tried pharmacological intervention: antipsychotics, antidepressants, beta blockers, anticonvulsants, lithium, stimulants. During an almost year-long hospitalization at the Kennedy Krieger Institute, Jonah was briefly stabilized on a combination of lithium and Abilify, but only a few weeks after he came home, the behaviors returned, and less than a year after discharge, they were worse than ever.

These fits came upon him under any and all circumstances, while he was doing schoolwork, eating meals, even watching his favorite videos. In October 2009, Jonah threw a tantrum in the car lashing out at his 80-year-old grandfather who was driving. While trying to restrain Jonah in the confines of our minivan, my husband accidentally broke Jonah's arm.

We were faced with the crushing realization that it was no longer safe to keep Jonah at home, not for him and not for his four younger siblings. At 10, Jonah was already over 100 pounds, and puberty loomed right around the corner, a time when the violent behavior of autistic boys

typically grows much worse. I didn't want to imagine what much worse would look like for Jonah, but I couldn't stop thinking about Kent State Professor Trudy Steuernagel who was beaten to death in 2009 by her 19-year-old autistic son.

But we didn't need to place Jonah in a residential facility after all. In March 2010, we decided to try ECT because we knew it had been used successfully at Kennedy Krieger on kids with dangerous behaviors who hadn't responded to medication. Less than a month later, Jonah's aggression was almost completely gone. Gone. And ECT stopped his rages without any of the personality changes or cognitive impairments you've heard a lot about during this hearing. Quite the opposite. According to Jonah's school data, before ECT, he acquired an average of seven new skills per month. In December 2010, he acquired 52 new skills.

And Jonah isn't alone. There's a growing group of patients whose quality of life depends exclusively on their access to ECT, developmentally delayed kids and teens who suffer from aggression, self-injury, and catatonia. I met several of these families over the past year, including a 14-year-old autistic boy who was self-injurious -- he detached his own retinas twice -- as well as a 16-year-old born with half a cerebellum due to an in utero stroke who vacillated between periods of uncontrollable rage and catatonic stupor during which he would remain frozen, unable to eat, toilet, or communicate for up to eight days at a time. ECT resolved the

extreme behaviors of both those boys as well as those in other cases reported in the psychiatric literature by doctors at Kennedy Krieger and the University of Michigan among other places. In fact, Jonah's case was just published in the *European Journal of Child and Adolescent Psychiatry*.

You have heard people get up and say that ECT doesn't have any long-term benefit. That's because ECT is, like dialysis, a treatment, not a cure. Jonah and his terribly affected peers need maintenance ECT to keep their symptoms at bay, which is why I drove eight hours through blinding snow to implore you to reclassify ECT machines as Class II medical devices and not to make any decisions that might make ECT less accessible for these children who need it so desperately.

What will happen if they can't get ECT? Well, the boy who detached his retinas would surely blind himself. The catatonic teen would end up on a feeding tube, and Jonah, well, Jonah would end up physically or chemically restrained on a locked ward instead of where he is now, home, in school, out in the community, enjoying just like my four other children a rich, happy, exciting life. This is Jonah now.

Thank you very much.

DR. BROTT: Next we had scheduled Evelyn Scogin, and speaking on her behalf is Mr. Kendrick Moxon.

MR. MOXON: Thank you. Ms. Scogin contacted me this morning. She was also one of the people that was stuck in an airport, and

she was very concerned that the FDA hear her statement. Although it apparently is anecdotal, it would be considered anecdotal, she wanted this to be heard, anecdotal being a dirty word.

My name is Evelyn Scogin. I'm here to tell you my story of assault from ECT so that you will understand the harm this machine does every time it is used. I came to psychiatry in 2004 at the age of 47. I was experiencing severe stressors at the time. So I naturally turned to a mental health professional for assistance and advice. I entered the psychiatric system at the time, trusting the psychiatrist as the health professional that would care for me in my time of need and perhaps help me solve my emotional issues. That is what I was led to believe.

I entered the hospital taking one psychiatric drug and left taking seven. My psychiatrist diagnosed me with bipolar disorder. At the urging of the psychiatrist, I gave up my hard-won career of teaching special needs deaf students. One month later, in January of 2005, I was in the hospital again because I was depressed.

My sister has informed me that the psychiatrist described ECT treatment as safe with only a loss of memory of the day of the treatment which would return shortly thereafter. I say my sister told me that because I have no recollection of any conversation with the psychiatrist concerning ECT. Never did it occur to me that anything that a so-called professional recommended would be harmful to me. I have no memory of the meeting or

any events thereafter.

I was subjected to six months of numerous treatments. During my course of treatment, my emotional, physical, and cognitive health severely declined.

My family has informed me, because I have no recollection, that when I was released from the hospital after treatment, I could not be left alone as I would wander off somewhere and become lost. I often could not tell you my name and the names of any of my children. I lost not only my memories of the time I was subjected to this torture, but I was robbed of almost all memories from 2003, two years before the treatment, to 2008, three years after the treatment stopped. I was unable to converse or write coherently because my word recall was so limited, just like someone who had had a stroke. Taking care of many of my everyday needs was beyond me. In fact, one of my sisters had to take charge of my bank account. I could no longer drive or go to the mailbox alone.

I've fought long and hard over the last several years to recover from the effects of this abuse and rebuild my life. However, I will never recover the part of myself that was stolen from me which consisted of my memories. Because of these lasting effects, I have, as of yet, been unable to return to my chosen profession of teaching. I'm training for a new job, but it remains a struggle for me each and every day to learn new tasks.

The persons that believe ECT helps are psychiatrists. If you ask

the patients, with some rare exception, they don't feel that it helped them. ECT destroyed my life. You, this Panel, should not be a party to destroying minds with this dangerous device when there's no evidence that it has any benefit. You should not permit these machines to create chaos in person's memories without first demanding proof that it can truly help humans. It has never been proven to be effective at curing anything, never.

Some think approval from the FDA means a product is effective and that it is safe. These people have been betrayed. By limiting the evidence, by limiting the issues they want you to address, by excluding all questions of efficacy, the FDA is using this Panel as a instrument of that betrayal. By agreeing to membership in this Panel, it is your solemn duty to protect others. Downgrading these devices to Class II would be unforgivably irresponsible.

That's the end of Ms. Scogin's statement. I'm willing to answer any questions of the Panel members of my previous statements.

DR. BROTT: Next we have scheduled Dian'na Posthauer and John Eastgate -- or it might be Jan Eastgate.

MS. EASTGATE: Jan.

DR. BROTT: Jan Eastgate is speaking on her behalf.

MS. EASTGATE: Thank you. Dian'na Posthauer, she's the founder of Christians United for the Ban on Electroshock, and she thanks you for allowing her to speak today. In fact, she recently had major surgery and

her doctor was furious that she was going to testify here rather than safely recuperating at home, but she wanted you to have her story.

She said, Shock killed me. At least it killed 16 years of my life as if I had never lived them. As a 24-year-old mother of a beautiful baby boy, I had postpartum depression and my husband convinced me to see a psychiatrist. He recommended ECT and told us that it was safe and effective. Against my will, I was repeatedly shocked.

After shock, I didn't know my husband or my baby. Shock had wiped out all my memory of my family. In fact, it wiped out everything but the first eight years of my life. My husband filed for divorce and disappeared with our son. I didn't find him until he was seven years of age. By that time, I had missed all the bonding years with him. I missed picking him up when he fell, reading him bedtime stories, cuddling him when he had a nightmare. ECT robbed me of my chance to experience the joy that a mother feels as she watches her child grow, and my son was robbed of his mother. Today he's a grown man, and our relationship is minimal at best. I have almost no relationship with my grandchildren who I so desperately want to be a grandmother to.

On the outside I look pretty normal, but you don't live with me. One, I have Post-It notes all over my house telling me what to do and when to do it. Two, my cabinets and drawers have labels everywhere so I know where things go. Three, it takes me forever to learn something new.

Four, I can't hold down a job because I get mixed up so much. Five, without this Day-Timer, I can't function day to day. Six, and worst of all, I live with the fear of having seizures anytime and anywhere, something I'll have to live with all my life thanks to ECT. Would you like to live with this?

Words don't do justice to explain the damage that ECT did to me and my family. The psychiatric profession markets ECT as safe and effective, but in my opinion, I'm living proof that this is false advertising. ECT has devastated two generations of my family. I have one more question for you. Will your family be next?

Please leave ECT in Class III. This procedure already does enough damage. Thank you.

DR. BROTT: The next speaker that we have scheduled is Dorothy Dundas.

MS. DUNDAS: My name is Dorothy Dundas, and I am 69 years old from Newton, Massachusetts, and I've been waiting 50 years to come before this Panel, those of you who have a power to make a humane decision.

When I was 19 years old, I became sad and lonely, and I tried to kill myself. I took a half a bottle of aspirin, my parents took me to the Massachusetts General Hospital, and thus began my three-year hellish odyssey as a prisoner in the horrors of the mental health system. I was diagnosed with schizophrenia and given 50 shock treatments against my will,

40 insulin comas and 10 superimposed electroshocks.

Very early on the dark winter mornings of 1961, three other teenage girls and I were awakened, dressed in johnnies, and told to lie flat on our beds, which we were lined up right next to each other. We were then injected with insulin, and on 10 of those mornings, a dark-suited man would walk through the door. He carried all his equipment in a small black suitcase, this man of death and destruction. He set up his machine behind our heads, one by one. We were curled up beneath our sheets. When they peeled the sheets off of us, forcing us onto our backs, bare and open and vulnerable, I was second in the lineup. Before being turned, I would often peek out from a small secret opening in my sheet to see what they were doing to Susan, the first to receive the treatment. I would make myself watch as if it might prepare me in some way, and then she would shake violently all over. I could no longer watch. I would shiver beneath my sheet, and then they would come to me. I can still feel the sticky cold jelly they put on my temples. My arms and legs were held down, and just before he pushed the shock button, he would ask, is everybody ready? Of course, he was not speaking to me, petrified and stone silent. Each time, I expected I would die. I would wake up with a violent headache and nausea. My mind was blurred. I permanently lost eight months of my memory for events preceding the shock. I also lost my self-esteem. I had been crushed as flat as a pancake. But I was very, very lucky because on one of those cold winter

mornings, exactly 50 years ago, my friend Susan never woke up from the shock. She had just turned 17, and when she died, she became a part of me.

The ECT was a violent and damaging assault on my brain and my very soul. It made me emotionally worse, not better. I became catatonic and desperately in fear for my life. To this day, I have great trouble staying focused in a conversation, keeping my train of thought. I forever lost the ability to do math in my head, and before this time, I had been a very good student. When I was given an IQ test a few months after the ECT and asked the population of the United States, I answered 1,000. When he asked me to guess again, I answered 2,000. I remember having no idea where to find the answer in my head.

For me, in addition to losing my train of thought, the most troubling residual effect has been the memories of those traumatic mornings, the violent and abusive assaults on my brain. For far too long, there has been a collusion between the FDA, the APA, the AMA, and the companies which make the shock machine. This is big business, and a lot of money is being made by many at the shameful expense of those who have been harmed over the years.

To me, informed consent is meaningless. Those of us who have already experienced ECT are only the truly informed. Right now this is a human rights issue, and this is a torture issue.

In the end, after three years of hell, it was a kind young doctor

who spoke to me in a gentle voice who gave me hope. He took me off all medication, expressed horror when hearing of my experience with ECT --

DR. BROTT: You have 20 seconds.

MS. DUNDAS: -- and recognized -- I urge you to ban the use of this dangerous and barbaric machine and, by doing so, finally to show the courage and understanding to support the many more humane and holistic approaches to healing emotional pain. Thank you.

DR. BROTT: Dr. Daniel Fisher.

DR. FISHER: I represent a national mental health consumer organization, to answer an earlier question, the National Coalition for Mental Health Recovery, which represents millions of mental health consumers. I do not have any financial relationship with the manufacturers of ECT devices.

I base my testimony on my practice as a board certified psychiatrist, my neurochemical research at National Institute of Mental Health, and my 19 years of directing a federally funded technical assistance center, the National Empowerment Center.

I'm appalled that the FDA is considering downgrading ECT devices from Class III to Class II, the same classification as a wheelchair. In my expert opinion, and that of a recent review of ECT literature by Drs. Reed and Mentel (ph.), any short-term gain of ECT is offset by its risks. I recommend, one, ECT devices continue to be designated as Class III; two,

that their use be suspended until meaningful long-term efficacy and minimal risk of memory loss, cognitive deficits, brain damage, and mortality are independently demonstrated by premarket approval.

Two of my cases illustrate some of the negative aspects of ECT.

I saw a 19-year-old young man in an outpatient clinic. He suffered from major depression, was slow to respond to Prozac. He was admitted to an inpatient facility where the psychiatrist immediately started a series of eight ECT treatments. Upon discharge, his depression had slightly lifted, but he could no longer recognize his friends. He was so distraught over the side effects of ECT that he hung himself. This case points out that ECT not only does not decrease suicidality but can actually increase it, and there are, by the way, much more extensive validation of this in my testimony that I submitted.

Case B, in my capacity as a consultant, I learned that a 51-year-old woman was experiencing memory loss and confusion which intensified once a month. Belatedly, she acknowledged that she was given monthly outpatient ECT. She had been threatened with rehospitalization by her doctor if she disclosed. She wanted to stop the ECT and, in my presence, was able to tell her doctor that she wanted to leave his care. She did so, was successfully switched to an antidepressant with fewer side effects. The case illustrates that ECT causes cognitive defects and memory loss.

The most detailed studies of memory were carried out by

Dr. Irving Janis, who found gross gaps and subtle losses of memory and a general slowness and great effort in recalling details. These side effects were also validated by a proponent of ECT, Dr. Harold Sackeim. In 2007, he reported that there are memory deficits and said, "This study provides the first evidence in a large prospective sample that adverse cognitive effects can exist for an extended period and that they characterize routine treatment by ECT in community settings."

The APA guidelines for ECT inaccurately contend that the memory loss with ECT is minimal. Furthermore, the APA consent form drastically underestimates mortality associated with ECT by stating a risk of 1 in 10,000, whereas the average of numerous studies indicated a tenfold higher rate of death than suggested by the APA. The APA also suggests that "Brain damage should not be included in the informed consent process as a risk of treatment."

It appears the APA Task Force on ECT overlooked considerable evidence that ECT does produce brain damage as summarized by neuroscientist Dr. Peter Sterling. One, ECT is designed to evoke grand mal seizures posing an acute rise in blood pressure well into the hypertensive range and is frequently the cause of small hemorrhages in the brain. Two, ECT ruptures the blood-brain barrier. This barrier normally prevents many substances in the blood from reaching the brain. Where the barrier is breached, nerve cells are exposed to the insult. Brain edema, anoxia, and

neuronal death occur. Three, ECT causes neurons to release large quantities of the neurotransmitter glutamate which releases more glutamate leading to excited toxicity and neuronal death.

According to Dr. Peter Breggin, the brain disabling hypothesis states that the more potent the somatic therapies in psychiatry, such as ECT and cingulotomy, they produce brain damage and dysfunction, and this damage and dysfunction is the primary --

DR. BROTT: You have 30 seconds.

DR. FISHER: -- beneficial effect.

I conclude by saying how is it possible that in a democracy with the most advanced constitution of any country, a whole class of people can be subjected to brain-disabling procedures without regulation by the Government. I can only conclude that being labeled mentally ill means you lose your rights and protection under the constitution. I entreat you to protect this labeled class of people by regulating these devices as they should be under Class III and that all conflicts of interest --

DR. BROTT: Carol Reynolds. Then we will go on to Lauren Tenney.

DR. FISHER: I may not look like Carol Jean Reynolds, but she is stranded in Newport News, and one thing, I wish that there were some alternative way for people to give their testimony themselves, either through video or through audio in circumstances like this. She flew from

Colorado and her plane was detained. So I'm reading her remarks, if you please.

DR. BROTT: Go ahead.

DR. FISHER: Okay. Thank you for permitting me as well as other members of the public to provide comments at this important meeting. I would first like to applaud this Panel for coming together on a matter of critical importance to people with disabilities. I'm here in my capacity as a board member of the National Council on Disability, an independent federal agency which advises the President and Congress on all issues affecting people with disabilities.

I also want to let you know that I'm a psychiatric survivor myself and therefore can speak as a person with a disability who has been impacted in a profound way by the subject at hand. I have been in recovery from my polar disorder, alcoholism, substance abuse for 25 years. I've had the privilege of having had excellent medical care when I was sick, something that many of my brothers and sisters have not had access to. At the same time, I would like to thank the FDA for approving medications Lamictal and Seroquel. These medications have helped me.

Medical devices have profound impact on the lives of people with disabilities. While many devices hold great promise for increased participation of persons with disabilities in the community, their safety and effectiveness needs to be carefully studied to ensure the potential negative

impacts are eliminated or mitigated.

The NCD wishes to specifically highlight its views regarding ECT and the classification of devices for ECT. I've drawn heavily from our groundbreaking report, "From Privileges to Rights: People Labeled with Psychiatric Disabilities Speak for Themselves," in preparing commentary. As noted in this NCD report, ECT is of great concern to the disability community. The advisory committee considers the FDA's role in regulating the device used to conduct ECT. NCD wants to help inform the committee about the role these particular devices have on lives of people who often don't have a voice. People with psychiatric disabilities are routinely deprived of their rights in a way no other disability group has been.

While I know this committee is focusing on how to classify ECT, NCD believes that ECT devices are inherently inhumane, unsafe, and ineffective and should not be classified as a therapeutic device. Public policy needs to move in the direction of a totally voluntary community-based mental health system that safeguards human dignity and respects individual autonomy. People labeled with psychiatric disabilities should have a major role in the direction and control of programs and services designed for their benefit, and most importantly, germane to this committee meeting, public policy should move towards the elimination of ECT and psychosurgery as unproven and inherently inhumane procedures.

Effective humane alternatives to these techniques exist now

and should be promoted. I've concluded from my own personal experience and from NCD's policy development research that one of the reasons public policy concerning psychiatric disability is so different from that concerning other disabilities is the systematic exclusion of people with psychiatric disabilities from policy making. It is rare that people with psychiatric disabilities are heard in public policy forums, and thus I want to take full advantage as a member of the psychiatric disability community as a presidentially appointed member of the Council to urge you to carefully consider classifying ECT devices as any type of therapeutic device.

Again, I thank you for allowing me to comment.

DR. BROTT: Lauren Tenney.

MS. TENNEY: Hi, thanks. My name is Lauren Tenney. I'm a survivor of psychiatry. I was never given electroshock, but it's much because of the work of advocates and activists in the 1960s and 1970s and 1980s that prevented me from being exposed to the treatment which is known to cause brain damage, including memory loss, damage to the body, and destruction of life.

I consider myself very lucky. At 15 I was institutionalized at a state facility in New York, and in recent meetings, as recent as the end of last year, the New York State Office of Mental Health justifies the young person that can be shocked in a situation that is identical to what would have been seen as my situation at 15. And so I feel, on top of everything

else, the idea of young people being shocked is a human rights violation and needs to be looked at, and as a matter of fact, the United Nations Special Repertoire on the Convention Against Torture has cited that electroshock along with several other psychiatries, several other practices such as forced drugging, may constitute torture or ill treatment.

Theopalproject.org collected over 80 comments and sent them onto the FDA when you were doing the initial commenting January 4th and 5th, I'm not sure of the date, but when you were doing it. We sent out over 80 comments and, you know, many of the people who are currently being shocked may have no idea that there is an opportunity to comment on the potential down-classification of the shock machine without a safety investigation.

Many of these people, including children and senior citizens, may be involuntarily committed, barred access to the outside world and the Internet, leaving options for their voice to be heard discounted. Various reasons such as poverty, illiteracy, fear of retaliation, lack of access to the Internet, fear of coming out, and saddest for those whose death was caused by ECT, which itself is a crime against humanity, will prevent some people's voices from being heard.

So while in numbers we may not be able to rise against the strength of the industries that will undoubtedly prosper from a down-classification of the shock machine, please bear in mind what it means for

someone to speak up and voice their opinion and share their personal experiences.

This is the reason that we sent this letter out to you. I think you all should have gotten this.

I'm appealing to your humanity here and I'm asking you to seriously consider what it is that people say. In 74 of the comments, about 12 or 13 people used the word "please." Please stop the use of ECT. Please do not cave into the industry on this issue. Please do not reclassify unless you undertake investigation. Please don't destroy any more brilliant minds like this. Please consider carefully the approval process and reclassification of ECT. Please do not reclassify the ECT device to Class II without further requiring premarket approval applications. Please stop this process until you have had ample time to hear from those of us who have had firsthand experience with ECT. Do not allow these companies to get away with this please. Please be sure to do safety exploration and testing before moving forward. Please stop them now. Please do not allow ECT machines to be used as safe without proper investigation. It seems to me that even if one was destroyed, that is one too many. Please stop this treatment.

You know, for centuries, we have been going through periods of time when psychiatric industry comes under investigation because of the way it acts, and we have this opportunity right now again to try to make some change and to try to make it stick.

The door has been open on a very important conversation that is silently brewed amongst people who are survivors of shock treatment and their allies for decades with little effect. Our battle is now, as it always has been, Will the people who have power to end psychiatric abuse and torture and require full and informed consent based on actual safety investigations do so?

Hundreds of attempts of thousands of people over the decades have left many of us unhopeful that --

DR. BROTT: You have 30 seconds left.

MS. TENNEY: Well, shock is a social justice issue. FDA, we want you to ban the use of all shock devices on minors, ban the use of shock devices for all forced, coerced, and uninformed shock procedures which routinely happen across this country, and institute a moratorium on all use of shock devices until proven safe. Thank you.

DR. BROTT: The next scheduled speaker is Dr. David Boger.

DR. BOGER: Good afternoon. My name is Dr. David Boger. I'm a board certified adult psychiatrist in private practice in New York City.

I come to you today both as a physician who supports the use of ECT in carefully selected patient populations and as a patient myself who has undergone extensive electroconvulsive therapy. I refer you to my personal article I wrote entitled, "Shocking the Shrink: A Psychiatrist Undergoes ECT." I've experienced episodic depressions characterized by

sleep and appetite disturbance, impaired concentration, complete loss of interest in usual activities, hopelessness, debilitating fatigue, and prominent suicidal ideations since the age of 10. My father, incidentally, was unofficially diagnosed with depression which eventually led to his tragic suicide.

I saw a plethora of psychiatrists who eventually made the diagnosis of bipolar II disorder, a variant of manic depressive illness. I was introduced to lithium by a prominent psychiatrist at NIMH and in combination with antidepressants, first the tricyclics and then the newer SSRIs like Prozac, was able to maintain a high function for several years at a time.

Despite all the interventions, I still experienced recurrent depressions and hypomanic episodes every few years that sidelined me often for months at a time. It was not until 2003, when I had another rapid-onset severe bout of bipolar depression that my New York psychiatrist recommended, of course, ECT. At that time, I was dangerously depressed and actively suicidal, unable to make a commitment to refrain from self-harm and was so admitted to New York University Hospital. I stayed there almost a month receiving three ECT treatments a week. At that time, the protocols and equipment left me dazed for at least 24 hours with significant amnesia for events occurring around the time of treatments. I enjoyed a brisk but incomplete recovery. The suicidal feelings were quickly

extinguished but a persistent sleep disturbance and low self-esteem persisted. I was discharged alert and fully oriented on a combination of antidepressants, antipsychotics, and mood stabilizers.

I suffered through manageable symptoms until December 2008, when the walls came crashing down. My mother's Alzheimer's disease took a major turn for the worse, and the responsibilities and challenges of resuming a medical practice seemed to overwhelm me. In January 2009, I was readmitted to NYU, imminently suicidal. I had made arrangements to buy lethal rat poison and ingest it.

By that time, the science of ECT, thank God, had evolved, and under general anesthesia, I received ultrabrief right unilateral pulse electric current administered to the right temple area only. The electrical current elicits a generalized motor seizure blocked from motoric expression by the inhibitory drug succinylcholine. I slept pain free during the process which lasted only minutes. In less than three weeks of three times a week treatment, I experienced a full recovery this time marked by absence of suicidal feelings, improved self-esteem, and the resumption of hope for the future.

In contrast to the treatments of 2003, the side effects were minimal. I was alert, clear-headed, and completely functional within an hour of treatment and experienced no lingering cognitive effects. It was decided with informed consent that I would receive monthly maintenance ECT

treatments on an outpatient basis to reinforce the remission and to prevent relapse. I've continued these sessions for nearly two years. I've experienced no discrete depressive episodes and have had no problems with memory, concentration, or abstractive reasoning. On the days of treatment, usually scheduled early in the morning, I set aside the rest of the morning to sleep off the effective of the general anesthesia. By afternoon, I'm ready to go and, in fact, once taught a seminar for medical students at Mount Sinai in which I demonstrated the absence of side effects from my own ECT treatments.

While other pharmacological treatments had been useful in achieving partial remission of depressive symptoms, only ECT has eradicated entrenched suicidal ideation and allowed me to function at my highest capacity. Thanks to the improvement in the medical devices and more sophistication in the anesthesia techniques, I feel now as well as I have in my entire life. I don't know how long treatments will continue, but to date I'm very satisfied with the results. I'm convinced that I would be dead if ECT were not available to me.

Thank you for the opportunity to speak here. Thanks.

DR. BROTT: Our next scheduled speaker is Mary Rosedale.

DR. ROSEDALE: My name is Mary Rosedale. I'm a board certified psychiatric nurse practitioner and an Assistant Professor of Nursing, and I'm here as a representative of the American Psychiatric Nurses

Association which has prepared a position statement on this issue.

The American Psychiatric Nurses Association, APNA, was founded in 1986 and is the largest professional association of psychiatric nurses representing both psychiatric nurses at the basic level of practice, RNs, and psychiatric nurse practitioners and psychiatric clinical nurse specialists. APNA is the only psychiatric organization that is inclusive of all RNs in the United States as well as having international members and represents over 7,000 members. It also has a panel of mental health consumers that offer advice to the governing board in formulating policy statements.

We are pleased to offer comments in support of the use of electroconvulsive therapy in the treatment of severe depression that has been shown to be refractory to medication.

For more than seven decades, psychiatric mental health nurses have provided customized treatment to patients receiving ECT. In addition to advancing evidence-based treatment modifications and developing advanced practice nursing roles, psychiatric nurses have been vital patient advocates, assuring that patients receiving accurate information about ECT, educating the public and influencing public policy.

ECT is an effective treatment for severe depression. The literature on the efficacy of ECT for treatment of depression is as extensive as for almost any other medical treatment. Moreover, ECT is a rapidly acting

treatment. Multiple trials of adequately administered ECT have demonstrated a speed of antidepressant response for patients experiencing severe major depressive episodes. For patients who urgently need relief of depressive symptoms, such as those who pose a danger to themselves or to others, ECT can be the treatment of choice. For patients who have not responded to or cannot tolerate medications, ECT may be the safest alternative.

Modern techniques and brief pulse devices have increased the safety of ECT. Morbidity and mortality are less than that of childbirth, with 1 to 2 deaths per 10,000 patients treated with ECT. Advances in anesthetic and ECT administrative techniques have greatly mitigated side effects.

The most significant concerns about ECT are the treatment-related cognitive impairment, but even this symptom has been markedly reduced with advances in ECT administration. ECT remains the treatment of choice for severely depressed patients with other concurrent health risks.

And so in conclusion, it is the position of the American Psychiatric Nurses Association that ECT is a proven therapy and that future and further clinical trials are not necessary to establish its safety and efficacy. APNA encourages the FDA to classify these devices in an appropriate manner to assure that patients have access to ECT while at the same time assuring that ECT devices function safely and in the manner intended. APNA believes that ECT operated by properly trained

professionals and in circumstances of medical necessity offer patients with severe depression an option that would otherwise be unavailable. APNA stands ready to assist in the development of additional standards of practice in the application of ECT.

Thank you for your attention, and we urge you to reclassify these devices in a manner that provides the proper balance between access to evidence-based treatment and patient safety. Thank you.

DR. BROTT: Donald Johnson.

MR. JOHNSON: I thank you for this opportunity. Forgive me my emotion. I was here at the FDA in 1985 and testified, and later on that year, the National Institutes of Health, the National Institute of Mental Health, had a two-day consensus conference on electroconvulsive therapy.

I don't have a memory. I don't know if it's because I argued with a psychiatrist and he dumped me in the locked ward and shocked me five times. I became violent. I tore my nails off grabbing onto the door, and he said after five times, he says, sometimes they don't help people.

The way I got in there was arguing with him. I had trouble with headaches. I've learned since then it's because I was deprived of coffee. I had a drunken acting first sergeant that had confined me to quarters, and he got away with it, and I had headaches and I complained. So I'm psychiatrically labeled. But I became a physics teacher, and I have degrees in mathematics and physics for Carver Arnum Research (ph.) and I

decided to go teaching physics.

I would ask any of these professionals here for the physics. You know, they say physics is an example. If I had a --

DR. BROTT: Can you stay close to the microphone so we can hear you.

MR. JOHNSON: A little physics to see if there's any -- this is high school physics. High school physics. If I had a 15-pound baby, talking about 200 joules, and when they talk about low treatments, every one of you that's involved in ECT knows that if they don't make a grand mal seizure, it doesn't count. Give it again. Turn up the voltage. All right. 200 joules. How high would I have to drop a 15-pound baby to have the equivalent of one shock treatment? All you professionals here. How high would I have to drop a 15-pound baby to have the same energy or how many pistol slugs would I have to shoot into its brain? This is just mechanical equivalence, high school physics. Anybody?

A joule is the energy of one kilogram being lifted a tenth of a meter. It's equivalent to dropping a baby from a 10-foot high building.

At the 1985 National Institutes of Health conference, I gave them the Winchester ballistics sheet from Winchester and a Thymatron electroconvulsive device showing the energy equivalent to three pistol slugs to the head.

Now, they use autism to justify it and use depression. Did

anybody watch the BBC with the G-20 last month? Obama was in South Korea, and BBC had a little spot on it, "The Devastated Seoul," now one of the most thriving affluent societies, and they said how much appreciation. They went back and said, "But there's a problem." They've got the highest suicide rate in the world. Between the ages of 10 and 40, the major cause of death now is suicide in Korea. Is it because they need a shock treatment? It wasn't like that before the war? Affluence.

My mother had to help a baby that was dying from diarrhea and vomiting from the woman next door. She was a good woman, but she had been raised in daycare and she couldn't bond to her baby. My mother was a teacher. So she cared for the baby during the summer, and it recovered and thrived.

We're talking about depriving children and then punishing them for the effects, whether it's autism or depression. Look into it. The breakdown of the home is what destroyed Korea. Yes, it's an affluent society, the highest suicide rate in the world. You want to electroshock all of them? They pay now $1,000 a treatment.

DR. BROTT: You've got 30 seconds to wrap up.

MR. JOHNSON: They pay $1,000 a treatment. Somebody just said, professional testimony, we need a million people treated. $1,000 million we're going to pay a year for this. Thank you.

DR. BROTT: We now will enter a phase where the Panel

members will have an opportunity to ask questions of the speakers. Before we start doing that, Dr. Claudio wanted to make a couple of comments about the process.

DR. CLAUDIO: Yeah, Dr. Ross had asked before how do we register the people. In this case, the FR notice was published on November 26th. We had a deadline until January 6th for people who wanted to speak here at the Open Public Hearing. During that time, they were registered in the order that the registrations were received. If they could not register at that time, they could submit written submissions until January 14th to me by e-mail and those submissions were scanned and sent to you in all the CDs. After that, if they were not able to submit any written submissions, there was a docket open from the time of the FR publication until January 25th, and those comments are also in the CD that the Panel received.

DR. BROTT: Thank you. For the Panel members, if you have a question for a specific speaker, if you can identify that speaker and then that speaker could come to the microphone, and again, as a reminder, when you speak, Panel members or speakers, please identify yourselves in the microphone. So do we have any questions of any of the speakers?

Yes, Dr. Duff.

DR. DUFF: Yeah, Kevin Duff. Unfortunately I don't know the names of the specific speakers. So this is really for any of the physicians that currently utilize ECT treatment. I'd like to know a little bit more about the

informed consent process, that apparently there are some APA guidelines on this. I don't have access to that.

DR. BROTT: Dr. Lisanby, do you want to address that?

DR. DUFF: But what type of information are they given about the risks and potential benefits associated with the ECT treatments? What's kind of standard of practice for information that gets communicated to them?

DR. LISANBY: So my name is Dr. Sarah Lisanby. I'm happy to answer your question about the informed consent process for electroconvulsive therapy, which is a very detailed and important process, and guidance is given to practitioners in the APA Task Force guidelines on ECT, and it includes a sample of the informed consent document.

The informed consent process is more than simply having the patient sign a form. The form itself documents a process that occurs between the clinician and the patient, and usually also family members are involved in this, where all of the risks and benefits are carefully detailed, the alternatives to treatments are discussed. Alternative treatments besides ECT include medications or psychotherapy, and these risks and benefits of the alternatives are weighed relative to the risks and benefits of ECT.

This process is quite extensive, and we do carefully go through each of the major and most common side effects of ECT. In particular, the different aspects of the effects of ECT on memory are very thoroughly

covered. Also the risk of the anesthesia itself, how long these risks are expected to last, how long their therapeutic benefit is expected to last, all of this is discussed.

DR. BROTT: Could you walk us through a patient? You do these treatments?

DR. LISANBY: Yes, I am --

DR. BROTT: So in terms of the timing, is it done on the day of the treatment, before the treatment, and just a specific example and how long it takes, how long the form is?

DR. LISANBY: Sure. I'm happy, this is Dr. Lisanby again, happy to answer those questions. So I am an active ECT practitioner, and I do see patients clinically and evaluate them for the treatment of depression, not only for ECT but also for other treatment.

DR. BROTT: Could you stick to answering the question?

DR. LISANBY: Yes. I want to describe in answer to your question the --

DR. BROTT: Please stick to the specific answer because we may have a number of questions.

DR. LISANBY: Okay. I typically perform the informed consent process days to weeks prior to the first treatment when the patient comes for a consultation to discuss whether ECT or other treatments may be appropriate for them. So it's not typically done, in my practice, on the day

of the treatment, but rather in the days to weeks prior to the first treatment. Usually this is, in my own practice, in collaboration and in the presences of the family members of the patient's choosing. Often it could be the spouse or other family members who are present, and how long the process takes is variable. I would say at minimum we spend at least, in my practice, 90 minutes in my initial consultation, but the duration of time is variable. The informed consent process could last beyond that initial visit. It could be on follow-up visits.

DR. BROTT: How long does the consent process take? I'm sure you don't take 90 minutes with the form. How long is the consent process itself with the form?

DR. LISANBY: Well, I would say once I've presented the form and we're at that stage -- and the typical informed consent forms are several pages long. Our sample APA ECT consent form, I don't have a copy with me, but it is several pages long. The one that we used at our hospital was multiple pages, and it does take time for the patient to read through this, for the family to read through it. Oftentimes they take it home and come back at the next visit and discuss it and answer their questions. So to answer your question, how many minutes this takes, it is variable. I would say, you know, minimum in my own personal practice, at least 30 minutes face-to-face giving them the form initially and then oftentimes they come back for another visit and we continue the discussion, which is why when I did say 90

minutes, I wasn't exaggerating. It is a process that --

DR. BROTT: Thank you.

DR. LISANBY: -- couple of days.

DR. BROTT: Thank you. Other questions. Ms. Carras.

MS. CARRAS: Can I ask a follow-up of Dr. Lisanby?

DR. BROTT: Yes.

MS. CARRAS: I wonder how you characterize the rate of persistent memory loss to patients that you're discussing ECT with?

DR. LISANBY: Yes, this is Dr. Lisanby. I'm happy to answer your question about how I characterize the rate of memory loss.

MS. CARRAS: Persistent memory loss.

DR. LISANBY: The rate of persistent memory loss. So in discussing the risks of memory loss with patients who are contemplating ECT, I explain the different types of memory that could be affected by the treatment. One distinction is memory for the ability to learn new events, which is anterograde amnesia. The other form is memory for past events, which is retrograde amnesia.

The evidence shows, and I explain this to patients, that anterograde memory, which is the ability to form new memories, that is typically a transient problem that is not, according to the published literature, anterograde memory loss has not been shown to be persistent over the long term.

So when you talk about risk of persistent memory loss, what we're referring to is the retrograde amnesia, and there are different types of retrograde amnesia depending on how long in the past the memories were formed, and so that can be broken up into recent events and remote events. Recent events could be events that happened in the days or even hours prior to the treatment, and remote events could be the weeks to months prior to the treatment. And I explain to patients what the published evidence suggests about the differential vulnerability of recent and remote memories to memory loss and persistent memory loss, and this has been thoroughly studied.

To summarize that, the events from earlier in life, from the months to years prior to the first treatment, the effects of ECT are less on those more remote memories, whereas the effects of ECT have been more seen in the recent memory, a closer time to the treatment, and so even though there may be cases where there is some memory loss for the near term or remote events, over time, these memories begin to come back. Evidence suggests that there is some recovery of some of that memory, but in terms of persistent retrograde memory loss, that has been, according to the evidence, found to be most marked for the events that occurred close in time to the treatment. So --

DR. BROTT: Thank you. I think we will be hearing a lot about that in terms of the presentation later today. Dr. Kim.

DR. KIM: This is addressed to Dr. Narrow. I believe you're representing the Task Force from the APA. I couldn't help but be struck by the testimony of Dr. Boger, the difference between 2003 and '9 and the type of treatment, and so two questions. One is does the APA Task Force have an updated position on various parameters for ECT since your 2001 recommendations? That's one question. And, currently, what's the feeling of the Task Force in light of the kind of experience that Dr. Boger expressed? Is there a strong recommendation about what is more accepted or acceptable practice using these machines?

DR. NARROW: This is William Narrow. The APA is currently updating its practice parameters, it's guidelines for ECT, and I am not actually staffing that Task Force, although in the audience we do have a number of our speakers today are participating in that and I think will probably speak as to where the Task Force is in terms of the specific questions you have.

DR. BROTT: I think we can maybe see if we can readdress that after the presentation. Is that acceptable? Or is there someone other than Dr. Lisanby? She's been up there for a little bit.

DR. WEINER: This is Dr. Weiner. This is Richard Weiner, and the Task Force is reviewing the literature dealing with the kinds of treatment parameters that were covered in that presentation, and the guidelines will be updated. The work is nearly complete on that. I don't know that there's

been a final determination on exactly how the wording would be in the guidelines, but certainly they are being updated in conjunction with the most recent literature that's been published on these parameters.

DR. BROTT: Thank you. Dr. Good.

DR. GOOD: David Good from Penn State. Thanks to all those who presented or gave presentations today. It was very informative, and my personal thanks.

I have a question regarding a very small part of the FDA presentation, and that's the figure that was given that over 100,000 individuals in the United States receive ECT each year, and it was also mentioned that there seems to be an increase in numbers in recent years, and I don't know if this is based on hard fact or this is just impression, but maybe this is a good question for Dr. Narrow or Dr. Weiner.

With the explosion in psychopharmacological treatments over the last 10 to 15 years, I wonder if there's an explanation why ECT is increasing, if that's really, really true?

DR. WEINER: This is Dr. Weiner again. To tell you the truth, I don't know if that data is valid. I'd like to know where that comes from. I'm not at all convinced that the use of ECT is increasing. I could only speculate as to use. My guess is that it's probably roughly the same. It's not increasing or decreasing.

Yes, there's been a lot more psychopharmacologic agents

coming out all of the time, but the fact that ECT is still around reinforces the idea that it is more effective, that none of the new drugs coming out appear to be more effective than the older ones, and so there's no reason to think that they would have a detrimental effect on the utilization of ECT.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Yes, Dr. Weiner, in your presentation, you stated that, David Mueller here, the major depressive episodes recent --

DR. BROTT: Push your button, sir.

MR. MUELLER: Sorry. Let's see. NIMH sponsored multicenter trials using contemporary U.S. ECT devices have demonstrated that modern evidence-based techniques associated with the response and remission rates is substantially greater and more rapidly achieved than reported elsewhere. We have a whole packet of information here, different articles, and I'd like to ask, are those NIMH studies in our packet, or which studies are those?

DR. WEINER: I believe they are. I think the multicenter trials are primarily those by a group called the CORE group -- I don't remember the exact wording, but Dr. Kellner who's here can speak to that. He's been leading that group for quite some time -- and a group that's been led by investigators at Columbia University, but it involved a number of other academic institutions, and Dr. Lisanby can speak to that group's work, but I would think that those studies were made available to the Panel. They're really the most prominent and largest studies dealing with the efficacy and

safety of ECT in recent years. So I'd be very surprised if they weren't.

DR. BROTT: Yeah, they, in fact, were provided to us. I don't know how many. I didn't really count them, but there are quite a number of studies that were provided to us, CORE being one study group.

Dr. Ellenberg, at one point you had a question?

DR. ELLENBERG: Yes. Thank you. This is Jonas Ellenberg speaking. Can someone that presented this morning at the society level care to characterize the uniformity of the consent forms that are used currently in going onto ECT? Is this a mishmash of forms that are less, more complete, what have you, or are we following a standard?

DR. BREEDING: John Breeding. That's certainly my experience. I just want to speak to that real quickly because Texas --

DR. BROTT: Identify yourself again.

DR. BREEDING: Yes. John Breeding.

DR. BROTT: Okay.

DR. BREEDING: I wanted to speak quickly to that because Texas has right now the most stringent informed consent law in the country. It was passed in 1993, and so it's kind of a model form in the sense that it requires really looking at the issue of brain damage and memory loss, also looking at the state of mind of the person who's receiving the consent. There's a real issue with informed consent if you are already in a clouded state of consciousness, you know, whether you can read clearly and

understand the information. So that's in there. So there's things like that, and most states don't have informed consent laws per se. What you have is this APA Task Force recommendation, and I've talked to literally hundreds of people who have received electroshock, and as in Evelyn Scogin's testimony, it's hard to reconstruct. She doesn't remember it, you know. So her sister was there to say what she was told, which was pretty minimal, you know, but I've seen where someone who really has, as this doctor stated, really taken some time with somebody, and I've seen a lot of other instances where that's not the case. Most states don't have informed consent laws.

And, also, the reason why it's difficult to get the data on the numbers, one reason anyway, is because most states don't have reporting laws. Texas is one of the few that does along with California and Vermont.

I want to, if it's okay, I have an article on informed consent in electroshock and --

DR. BROTT: If you can give it to the staff so that they can distribute it to us, and I guess in terms of the informed consent, and Dr. Ellenberg's question, is there someone from the APA who could answer, you know, the timing question with Dr. Lisanby. Has anyone studied recollection of the informed consent process?

DR. BREEDING: That's a great question.

MS. TENNEY: Hi.

DR. BROTT: Excuse me. This is a specific question that I don't

think you would be able to answer, okay. So it's a specific --

MS. TENNEY: About the importance of the consent?

DR. BROTT: No, no, it was a specific question about whether or not a study has been performed to examine recollection of the informed consent process and published in the peer review literature.

DR. BREEDING: I do have one --

DR. BROTT: Do you have an answer to the question? If you do, come back.

DR. BREEDING: John Breeding. There's a report by the Wisconsin Coalition for Advocacy, 1995, that looked at informed consent guidelines application in that state's system, and it's referenced in this article I gave you. What they found was pervasive and systematic violations of that state's informed consent guideline on ECT.

DR. BROTT: Thank you.

DR. BREEDING: Another study by --

DR. BROTT: No, that's --

DR. BREEDING: -- in 1987 --

DR. BROTT: That covers it. Thank you. It's Dr. Narrow.

DR. NARROW: Yes, this is William Narrow again. We're not aware of any study that has addressed the issue of recall of the informed consent process.

DR. BROTT: Thank you. Questions? Ms. Carras.

MS. CARRAS: I have a question for Dr. Weiner. Dr. Weiner, I did a lot of outside reading to prepare for this appointment, and I was wondering if you could answer Linda Andre's assertion that you have worked for companies that make electroconvulsive shock machines.

DR. WEINER: Yeah, I'd be glad to answer that. Earlier in my career, I did a small amount of consulting with the device companies. As I said, I was trained in electrical engineering and systems engineering. So I was familiar with more than most psychiatrists are with the electrical properties and gave them advice. It was never more than a miniscule part of any income I had.

DR. BROTT: When was the latest date of that activity?

DR. WEINER: The latest date of that activity, I don't recall, but I don't believe any of it was within the past 10 years, but let me add that some of the research that I did in conjunction with a colleague, Dr. Krystal, resulted in a patent by Duke University which is licensed to one of the companies, MECTA, and to avoid conflict of interest, I do not personally receive royalties from that.

DR. BROTT: While you're up there, do you practice, do you administer ECT?

DR. WEINER: Yes, I do. Yes, I do.

DR. BROTT: And, you know, I noticed you mentioned you have this engineering background. What machine or what device or devices do

you use?

DR. WEINER: Well, I've used both the presently marketed ECT devices.

DR. BROTT: And you currently use both of them?

DR. WEINER: Yes, I use one more than the other just because that happened to be the one that we had.

DR. BROTT: And how do you, you know, how old are they, and how do you maintain them, and do they ever develop problems? How do you detect problems? What can you tell us about these devices in everyday use?

DR. WEINER: Well, they're pretty robust. They tend not to break down, and if there's anything we think wrong with it, then we have it either fixed locally -- there are service manuals that come with the machines -- or we send it back to the factory to work on, but that's been very rare that something like that has happened.

DR. BROTT: Could you give us any recent examples with the date? Like the last time it broke down was 1950 or, you know, 19-whatever and what it was.

DR. WEINER: Oh, I think, you know, two, three years ago, one of the knobs that control the chart drive got loose and wasn't functioning. We had that fixed.

DR. BROTT: Is there any standard maintenance or, you know,

in the manual that comes with it or who's responsible for the machine just to see that it's doing what it's supposed to do? I presume this is in a medical center, hospital setting?

DR. WEINER: Right, right. It's subject to the same medical equipment testing practices that any medical equipment is within a medical center that the medical center tends to have policies and procedures for. They're not specific to ECT but to all medical devices.

DR. BROTT: What does that mean in terms of this device? Do they come in and look at it or do anything with it?

DR. WEINER: They generally look at it and make sure that there's no problems with leakage current. There's not specific tests that they generally carry out. There have been some places that have done those. The service manual includes instructions on how some of those things could be carried out, but there's not specifics, and that's true for most medical devices that are used in hospitals.

DR. BROTT: Other questions of the Panel members? Dr. Ellenberg.

DR. ELLENBERG: If you wouldn't mind staying up. This is Jonas Ellenberg. Is there a fail-safe mechanism on the ECT machines that would not allow a certain current level with a certain level without an override by a senior official at the hospital or are they --

DR. WEINER: Yeah, there are constraints on the maximum

output charge that actually come actually through the FDA. The FDA has maintained a limit which goes back a number of years so that there's been no increase allowed in quite a number of years.

DR. ELLENBERG: That's not my question. Does the machine regulate that? Does it stop?

DR. WEINER: Oh, you cannot --

DR. ELLENBERG: You cannot do it.

DR. WEINER: -- set it to go higher than that. Plus, there's voltage limiting built into the machine. So if the impedance was apparent, the machine would shut off.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Yeah. My question may be better directed at FDA, but I'll let you decide. It seems like some of these questions are falling in the area of postmarketing surveillance, and maybe we'll address that later today, but it wasn't clear to me what kind of ongoing postmarketing surveillance there is, what kind of reporting there is of like what you were just addressing in terms of hardware failures, you know, unusual, serious adverse events. So I'd like to get a little bit of a picture of that.

DR. BROTT: Dr. Eydelman, would you like to respond to that?

DR. EYDELMAN: I would like to defer the questions to the FDA to the FDA question period in the afternoon, and this time is dedicated to the questions to the open public speakers.

DR. BROTT: Ms. McElveen?

MS. STOKES McELVEEN: Yes. Dr. Weiner, I have a question for you. In your written statement, you indicated that the benefits and risks of any treatment are relative as opposed to absolute. Keeping that in mind, I'd like to ask you, based on your experience, have you studied outcomes relative to particular populations such as those patients who may have coexisting morbidity or particular to children or to seniors?

DR. WEINER: I've not specifically studied that myself, but I'm familiar with a lot of that literature, and I'm not sure what you mean about what specifics in terms of those findings that you're looking for.

MS. STOKES McELVEEN: In other words, if you have a population, individuals with comorbid conditions --

DR. WEINER: Yeah.

MS. STOKES McELVEEN: -- in that particular instance, does the risk outweigh the benefit based on your experience?

DR. WEINER: No, no, it does not. I mean if you look at the elderly, the risk of any treatment go up with age because of the associated medical comorbidity. It's not age itself. It's the associated medical comorbidity. In my presentation, I noted one study that was done from the University of Iowa where they did long-term follow-up of a number of elderly individuals, some of whom received ECT, some of those who didn't. They tried to manage those for level of medical comorbidity, and what they

found is the multiyear survival rate was significantly higher for those people who had received ECT than those who did not.

MS. STOKES McELVEEN: Okay. Thank you.

DR. BROTT: Dr. Good.

DR. GOOD: So this may be the only chance I have to ask this question. So this is for any of the practitioners of ECT. I'm a neurologist and the fact that ECT causes seizures may be the reason for efficacy, if efficacy does exist, and might also be one of the reasons why some of the memory problems occur.

So I know that EEGs are used to monitor the seizure activity. I'm sorry that I don't know the answer to this. It's been years since I actually personally watched an ECT, but how long does the seizure last and do measures ever have to be taken to terminate the seizure?

DR. BROTT: Let's get Dr. Fochtmann. Is Dr. Fochtmann here? Can you try to answer those questions?

DR. FOCHTMANN: In general, the seizures that's induced lasts from 20 to 40 seconds. There are occasions when the seizure does go on a bit longer than that, and generally after approximately 90 to 120 seconds, we would give first either more of a barbiturate anesthetic if that's what we were using for the anesthetic or a benzodiazepine to break the seizure. That in my experience is almost invariably successful in stopping the seizure activity at that point.

DR. BROTT: Frequently in the absence of ECT, just when a seizure occurs spontaneously, the patient may have another one, and we speculate something perhaps happens to the seizure threshold with a spontaneous seizure. Is that something that you see with ECT-induced seizures, a second seizure?

DR. FOCHTMANN: I've personally only seen it in one individual who had many other concomitant difficulties both in terms of their underlying brain function. In general, ECT actually has anticonvulsant effects which seems somewhat paradoxical, but it actually after an initial ECT seizure becomes more difficult, even if it's a very brief seizure, oftentimes for an adequately -- a seizure of an adequate duration to be induced and also over time.

DR. BROTT: How do you know that? Is that the next time? It's harder to get the seizure at the time of the next treatment? Is that what you're referring to?

DR. FOCHTMANN: Sometimes the seizure threshold does appear to go up. There have been some studies that show at least some increase in that. So the evidence is, depending on the study, more variable, but there is some suggestion that it actually has some anticonvulsant effects.

DR. BROTT: Dr. Duff.

DR. DUFF: We've talked some about the consent process that's associated with ECT, but I don't know yet we've discussed how

informed that consent process actually is, especially since some of the patients, or at least what we've heard about, are patients that are sort of designated for ECT are severely depressed, likely have delusions or hallucinations or catatonic. How informed can their consent actually be? And I'd actually like to hear -- I mean we've heard from some speakers from the public who are either patients or families of patients who are proponents of ECT, and I'd like to hear what they recall or their experiences with the consent process, not from the practitioners who actually administer ECT.

DR. BROTT: Yeah, could you identify yourself?

MS. HERSH: Yes, I'm Julie Hersh, and I had ECT both in 2001 and 2007. What I remember in 2007 is going up and down the elevator. I can remember talking to my psychiatrist, looking at the consent form, being very concerned about it because, you know, I've heard stories like everybody's talked about today where people had issues with memory function and brain function, and I really did not want to do the procedure, and so I think I went down, I thought it was twice, but I had actually written about this. My husband said it was three times, up and down the elevator, and finally went back and signed the forms and went through.

So it was, I felt like it was -- in fact, what's ironic about it is the consent process is so frightening that I think a lot of people are deterred from doing ECT because you're so fully warned about the negative effects.

DR. BROTT: Could I ask you while you're there --

MS. HERSH: Sure.

DR. BROTT: -- when did you last have ECT?

MS. HERSH: 2007.

DR. BROTT: And could you tell that you had had it? And if you could, how could you tell?

MS. HERSH: Definitely. I think what's interesting is the comparison like you were talking about earlier. When I had it in 2001, I had a bilateral ECT, and the memory issues were more severe, and they were all short-term memory issues. For example, I can remember stopping at a stop light and trying to remember how to get --

DR. BROTT: What I'm really interested in is immediately afterward, you know, so you get it at noon.

MS. HERSH: Right.

DR. BROTT: Between noon and 6:00 p.m. let's say.

MS. HERSH: Well, yeah. You feel, you probably feel fuzzy. You feel fuzzy, and I felt fuzzy and maybe a little bit more slowly thinking but not dramatically. Almost -- I think it might have been more from recovering from the anesthesia than --

DR. BROTT: Did they ever tell you that at that particular time you didn't have a seizure in response --

MS. HERSH: No.

DR. BROTT: -- to the stimulation? Dr. Boger, could we get you up to the microphone, please?

DR. BOGER: Yes, Dr. David Boger.

DR. BROTT: Yeah. And the same question to you. With your -- do you still, I would think you should undergo an informed consent process each time?

DR. BOGER: Each time.

DR. BROTT: And what's your recollection of the informed consent process? You know, what's the timing of it and what do you remember about it?

DR. BOGER: The first time I was treated with ECT, I had an extensive discussion about risks and benefits before taking it. I was quite depressed at the time, really morbidly suicidal, but I was cognitively not impaired. I was able to make competent decisions. So I listened to the practitioner talk about the risks and benefits. I was thinking about dying imminently. So it seemed like a pretty good choice for me.

DR. BROTT: And could you tell that you had had it? And could you describe the minutes and hours after --

DR. BOGER: Absolutely.

DR. BROTT: -- you had it?

DR. BOGER: The first hour afterwards, I'm always recovering from anesthesia. I'm sort of groggy, but then it's a very rapid return to

normal function. I wouldn't probably drive a car for the first couple of hours because after I had the treatment, I don't think my reflexes were probably as good, but again I think that's more the effect of anesthesia than anything else. After five or six hours, I don't notice anything. I don't have a headache. I don't have any known cognitive impairment.

DR. BROTT: Did you ever have a time where you were told that the stimulus did not induce a seizure?

DR. BOGER: No, no. I have had an incident or two where the seizure was not the recommended length of time.

DR. BROTT: We've got, you know, we've heard about different electrode placements --

DR. BOGER: Right.

DR. BROTT: -- and so forth. We'll have a report from the FDA, but we may not have this opportunity again. We've got people with experience with thousands of these procedures. Is there anyone in the audience who has experience with the electrical stimulus not inducing a seizure?

MS. WINKLER: I do.

DR. BROTT: Could you come to the podium?

MS. WINKLER: I'm Barbara Winkler. I had my treatments at Yakima Memorial Hospital in Washington state. There were a couple of times when I was told by the psychiatrist that he had to hit the button a

couple of times because my seizure threshold apparently wasn't allowing me to go into a seizure that was long enough that he wanted that met that 20 to 40 seconds, and he always said he wanted to --

DR. BROTT: So, so you always left having had a seizure.

MS. WINKLER: Always left had a seizure --

DR. BROTT: Okay.

MS. WINKLER: -- and I always felt really good.

DR. BROTT: Could I have Dr. Fochtmann up there again? Okay. What I'm driving at is we're reading about sham, and I'm wondering, you know, how sham is sham? Sham ECT. You know, we've got a problem, you get anesthesia, drugs, and so forth.

DR. FOCHTMANN: Right.

DR. BROTT: What has been done to examine the quality of blinding with sham procedures? What's the data?

DR. FOCHTMANN: In the older studies that were done.

DR. BROTT: In any studies whatsoever. In other words, you know, we have standard procedures to assess --

DR. FOCHTMANN: Right.

DR. BROTT: -- blinding.

DR. FOCHTMANN: Right.

DR. BROTT: What has been done to assess blinding with sham ECT?

DR. FOCHTMANN: My understanding of the literature in the past with the sham ECT was done in an era before we had the rigorous sorts of blinding requirements and blinding procedures that we have now, but Dr. Weiner, do you have more of a sense of recall on the data?

DR. WEINER: Yeah, I'm not aware that that was assessed, and it's unfortunately not a feature of other kinds of studies that have looked at sham treatments particularly during that era. It just wasn't something that was done. It would have been good to do.

DR. BROTT: Okay. Any other questions from the Panel? Dr. Kim.

DR. KIM: Yes, I have a question for Dr. Sullivan from ISEN. I just wanted to get a sense of, it's a variation of my question to the APA, which is that you specifically mentioned the benefits of the unilateral brief and ultrabrief pulse. Is there some kind of a policy or practice that you as an organization see as the emerging standard or what you expect your membership to do related to these parameters?

DR. SULLIVAN: This is Dr. Pamela Sullivan. And to answer that, what our organization does is we try to include in our national meetings and actually international as well which occur on a yearly basis during the time of the American Psychiatric Association meeting, usually at the same location, and what's looked at is research in particular. We have presentations to that effect. We have a good number of clinical researchers. We also have clinical

practitioners as well, and many of those do both. Our policies actually are based on right now what I would want to refer to as what the APA Task Force is doing.

Many of our members are joint members of both the Task Force itself, and I had actually taken part in being on a committee in the APA which no longer actually exists because they had changed their membership groups. So the APA Task Force could probably answer that better, and that's what we --

DR. BROTT: What is your sense of the variability and practice among practitioners of ECT in this country?

DR. SULLIVAN: What I would say is that several articles came out. I didn't mention in my presentation, but certainly *New England Journal of Medicine* as well as the *Journal of the American Medical Association*, JAMA, both have had articles, also the A*rchives of* G*eneral Psychiatry*, and in that particular journal in the year 2000 in particular, there were two separate articles that came out, one by Harold Sackeim and another with one of the lead authors being Dr. Vaughn McCall. Out of both of those, it was found that the right unilateral ECT electrode placement appeared to have significantly fewer cognitive side effects. And so I would say that our members in particular would tend now to be using the unilateral --

DR. BROTT: That's something that's puzzled me a little bit, and Ms. Tenney, we want to hear from you, too, before we leave, but a little

question on that. You know, the seizure is supposedly what makes the difference and, you know, we've been given and we've done our homework. There's a lot of literature about the electrode placements, sine wave, brief pulse, voltage and, you know, what's the connection between what's supposed to be primary, which is the seizure, and the electrode placement? And what's the data?

DR. SULLIVAN: Well, the sine wave is certainly -- the machines that produce the sine wave, of course, are not the machines that are currently marketed and for the reason --

DR. BROTT: Do they produce shorter seizures, longer seizures, more violent seizures? And is there any evidence on the degree of seizure correlating it to the type of electrode or type of electric pulse?

DR. SULLIVAN: Not to my knowledge. What I would say is that the machines themselves, of course, each because of the electrical voltage do produce seizures, and what it is, is the actual individual seizure threshold of the person, the patient that's receiving the treatment is what determines how long the seizure lasts. There are also other variables. I'm not going to go into all of those details but, you know, based on age, based on a variety of other possible variables.

But each person has an individual seizure threshold. Everybody sitting here right now, we all have that. We really don't know what it is. Of course, one way to find out would be if you did receive ECT

and then it could be determined. And those can vary.

We do know that it tends to be that the threshold is higher in older individuals and particularly in male.

DR. BROTT: You mean it takes more electricity?

DR. SULLIVAN: It can, yes. On the average. Again, this is on the average. You know, we always have that spectrum.

DR. BROTT: Okay.

DR. SULLIVAN: But, yes.

DR. BROTT: Okay. Thank you. Before we leave, and we only have a couple of minutes, Mr. Moxon -- you don't have to come to the podium -- Dr. Breeding and Dr. Fisher, I think that if you could come up with some citations that relate to pathological examinations that would show brain damage, or MRI imaging which shows brain damage, and you could supply, any of the three of you, citations from peer-reviewed literature to the FDA staff, that would be appreciated. If you want to --

MR. MOXON: When would you like that?

DR. BROTT: Pardon me.

MR. MOXON: When would you like that?

DR. BROTT: Whenever you can give it to us. Of course, it would be great -- sometimes we go to Panel meetings, and they say you have to have it done after lunch, believe it or not.

MR. MOXON: Well, you'll find that there's a great amount of

information.

DR. BROTT: We just need for you to, whatever they are, if you could supply them to the staff. Okay.

MR. MOXON: All right.

DR. BROTT: Ms. Tenney, would you -- yes.

MR. MOXON: May I clarify something on your last question? You asked about the seizure as the item and unilateral versus bilateral, and obviously you want to have a seizure, an appropriate seizure, but what you may not have noticed in the materials that have been provided by others is that the manufacturers and proponents have all now agreed that it's not a seizure that causes -- just the seizure provides no therapeutic effect. Therefore, they up the voltage, the dosage, the electricity two to four times above what it takes to cause a seizure. The electricity is what causes it. The electricity is what causes it.

DR. BROTT: Well, we're going to hear extensive presentation, but thank you for that. Ms. Tenney.

MS. TENNEY: Thank you. Besides being in special education when I was 15 years old, I'm a Ph.D. candidate, and I've spent a lot of time working on issues of informed consent. There's an article by Michael Cummings and his colleagues called "How Informed Is Informed Consent?" where they looked specifically at mental health treatment and found that well over half of the people that were saying to be giving informed consent

weren't. Informed consent is actually two different processes that need to be held out. The first is informing, which contains four different things of giving information, giving options, giving time, and then reassuring that the person understands what you're talking about, and the consent, which is a three-step phase process which includes reviewing all the information that they have, making of the options of what they're taking or doing, and having the amount of time for somebody to then be able to withdraw that consent. One of the most important things about informed consents is that it is an ongoing and continuing process. Once the form is signed, it is not over. At any given point, somebody can revoke their consent. What's happening in many states, and in New York State specifically, is that people aren't even being given -- well, first, if you don't have all the information, you can't really give informed consent. So the idea of down-classifying the shock machine without doing any kind of safety and efficacy testing further removes the opportunity to give real informed consent.

In New York, they don't require informed consent. They take you to court, and they court-ordered 200 rounds of electroshock to somebody who they later found out was linguistically isolated and spoke Spanish, and that was why they couldn't communicate with the woman, and the state, they knew the injunction came down, and the state shocked her that day even though they knew that they were supposed to stop doing it.

And so when you're looking at forced treatment, which the

Federal Government has said is a failure of the system, and that that alternative needs to be --

DR. BROTT: I have to ask you to wrap up your answer.

MS. TENNEY: Yeah, absolutely. But I mean to understand, the most essential part of the informed consent is that it is ongoing and that it is hierarchical, and you can't get to one step without the other. So to say something happens, that somebody gives informed consent in 15 minutes, by the definition of informed consent, it's impossible because you're supposed to have a very good amount of time to be able to consider your options and weigh them out before you decide to enter into this.

DR. BROTT: Thank you very much. We're running a little over. Do we have any final questions from the Panel members? Dr. Ellenberg.

DR. ELLENBERG: Yes. Can someone comment on whether or not the kindling effect of an epileptic coming in for this sort of therapy has a lower threshold for the stimulus to cause a seizure?

DR. WEINER: This is Dr. Weiner. There's no evidence that seizure threshold goes down. There's plenty of evidence that it goes up with ECT. In fact, to get an anticonvulsant drug on the market, it's pretty much required to use a rodent model of electroconvulsive seizure to show that it suppresses that. ECT was tried as an anticonvulsant treatment in the '40s. Those of you who are neurologists probably heard the name Foster Kennedy. He was co-author on a study where they treated patients who had no

psychiatric disorder at all but had grand mal epilepsy, and ECT was found to be an effective treatment. It's not used for that anymore. People use anticonvulsant medications, but actually there have been some case reports of it being used in treatment-resistant epilepsy, particularly status, and it has been effective.

DR. ELLENBERG: Thank you.

DR. BROTT: Thank you very much. Dr. Duff. We'll have to make this -- well, we'll have two more questions, and then that's it, and the answers will have to be very brief.

DR. DUFF: Sorry about that, and if this is going to be addressed later, then I'm fine with finding out later, but I'd like to know what type of training is required by someone to administer ECT?

DR. BROTT: I'm sorry. Could you repeat that question?

DR. DUFF: What type of training is required to administer ECT? Not what's recommended, but what's required.

DR. BROTT: Dr. Lisanby, your answer has to be very brief.

DR. LISANBY: In order to administer ECT, the practitioner must be credentialed by the hospital, the facility where the ECT is being administered, and each of these hospitals have their own criteria. An example would be those at hospitals where I've worked where typically it's required that the individual be a certified psychiatrist, have received hands-on training, have performed at least 20 ECT treatments under direct

supervision of an ECT expert, have taken a course. Typically these courses are week-long courses, nine hours a day, five days a week, where they perform many ECT treatments under supervision and receive didactic training. These are CME-certified courses that have passed criteria for continuing medical education course.

DR. DUFF: And that's hospital specific? That's not required for everyone who does this procedure. Is that right?

DR. BROTT: Hospital credentialing is an individual hospital --

DR. DUFF: Right.

DR. BROTT: -- process.

DR. DUFF: So that can vary dramatically from state to state, hospital to hospital.

DR. LISANBY: No, in my experience, what I've described to you is fairly standard. I have directed one of the courses. Dr. Weiner is a real expert also. He teaches one of these courses every other week, and also Dr. Prudic, who is here in attendance, directs an ECT course, and I would say this is typical that we are training individuals who take these week-long courses because they are required to do so by the credentialing agency where they are preparing themselves to perform ECT. So I would say this is representative.

DR. BROTT: Great. Thanks. Final question. Ms. McElveen, you get the last question.

MS. STOKES McELVEEN: Yes, this is Francine Stokes McElveen. If, in fact, you're dealing with psychiatric patients, at what point do you determine that the individual has a mental capacity to understand the nature of informed consent?

DR. BROTT: How about Dr. Fochtmann?

DR. FOCHTMANN: All determinations of capacity require that an individual be able to understand and appreciate the pluses and minuses of whatever treatment decision it is. So whether it's a decision to have ECT or a decision to have a surgical procedure, you have to first of all determine whether the individual has any, for example, delusional beliefs that are having an impact on their ability to make a clear, rational, logical decision. So if an individual, for example, believes that applying the electrodes is going to cause a transmitter that someone implanted in their brain to explode, they obviously would not have capacity to make a reasonable decision.

Then you also have to look at whether they can appreciate and understand the information that's being conveyed about the risks and benefits of treatment, and when I'm speaking to a patient in the informed consent process, I speak to them about the pluses and minuses and I ask them to repeat back what their understanding is of what I've just said. I give them a chance to ask --

DR. BROTT: Is a mental status examination part of what a

psychiatrist does in this setting?

DR. FOCHTMANN: The mental status examination is part of the whole evaluative process. So if, as part of the mental status examination, there were any clues that a person lacked capacity, that would certainly be important information.

DR. BROTT: Is this patient group ever considered a vulnerable population?

DR. FOCHTMANN: I think for purposes of any research studies, individuals with psychiatric disorders are considered a vulnerable population, yes.

DR. BROTT: Thank you very much. And with that, we will have to -- did you have a final word?

DR. FOCHTMANN: There is actually a study that's actually looked at the decisional capacity of individuals giving consent for ECT, and have shown that in the vast majority of situations, individuals do not lose capacity simply by virtue of having a severe depressive disorder. So I think that that's important to note.

DR. BROTT: Thank you. I'd like to thank, on behalf of the Panel, the speakers and those who answered the questions. I think that a lot of important, valuable information was conveyed that couldn't have been conveyed effectively in any other way. So thank you very much.

We will break for lunch, and we will reconvene, since we went

over a little bit, we'll have a little less time on the break, and we will reconvene at 1:30. Thank you.

(Whereupon, at 12:43 p.m., a luncheon recess was taken.)

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

(1:40 p.m.)

DR. BROTT: So it's 1:40 p.m. We're ready to reconvene the Panel meeting. We will now hear the FDA presentation. At the conclusion of this presentation, there will be time for questions from the Panel members to the FDA presenters.

At this time, we'll hear the FDA speaker, and if you could identify each of you as you come forward. Thank you.

DR. GEORGIOPOULOS: Good afternoon. My name is Dr. Anna Georgiopoulos. I'm a Psychiatric Medical Officer at the Center for Devices and Radiological Health, Office of Device Evaluation, Division of Ophthalmic, Neurological and ENT Devices.

To review where we are in today's FDA presentation, Ms. Shulman opened with a general discussion of regulatory issues regarding device classification and reclassification, and Mr. Cunningham provided a brief overview of clinical considerations and regulatory considerations specific to ECT, including the 515(i) reclassification process.

From this point on, the FDA will present the findings from its comprehensive review of the safety and effectiveness of ECT devices. I will begin with a description of the strategy and methodology of the overall review process and then introduce the FDA safety review with aspects of our adverse events analysis. Dr. Como will review the findings of the FDA review

of cognitive and memory adverse events. Dr. Krulewitch will present the cognitive meta-analyses conducted by the FDA. And Dr. Komiyama will review the data on neuropathological changes and death. Dr. Park will then present the FDA review of effectiveness, and we'll close with a discussion of adverse events identified as key risks of ECT and potential mitigating factors for those risks.

My portion of the presentation will start with a brief description of the strategy and methodology of the overall review process. Then I will provide a specific description of the FDA safety review including presenting information submitted in the public docket and manufacturer docket. I will review safety information contained in the FDA Manufacturer and User Facility Device Experience, or MAUDE, database and review of the literature.

These sources of information were used to construct a list of all reported adverse events associated with ECT. I will conclude with a description of how the FDA identified potentially significant adverse events, events requiring further review from this initial comprehensive list.

The overall FDA review for ECT devices incorporated four basic elements: the safety review, the effectiveness review, the identification of key risks of ECT, and a consideration of potential mitigating factors for those key risks. Because in this review safety issues are paramount, I will begin with the safety review.

The sources for the FDA safety review included the public docket, the manufacturer docket, the Manufacturer and User Facility Device Experience, or MAUDE, database, and the FDA literature review. The safety portion of this review consider all articles providing a primary account of adverse events, including case reports and case series, observational studies, retrospective studies, and randomized controlled trials. In addition, the FDA examined systematic reviews, meta-analyses, and practice guidelines available in the medical literature that included information on the safety profile of ECT devices.

I will begin with the public docket. On September 10, 2009, the FDA issued a Federal Register Notice announcing the opening of a public docket to receive information and comments regarding the current classification efforts related to ECT devices. The docket closed on January 9, 2010, after receiving 3,045 response.

All responses were entered into a searchable database and were reviewed and coded according to certain key variables. The variables included the type of respondent, affiliation with an institution or organization, responses from within or outside the United States, the use of a form letter, the number of individuals represented if a group comment was submitted, the respondent's position on the reclassification of ECT, the reported effects of ECT, any reported adverse events, the supporting evidence provided by the respondent, and any focus in the comments on a

special population treated with ECT, such as elderly patients.

As you can see in the bar graph, the majority of respondents, 1798 or 59 percent, were members of the public not affiliated with an organization or the medical profession. Relatives or friends of ECT recipients constituted 378 or 12 percent of respondents. Medical, including mental health professionals, constituted 342 or 11 percent of respondents.

A majority of respondents, 79 percent, expressed an opinion against reclassification; in other words, they supported maintaining the Class III designation for ECT. Fourteen percent supported reclassification of ECT into Class II.

In addition, there were 92 group submissions. These group form letters represented 6,462 individuals against reclassification and 462 individuals in favor of reclassification.

Most respondents to the public docket reported an adverse event of ECT treatment. The most common type of adverse event reported in the public docket was some type of memory dysfunction with 529 such reports. This was followed by non-memory cognitive complaints with 357 reports, brain damage with 298 reports, and death or perceived shortened lifespan in those who had been previously treated with ECT with 126 reports.

The full list of reported adverse events is shown on this slide and the next slide in the order of frequency and includes worsening

psychiatric condition, decreased functioning or quality of life, apathy, suicidality, seizures, physical trauma, cardiac problems, emotional trauma, incoordination or balance problems, motor symptoms, pain, headache, speech difficulty, dental or oral trauma, loss of creativity, stroke, vision problems, sleep disturbance, coma, nausea or vomiting, respiratory problems, substance abuse, hypertension, burns, falls, homicidality, nerve damage, fibromyalgia, hair loss, immune compromise, incontinence, ruptured aneurysm, sensory symptoms, tinnitus, and other or unspecified adverse events.

Another concern registered in the responses to the public docket was the question of inadequate informed consent or treatment without consent, particularly in decisionally challenged patients, with 291 such reports. There were 213 reports of a concern that ECT could be misused as a punishment for behavioral problems or as a form of torture.

The next source of information I will review is the manufacturer docket. On April 9, 2009, the FDA issued a Federal Register Notice requesting information from manufacturers on the safety and effectiveness of their device. The FDA requested information on indications for use, device description, device labeling, risks, alternative practices and procedures, a summary of preclinical and clinical data, and a bibliography.

In addition, manufacturers were informed that they could also submit any information that would support reclassification into Class I or II,

including a formal reclassification petition which should include device identification, risks to health, recommendations, a summary of reasons for recommendation, including special controls that would be sufficient to provide reasonable assurance of safety and effectiveness, and a summary of the valid scientific evidence on which the recommendation was based.

The two manufacturers that currently market ECT devices in the United States responded to the request for information. Both manufacturers supported reclassification to Class II, providing the requested information.

I will next review the manufacturer summary of identified risks as well as proposed special controls or mitigating factors submitted by the manufacturers. The list presented here is a compilation of identified risks from both manufacturers. This list includes brain damage, including structural injury, brain cell injury, and hippocampal damage; cardiac arrhythmias; cognitive adverse events include short-term confusion, short-term memory loss, long-term persistent or permanent memory loss, and everyday or semantic memory loss; complications of preexisting medical conditions; death; device malfunction including electrical hazards, such as the risk of excessive dose administration; prolonged seizures; and skin burns.

Special controls or mitigations factors proposed by the manufacturers included reducing the frequency of treatments during a course, in other words, increasing the time between ECT treatments;

temporary or permanent interruption of treatment; reduction of the stimulus dose with dose titration to determine the minimally effective treatment levels; electrode placement such as the use of right unilateral electrode placement; dosage or type of anesthetic or other medications including minimizing psychotropic medications; the use of brief pulse or ultrabrief pulse waveform stimulus; and EEG monitoring to determine seizure length and quality so that appropriate adjustments may be made for subsequent dosing levels. Please note that the mitigating factors proposed by the manufacturers did not provide specific details regarding suggested treatment parameters such as specific stimulus doses, length of brief pulse stimulus, energy level, or use of specific medications and dosages.

The next source of information I will review is the Manufacturer and User Facility Device Experience, or MAUDE, database. The MAUDE database is maintained by the Office of Surveillance and Biometrics at the FDA. This database contains adverse events and reportable product problems of medical devices. The database was fully implemented in August 1996 and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. The reports are associated with all legally marketed devices.

As of December 7, 2010, the FDA has received 151 original adverse event reports, including 135 voluntary reports and 16 user facility reports associated with ECT devices.

As with the public docket submissions, the most commonly cited adverse event type in the MAUDE database was memory loss. Some type of memory loss was reported in 117 cases or 77 percent of all reports. After memory loss, general emotional or psychiatric events were reported most commonly. General motor symptoms, general functional disability, headache, cognitive side effects, seizure, and pain followed in order of frequency.

Other events reported in the MAUDE database included burns, neurological complications, ineffective treatment, brain damage, sleep disturbance, visual change, reports of forced treatment, nausea, personality change, mechanical malfunction, cardiac problems, stroke, improper consent, death, one instance of which occurred within two months of ECT, auditory complaints, dental or oral trauma, hypertension, hypotension, suicide with one completed suicide and one attempt, urinary complaints, incontinence, anesthesia-related complications, coma, miscarriage, and a pulmonary complication.

While information from responses to the Federal Register Notices and MAUDE reports was considered critical to the review of ECT devices, the review team also reviewed the existing literature for evidence on the occurrence and severity of adverse events. All published reports of adverse events were included, case reports, case series, observational studies, retrospective studies, and randomized controlled trials. In addition,

the FDA reviewed systematic reviews, meta-analyses, and practice guidelines that examined the safety profile of ECT devices.

Three primary medical and psychiatric databases were queried to identify potential titles for safety or adverse events as well as effectiveness. That is, titles, abstracts, and key words for both safety and effectiveness were queried together within the initial search strategy. The literature search was conducted by searching PubMed, CINAHL, and PsycINFO for all studies published from the inception of each database through September 7, 2010.

Search items were included as both text and mesh headings and included the following: major depression, electroconvulsive therapy, bipolar depression, schizophrenia, schizoaffective psychosis, schizoaffective disorder, catatonia, mania, and mixed states. Studies were limited to English, human, clinical trial, Cochrane review, controlled clinical trials, meta-analyses, randomized controlled clinical trials, systematic reviews, research studies, cohort studies, case-control studies, cross-sectional studies, case studies, observational studies, and case reports.

In addition, the citations were cross-referenced with references provided in the public and manufacturer dockets and from bibliographies of published guidelines, systematic reviews, and meta-analyses. Any additional relevant titles were added for consideration. Using this search strategy, 1,231 citations were identified. These citations,

including abstracts when available, were reviewed for inclusion.

For the safety review, all citations thought to report adverse events of ECT were identified. Citations and articles were reviewed by two independent members of the review team. Any disagreements regarding inclusion were presented to the entire review team and were settled by majority decision.

Combining information from the dockets, MAUDE database, and literature review of adverse events, the review team constructed this list of all reported adverse events. When possible, categories were based on physiological systems. The list of categories is not intended to cover all possible types of adverse events. It is not exhaustive, and categories are not mutually exclusive. For example, change in blood pressure may also be considered a cardiovascular risk but was classified separately here.

Of note, events marked by superscript 1 have been determined to be risks of significant severity and will be the subject of further analysis later in the presentation today. Events marked by superscript 2 have been identified as key risks, risks that may be of significant severity and for which mitigating factors have been proposed. They will be the subject of the key risks and mitigation discussion later in the FDA presentation.

Reported adverse events included memory dysfunction, cognitive dysfunction, neuropathological changes or brain damage, death or

reduced lifespan, onset or exacerbation of psychiatric symptoms, general motor dysfunction, general functional disability, pain or discomfort, prolonged seizures. To continue the list of all reported adverse events, physical trauma, skin burns, neurological symptoms, pulmonary complications, sleep disturbance, visual disturbance, nausea, alterations in blood pressure, cardiovascular complications, stroke, auditory complications, dental or oral trauma, suicidality, homicidality, substance abuse, urinary complaints, coma, and adverse reactions to anesthetic or neuromuscular blocking agents.

From the list of all reported adverse events, the review team made a determination regarding which of the reported adverse events should be considered potentially significant adverse events. Significant adverse events were identified as being substantiated by a comprehensive review of all sources of data demonstrating sufficient evidence of significant frequency and severity and demonstrating evidence of being associated with ECT device use.

Adverse events that were determined to occur in sufficient frequency and were of significant severity in which there was a potential association with ECT device use warranted further investigation. This list includes adverse reaction to anesthetic agents or neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, cognitive dysfunction, death or reduced lifespan, dental or oral trauma, device

malfunction, memory dysfunction, neuropathological changes or brain damage, onset or exacerbation of psychiatric symptoms, pain or discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, stroke, and suicidality. This list of potentially significant adverse events was used to identify the key risks of ECT requiring mitigation.

In our review of potentially significant adverse events, we found the following:

Anesthesia-related events are rare, similar in frequency to other procedures using general anesthesia. Severity is variable, and there is a clear association with ECT treatment which requires the use of anesthesia. Alterations in blood pressure are common, with variable severity and a clear association with ECT. Significant cardiovascular problems are uncommon with variable severity and a clear association with ECT. Cognitive dysfunction is common with variable severity and a clear association with ECT. Death is a rare but severe complication which was found to be associated with ECT. However, reduced lifespan, while was also rarely reported and potentially severe, was not found to be clearly associated with ECT treatment. Dental or oral trauma is uncommonly reported, of mild to moderate severity, and was found to be associated with ECT. Memory dysfunction is commonly reported, can be mild to severe, and was found to be associated with ECT. Neuropathological changes in the mild to severe range are rarely reported but were not found to be clearly associated with

ECT. The onset or exacerbation of psychiatric symptoms was found to be uncommon with mild to moderate severity. There was only an established association with ECT in the case of manic switching, which is rare. Pain and discomfort are commonly reported, of mild to moderate severity, and clearly associated with ECT treatment. Physical trauma is uncommon, of mild to moderate severity, and clearly associated with ECT treatment. Prolonged seizures are uncommon, of mild to moderate severity, and clearly associated with ECT treatment. Pulmonary complications are rare, may be moderate to severe, and are clearly associated with ECT treatment. Skin burns are rare, of mild severity, and associated with ECT. Stroke is rare, can range from mild to severe, and was found to be associated with ECT. Suicidality is potentially severe but is rare, with no increase from the rate of suicidality in psychiatric populations not receiving ECT. It was found not to be associated with the use of ECT.

From this review of potentially significant side effects, it was determined that the following adverse events were the most significant potential risks of ECT: cognitive and memory dysfunction, neuropathological changes or brain damage, and death. The basis of this determination was made with the following criteria: the frequency of reports from all sources of information, the estimated frequency of occurrence from literature reports, and the potential severity.

A focused review of the literature was conducted on these

adverse events. Dr. Como will review cognitive and memory dysfunction. Dr. Krulewitch will present the FDA meta-analysis of the literature on cognitive and memory effects of ECT, and Dr. Komiyama will review neuropathological changes and death associated with the use of ECT.

DR. COMO: Thank you. Good afternoon. My name is Dr. Peter Como, and I am a neuropsychologist and lead reviewer in the Neurodiagnostic and Neurotherapeutic Devices Branch.

My presentation will focus on the cognitive and memory adverse events findings derived from the FDA systematic review of the literature.

As you heard earlier in the discussion of the public docket, manufacturer docket, MAUDE database, and the published literature on ECT, the cognitive and memory effects of ECT have been a longstanding safety concern, particularly the effects on retrograde personal memory, sometimes referred to in the literature as autobiographical memory.

Unfortunately, the literature on cognitive and memory adverse events has yielded mixed results due to a variety of methodological issues including the use of non-standardized cognitive tests, notably in many of the older studies that were published in the 1960s and 1970s; the availability of numerous different cognitive test batteries, which can make meta-analyses of these data more complex; the variability in the results that occur due to the timing of when cognitive assessment is performed; and the relative lack

of long-term data assessing cognitive outcomes at more than six months.

In addition, a significant confounding factor is the fact that ECT, when effective in ameliorating the cardinal symptoms of depression, can influence cognitive and memory function due to the well-established link between depression and cognitive test performance.

Finally, more recent data are limited by the lack of double-blind, sham-controlled ECT trials.

The FDA systematic review of the cognitive adverse events literature included review of three published practice guidelines, five published systematic literature reviews, four published meta-analyses, and in addition, FDA conducted a systematic search of the literature for randomized controlled clinical trials in which cognitive and memory adverse events were the primary endpoints of these studies.

Finally, FDA conducted meta-analyses of cognitive functions, specifically time to reorientation; global cognitive function as typically assessed by the Mini Mental State Examination, or the MMSE; and autobiographical memory as measured by the Autobiographical Memory Interview. These analyses will be presented by Dr. Krulewitch following my presentation.

The FDA systematic review of the literature of cognitive adverse events included only randomized controlled trials as I mentioned. However, we did examine data from crossover designs if analyzable pre-

crossover data were available. In addition, studies had to use standard psychometrically validated neuropsychologic tests.

The statistical comparisons that were examined included comparisons among various ECT treatment conditions, such as electrode placement, energy dose, frequency of treatment, waveform, and pulse. The comparisons also included ECT versus sham, ECT versus other treatments such as drug and medication placebo, and comparison of pre- and post-ECT changes in baseline cognitive test performance, although the pre- to post-ECT comparisons in themselves were non-randomized.

From this literature search, a total of 68 studies were identified which met these criteria.

This slide summarizes the findings of the published systematic reviews, meta-analyses, and practice guidelines. Overall, these sources indicate that there is evidence for impairment in orientation, anterograde and retrograde memory, and global cognitive function immediately after ECT that may last up to six months. Autobiographical memory is the most commonly reported memory impairment in these reviews. There is limited evidence to suggest that the effects of ECT on memory and cognitive function may not last more than six months.

A greater risk of memory or cognitive impairment is associated with sine wave compared to brief pulse ECT, bilateral and dominant hemisphere electrode placement, and the use of high energy dose ECT. This

literature also suggests that raising the electrical stimulus above the individual seizure threshold increases the efficacy of ECT but at the expense of greater memory and cognitive impairment.

To continue, these summaries report that patient self-reported memory loss tends to be more persistent than the deficits that can be measured on formal neuropsychological testing. However, for those patients who do experience memory or cognitive impairment, they consider this to be a considerable source of distress for themselves and their families. The effects of ECT on cognitive function do not appear to differ among various psychiatric diagnoses such as schizophrenia and mania.

These summaries also suggest that factors other than the ECT treatment may impact cognitive function. These include individual variability, degree of improvement in depression, and the use of psychotropic medications at the same time as ECT.

I will not present the findings from the FDA systematic review of the cognitive adverse events literature. As noted earlier, FDA identified 68 studies which met the search criteria.

The specific cognitive domains for which data was available are listed on the next two slides. Bear in mind that the classification of cognitive domains is not mutually exclusive as there is considerable overlap among various cognitive functions.

Orientation includes person, place, and time, is most often

measured by the number of seconds to minutes needed for a patient to become reoriented following ECT. Executive function includes aspects of attention, mental tracking and planning, problem solving, response inhibition, set-shifting, and working memory. Global cognitive function is typically a composite score on tasks of multiple cognitive domains. In the ECT literature, the most commonly used measure is the Mini Mental State Examination. Global memory typically is a composite score on a standardized memory battery. The most commonly used measure in the ECT literature is the Wechsler Memory Scale, although there are numerous other batteries that have been studied.

Anterograde memory, also commonly referred to as short-term memory, is the capacity to encode, store, and retrieve novel verbal and non-verbal information. Retrograde memory, also commonly referred to as long-term memory, is the capacity to retrieve information encoded prior to the initiation of ECT and is typically reported in the literature as personal or autobiographical memory, which is the ability to recall past personal information and events, such as birthdays, anniversaries, et cetera. Impersonal retrograde memory is the ability to recall historical or factual information such as the colors of the American flag or past presidents. Subjective memory is typically a patient's self-report scale of perceived memory problems.

Other cognitive abilities, including language, visual, spatial,

and motor function, among others, are typically part of a formal neuropsychological test battery. However, there are relatively few studies in the ECT literature examining these cognitive functions and therefore are not included in this presentation.

In reviewing the cognitive adverse events literature, there is a lack of consistent methodology regarding the time points of when cognitive assessment takes place. In reviewing the literature, the cognitive assessment time points generally fell into these categories. Acute effects are those occurring within the first 24 hours of ECT seizure termination. Subacute effects are those occurring from 24 hours to less than 2 weeks. Medium-term effects are those occurring from 2 weeks to less than 3 months. Longer-term effects are those occurring from 3 months to less than 6 months, and long-term effects are those occurring at 6 or more months.

There's also some lack of consistency in the literature with respect to energy dose utilized. The FDA review of the cognitive adverse events literature generally categorized energy dose as follows. Low dose is considered to be 1 to 1.5 times the seizure threshold, moderate dose is 1.5 to 3 times the seizure threshold, and high dose is defined as more than 3 times the seizure threshold.

The cognitive and memory adverse events literature also looked at the effects of electrode placement. Electrode placement is generally categorized in the literature as bilateral, which for many studies

consists of bitemporal placement, bifrontal placement, unilateral which consists of unilateral nondominant hemisphere and/or right unilateral hemisphere, and finally left unilateral or unilateral dominant hemisphere. All of these terms are in the literature.

The next set of slides summarizes the FDA systematic review of the cognitive and memory adverse events literature. For each of these specific cognitive domains, more specific detailed information is available to the Panel if needed.

For time to reorientation, the literature suggests that there's a longer period of disorientation with bilateral electrode placement and with high dose ECT, although disorientation was generally quite brief. There does not appear to be any evidence of persistent disorientation over the long term. These data will be discussed in more detail by Dr. Krulewitch in her discussion of the meta-analyses conducted by FDA.

For executive function, there is no evidence of significant differences among the various ECT treatment parameters, although there was a single study which suggested greater executive dysfunction with left unilateral ECT compared to right unilateral ECT. Overall, the literature suggests that there is improvement or no statistically significant change from baseline at up to six months after ECT.

For global cognitive function, bilateral electrode placement was associated with greater impairment than right unilateral ECT. There's

no consensus in the literature on change in test performance on the Mini Mental State Examination from baseline up to two weeks following ECT. However, there was an apparent improvement or no change from baseline by three to less than six months. There are no reported effects of energy dose. Again, these meta-analyses of the MMSE conducted by FDA will follow my presentation.

For global memory function, there were no significant differences by energy dose or waveform or with ECT compared to sham, in the medium term, up to three months. There is limited evidence that bilateral ECT typically performed three times a week may be associated with greater global memory impairment. There's no change from baseline test performance up to six months identified in the literature.

For anterograde memory, I'm going to break it down into verbal and non-verbal memory. For verbal anterograde memory, overall there are inconsistent results in the literature comparing ECT to sham. However, there does appear to be a greater risk of verbal memory impairment with sine wave compared to brief pulse ECT, bilateral and dominant hemisphere electrode placement, and high energy dose ECT.

With respect to change from baseline, after about one week of treatment, verbal memory function may return to baseline and might improve following right unilateral electrode placement or low moderate energy dose ECT. After about two weeks of treatment, verbal memory

functioning following bilateral electrode placement may return to baseline and may actually improve. From three to six months and beyond, there is limited data to determine if verbal memory impairment persists beyond this time period.

I will now turn to anterograde non-verbal memory data. For non-verbal memory function, the literature review yielded the following. ECT is associated with greater impairment compared to sham ECT immediately after treatment. There do not appear to be any differences in non-verbal memory function with respect to electrode placement. Brief pulse ECT may be associated with greater impairment compared to ultrabrief pulse ECT. After about two weeks of ECT treatment, there is no conclusive evidence in the literature to support any differences among the various ECT treatment parameters. However, there is relatively conclusive evidence of no significant changes in non-verbal memory test performance compared to baseline in the short term, which is the two week to three month period. There is limited data to suggest that in the longer term, non-verbal memory deficits may return to baseline levels.

For impersonal retrograde memory impairment, the literature review yielded the following. Immediately post-ECT, bilateral electrode placement may be associated with greater impairment. There are inconsistent findings with respect to electrode placement, pulse, or energy dose from about 24 hours to 3 months post-ECT. There are no differences

between sham ECT and ECT, electrode placement, or pulse wave at six months. Detectable changes from baseline are inconsistent up to six months post-ECT. However, again the literature suggests no significant change from baseline appear to be present at six months.

There was a significant amount of information in the literature regarding the effects of ECT on autobiographical or retrograde personal memory. The majority of the studies in the literature tend to focus on the subacute affects, which is the 24-hour to 2-week time period after ECT. Immediately after ECT, there's limited evidence to suggest that bilateral electrode placement is associated with greater impairment. In the subacute time period, 24 hours to 2 weeks, there is conclusive evidence to suggest that bilateral ECT is associated with greater impairment of autobiographical memory compared to unilateral, right unilateral or unilateral nondominant ECT. However, there's limited evidence with respect to the effects of sine wave or high energy dose. There's also evidence to suggest a decline from baseline test performance during this time period.

For the medium term, which is the two week to less than three month time period, there are limited data regarding the effects of electrode placement, pulse, or energy dose. The data are also limited with respect to change from baseline, although there are some studies that suggest no change or improvement with the use of ultrabrief pulse.

There was a single study comparing maintenance ECT with

drug therapy. The results suggested that pharmacologic treatment demonstrated improvement relative to post-ECT performance whereas maintenance ECT demonstrated no change from the post-ECT baseline. At six months, there was only one study which suggested a return to baseline test performance with unilateral ECT. However, there was continued decline with bilateral placement in sine wave pulse.

The meta-analysis of the most commonly used instrument, the Autobiographical Memory Interview Scale, conducted by FDA, will be discussed following my presentation.

Assessment of subjective memory is problematic according to the literature due to the use of self-report scales, are dependent upon the timeframe which these scales are completed by patients, and may be related to the degree of improvement in depressive symptoms. In general, patients are more likely to report memory impairment immediately following ECT treatment. Bilateral was associated with greater impairment than unilateral ECT in the subacute time period, but by six months, there was no difference with respect to electrode placement, waveform, or sham versus ECT. Improvement or no change from baseline appears evident at six months post-ECT.

To summarize, the systematic review of the cognitive adverse events literature indicates that ECT is associated with cognitive and memory impairment. The degree and duration of the impairment appears to be

domain-specific and related to certain ECT treatment parameters. Specifically, there appears to be a greater risk of cognitive and memory impairment associated with bilateral and dominant hemisphere electrode placement and high energy dose ECT.

The key impaired cognitive domains from the review of the literature include disorientation, which is common but typically transient and resolves within seconds to minutes after seizure termination. Of the major cognitive domains, memory dysfunction is apparent for both anterograde and retrograde memory over the short term but may return to either baseline level or possibly improve. Specifically, the literature suggests that bilateral ECT is associated with greater autobiographical memory impairment compared to unilateral ECT, and there's limited evidence to suggest these deficits may return to pre-ECT baseline test performance at six months.

The next slide, this next table, is a little busy but attempts to summarize the evidence in the literature regarding the pre- to post-ECT changes from baseline cognitive test performance. To try and orient you to the slide, the upward arrows indicate consensus in the literature of improvement relative to baseline test score. The downward arrows indicate consensus in the literature suggesting a decline from baseline test performance. The dashes indicate that the consensus in the literature suggest no change from baseline, and the one +/- sign that you see at six

month under retrograde memory indicates that the results are different depending upon the ECT treatment parameter. Finally, the color coding is an attempt to indicate that the red arrow indicates that there is relatively conclusive evidence in the literature to support the finding. The blue arrow indicates that there is limited or equivocal evidence in the literature to support the finding.

So to try and summarize this table for you, immediately post-ECT, there are deficits across nearly all cognitive domains. The cognitive deficits tend to persist up to two weeks with perhaps the exception of non-verbal memory function. From about two weeks to less than six months, cognitive test performance appears to either return to baseline or possibly improve. The data are limited at six months or greater. However, the available studies reviewed suggest there's no evidence for persistent cognitive deficits except for perhaps autobiographical memory in which bilateral electrode placement in sine wave ECT appear to be associated with decline from baseline while unilateral brief pulse ECT appears to approach or return to baseline.

I will now turn the presentation over to Dr. Krulewitch, who will present the specific cognitive meta-analyses conducted by FDA. Thank you.

DR. KRULEWITCH: Good afternoon. I am Dr. Cara Krulewitch, and I am a Branch Chief in the Division of Epidemiology, Office of

Surveillance and Biometrics. I will discuss the FDA safety meta-analysis which evaluated memory and cognition.

The FDA safety meta-analyses evaluated acute immediately following the seizure termination; subacute, 24 hours to 2 weeks following the treatment; and medium term, 2 weeks to 3 months following treatment. Published data were insufficient to evaluate longer term, greater than the 3 months of facts.

We used the following selection criteria. There were at least two groups and two studies for each meta-analysis that used the same or cross-validated measure, and there was sufficient data for analysis on the number of patients per group and a standard deviation. We used DerSimonian and Laird Random Effects Model.

Studies identified for inclusion compared some form of right unilateral and bilateral electrode placement at low or moderate threshold. There were no studies that met the criteria using the high threshold. Three measures included in the identified RCT studies were included in the meta-analyses, including orientation, time to reorientation; global cognitive function through the MMSE that was described by Dr. Como; and retrograde personal memory through the AMI, also described by Dr. Como.

Just a point to make about meta-analyses in general. There are limitations. Data included in meta-analyses are limited to the studies, and usually these are the more recent ones, with adequate data, effect size,

et cetera, of the criteria that I just discussed. A meta-analysis is a quantitative summary of published studies. As such, the quality of conclusions based on this methodology is entirely dependent on the quality of the studies included. There are potential biases including publication bias, temporal bias, thus more recent studies are likely to be included, and we could not assess publication bias because there were too few studies. Therefore, it's very important to keep such limitations in mind while evaluating how much weight to attribute to the evidence of meta-analyses.

For the safety meta-analyses, there were two to five studies that met all criteria for each of the three study groups, and this limited the generalizability of the findings. Therefore, findings should be reviewed with caution.

In the evaluation of time to reorientation, the number of seconds to reorient was used. It took 29 seconds more to reorient among those receiving bilateral moderate energy compared to those receiving unilateral low energy.

In the acute period following ECT treatment, overall patients who received bilateral moderate treatment had a 9.8 percent lower score on the Mini Mental State Exam, which is in this box right here, compared to those who received unilateral lead placement at low energy.

Again, in the box, at two months post-treatment overall, patients who had ECT with bilateral lead placement at moderate energy

levels had a 6.5 percent increase in their Mini Mental State score compared to those who had unilateral lead placement at moderate energy levels.

At 24 hours to 2 weeks after ECT, patients who received bilateral lead placement at low energy had a 19.3 percent decrease in Autobiographical Memory Interview scores compared to patients who had unilateral lead placement at moderate energy levels.

We also evaluated Autobiographical Memory pre- and post-treatment by lead placement and energy level. The scores decreased for all groups post-treatment. However, although the confidence intervals overlap, the point estimates among the unilateral group were a little better. There was less decrease in their score compared to the bilateral lead placement. This finding, however, does not appear to be clinically meaningful.

In summary, bilateral lead placement had a larger adverse effect on time to reorientation for the MMSE and AMI compared to unilateral lead placement. Energy level does not have a significant effect on these measures when comparing pre-treatment to post-treatments.

I will now turn the podium over to Dr. Allison Komiyama who will discuss neuropathological changes and death related to ECT.

DR. KOMIYAMA: Hello, my name is Dr. Allison Komiyama, and I am a neurobiologist at the FDA in the Center for Devices and Radiological Health, Office of Science and Engineering Labs. I will be presenting on the neuropathological changes due to ECT as well as death.

We approached the investigation of brain damage reported in the public docket by performing a review of the literature regarding neuropathological changes associated with ECT. This review searched for articles that included neuropathological changes or lack thereof in human and animal studies of ECT. Neuropathological changes might include brain lesions, neurodegeneration, DNA damage, gross loss, glial proliferations, neuroproliferation, or gross gain.

Because the brain is the target of the electrical stimulus of ECT, it is necessary to consider the potential mechanisms of brain injury, whether it be directly due to the electrical stimulus itself or indirectly via the induced seizure. Direct brain injury from ECT is most likely to occur from electrical stimulus including dielectric breakdown of neuronal membranes or electrochemical toxicity, temperature elevation from heat liberated by the electrical stimulation, which may lead to burns, or from cerebral anoxia occurring during the induced seizure.

During the passage of the electrical stimulus for ECT, the high impedance of the skull relative to the skin and subcutaneous tissues causes most of the stimulus current to be shunted through the scalp. Considering the worst case calculation that assumes the heat generated in the brain to be evenly distributed, the output of modern brief pulse ECT devices would elevate deep tissue temperatures by less than .092 degrees Celsius or .166 degrees Fahrenheit.

Also because ECT has for more than 50 years been administered concurrently with full oxygenation of the patient to consistently yield a partial oxygen pressure, cerebral anoxia has been essentially eliminated as a possible cause of any punitive brain injury during ECT.

There is a growing body of literature examining changes in brain morphology after induced seizures. Brain injury by indirect means from ECT-induced seizures is an obvious safety concern, and recent research is aimed to understand both the gross and microscopic changes that occur in the brain due to ECT.

Additionally, researchers have hoped to garner a better understanding of the potential mechanisms that underlie this treatment. Both animal and human studies have aimed to elucidate the biological response in the brain at the gross pathologic and molecular levels.

A PubMed search was conducted to review the literature regarding neuropathological changes associated with ECT. Search terms included the following: electroconvulsive therapy, electroshock, electroconvulsive shock, brain/pathology, brain injuries, brain damage, tissue damage, adverse effects, and nervous system. Studies that did not focus on neuroanatomy or neurophysiology or performed electroshock that was not electroconvulsive in nature, such as foot shock or tail shock, were not included in this review. Studies that solely addressed adverse effects

due to status epilepticus or kindling were also not included in this review. The bulk of these studies took place between the mid 1980s and present.

Using these criteria, studies were identified and evaluated for scientific rigor in the review of neuropathological changes or brain damage. To investigate brain injury by an indirect means, scientists have turned to autopsy and neuroimaging data, immunohistochemical studies, as well as biomarkers of injury in the blood and vertebrospinal fluid. Some data from each of these areas will be discussed on the following few slides.

Very little autopsy data is available for patients that have gone through ECT treatments. However, in 2007, researchers studied the brain of a deceased 92-year-old woman with intact cognition and major depression who received 91 sessions of ECT during the last 22 years of her life. Compared to normal brains, they found no evidence of gross cell loss or gliosis in the dentate granule cell layer, the subiculum, as well as other regions of the hippocampus, and the cytoarchitecture of these regions also appeared normal. These data are further supported by magnetic resonance imaging studies by Coffey et al. in 1991 and Ende et al. in 2000, where they find no acute or delayed changes in brain structures after ECT treatments.

Next, while most animal studies have focused on a rodent model, there are recent non-human primate studies of the effects of electroconvulsive shock or ECS, which is the animal model of ECT. Two papers by Dwork et al. in 2004 and 2009 demonstrate that electroconvulsive

shock at a dose comparable to human treatment does not produce histological lesions, nor does it lead to change in number of neurons or glia in the vulnerable regions of the brain.

Many rodent studies as well as recent human MRI studies suggest a neuroproliferative role for ECT. Researchers have witnessed post-treatment increase in hippocampal volume in frontal white matter, two brain regions that are often implicated in the pathophysiology of psychiatric disorders.

As you can see in this figure from the paper by Nordanskog et al. in 2010, there is a significant increase in hippocampal volumes in post-ECT treated brains compared to pre-ECT. This is pre on the left and post on the right. The table shows the significant increases in hippocampal volume in microliters for both the right and left hippocampus of these patients.

Similar neuroproliferative results have been demonstrated in immunohistochemical studies of the brain when comparing sham and electroconvulsive shock treated animals. In a study by Perera et al. in 2007, no cell death was noted in the brains of non-human primates post-electroconvulsive shock. The authors instead witnessed an increase in neuronal precursor cell proliferation in the hippocampus which is shown in this chart on the left, the red box. In the magnified confocal image on the right, neurons in the hippocampus are labeled in red and have been co-stained with a marker for self-proliferation in green. On the far right, you

can see the superimposed image demonstrating the neuronal cell proliferation that is taking place in this brain.

After brain injury in humans, there are detectable increases in a variety of molecules in blood and/or cerebrospinal fluid. These molecular entities can be measured before and after ECT in an attempt to determine whether ECT leads to damage. In a study that measured cerebrospinal fluid biomarkers, markers of neuroglial dentate degeneration and blood-brain barrier dysfunction were not significantly changed by a therapeutic course of ECT.

In a study by Giltay et al. in 2001, researchers found that concentrations of brain cell damage markers and blood serum all remained within a normal range in patients tested before and after ECT treatments. In similar papers, looking at biomarkers in blood serum, no differences were found before and after treatment with ECT when measuring neuron-specific enolase and protein S-100. These two proteins are considered sensitive biochemical markers per acute brain damage caused by generalized seizures, trauma, hypoxia, and ischemic stroke.

In summary, these studies provide some evidence that ECT does not lead to brain inflammatory response, brain cell leakage, neuronal damage, or blood-brain barrier dysfunction.

The Panel will be asked to discuss and address the following question. Regarding neuropathological changes, the manufacturer and

public dockets both indicated brain damage as a potential risk associated with ECT. However, FDA's review of the literature did not identify evidence of gross anatomical, histological, or immunohistochemical evidence, or evidence from biomarkers of injury, to support this association. Please discuss whether the existing clinical data support brain damage as a potential risk of ECT and, if so, how this risk might be mitigated.

Death was reported as an adverse event from several sources. Estimates of the mortality rate associated with ECT treatment are 1 per 10,000 patients or 1 per 80,000 treatments. This rate is estimated to be approximately the same as the rate associated with minor surgery.

An examination of ECT use in California from 1977 to 1982 demonstrated that approximately 1.12 persons per 10,000 population received ECT. The mortality rate was .2 deaths per 10,000 treatments. In a follow-up to this study, ECT used in California was examined from 1984 to 1994. During this time, a total of 28,437 patients received 160,847 treatments. Three deaths were reported, which resulted in a rate of 0.19 deaths per 10,000 treatments.

Nuttall et al. conducted a large retrospective review of ECT. They examined 2,279 patients who underwent 17,394 ECT treatments. Twenty-one patients or .92 percent experienced a complication during their series of ECT. Cardiac arrhythmias represented the majority of complications. Although there were no occurrences of permanent injury or

death immediately after ECT, there were 18 deaths within 30 days of the last treatment, but none were thought to be related to ECT. The authors concluded death rates have been declining in recent years possibly due to improved monitoring and medical management during ECT treatments.

The Panel will be asked to keep this discussion in mind in their deliberation on the question regarding identifying the key risks of ECT that require mitigation and whether death should be included on this list. The Panel will also be asked to comment on the completeness and accuracy of this list and comment on the inclusion of death as a key risk.

I will now invite up Dr. Lawrence Park who will be discussing the FDA effectiveness review.

DR. PARK: Good afternoon. My name is Lawrence Park. I'm a Psychiatric Medical Officer at the Center for Devices and Radiological Health, Office of Device Evaluation, Division of Ophthalmic, Neurological and ENT Devices.

My presentation will start with a review of the public docket responses related to effectiveness and then proceed to a brief description of the FDA effectiveness literature review and a presentation of our findings.

Earlier, Dr. Georgiopoulos described the public docket process and results with regard to adverse events and concerns about ECT devices. Of 3,045 responses to the public docket, 79 percent opposed reclassification and 14 percent supported reclassification. Some responses also included

information regarding the effect of ECT. Both positive and negative effects were reported, with 471 respondents or 15 percent reporting a positive effective ECT, and 1,857 or 61 percent of respondents reporting a negative effective ECT. Of note, because these data were not systematically collected, estimates of ECT effectiveness cannot be based on these data.

In order to address the issue of ECT effectiveness further, FDA conducted an independent review of the literature. The methodology of the effectiveness systematic review was similar to that of the safety review, including examination of previously published systematic reviews, meta-analyses, and practice guidelines, as well as performing an independent analysis of clinical research studies.

For the independent FDA analysis, only prospective randomized control trials were included. In addition, studies were included for consideration if they used standardized rating instruments and conducted appropriate statistical analyses for the comparisons under investigation.

A subgroup of these studies were included in the FDA meta-analysis. These studies were required to examine two or more comparison groups, use of the same validated and standardized scales and report sufficient data, that is average score, number of subjects, and measure of variation, standard deviation or standard error, to be included in the meta-analysis. What this turned out to be was for depression studies. We looked

at the Hamilton Rating Scale for Depression, and for studies examining psychosis, schizophrenia, we used the Brief Psychiatric Rating Scale.

Indications undergoing review included depression, both bipolar and unipolar, schizophrenia, acute mania and mixed states, catatonia, and schizoaffective disorder. The majority of studies examined ECT for depression. Trial designs for these studies included ECT versus sham, ECT versus placebo medication, ECT versus antidepressants. Other studies examined effectiveness if certain treatment parameters were varied, such as electrode placement, energy dose, frequency of treatment, and pulse width.

Several randomized controlled trials were found examining the use of ECT for schizophrenia and acute mania. These results will be presented as well. Few or no studies examining catatonia or schizoaffective disorder met criteria for inclusion in this review. Finally, several studies examined the use of maintenance ECT to prevent exacerbation of symptoms. However, these results will not be presented at this time but are available at the Panel's request.

With regard to previous published systematic reviews, meta-analyses, and practice guidelines, 10 systematic reviews, 7 published meta-analyses, and 3 practice guidelines were identified.

From these reviews and analyses, there is general agreement on the following points: First, the literature only supports effectiveness claims for ECT for the time period immediately post-ECT to approximately

one month. There is little evidence supporting the effectiveness of ECT beyond the one-month time point. There is also general agreement that ECT is more effective than sham or placebo and may be more effective than some antidepressants. Limited evidence supports the conclusion that ECT is more effective than repetitive transcranial magnetic stimulation and is effective for elderly depressed patients. The overall response rate of ECT has been estimated to be 72 percent. That is, if subjects are categorized as responders or non-responders, 72 percent of those receiving ECT were considered responders. This is compared with a 40 percent response rate for sham or placebo.

In addition, bilateral ECT is more effective than unilateral, though moderate to high dose unilateral ECT may be as effective as low dose bilateral, and low dose ECT may be no more effective than sham. When using the unilateral ECT, it appears that increasing energy dosage increases effectiveness at the expense of memory and cognitive impairment. The presence of psychotic symptoms may better predict response.

For schizophrenia, like depression, ECT effectiveness is demonstrated only for the period immediately post-ECT to one month. That is, there is no evidence that ECT demonstrates effectiveness in other than the acute setting. In addition, conflicting data suggests that ECT may be more effective than antipsychotic medications for acute episode. Use of ECT demonstrates an association with greater likelihood of being discharged

from the hospital. Finally, limited evidence suggests that ECT may reduce relapses.

For other indications, there's limited evidence that ECT may be effective in treating manic or mixed states. There is no randomized evidence for the effectiveness of ECT for catatonia, and there is no evidence that ECT is effective for schizoaffective disorder at any time point.

Three major practice guidelines have been published on ECT, the APA Task Force on ECT, the Royal College of Psychiatrists in the U.K., and the National Institute for Health and Clinical Excellence, the body charged with setting clinical standards of practice in the U.K. These guidelines represent the recommendations of the respective organizations on the use of ECT. There appears to be general agreement between these sets of recommendations.

Generally, the practice guidelines recommend the use of ECT for the following indications: severe depression both unipolar and bipolar, schizophrenia, acute mania and bipolar mixed states, and catatonia.

ECT should be considered for primary use, that is prior to medications when there is a need for rapid, definitive response because of the severity of a psychiatric or medical condition, that is, when illness is characterized by stupor, marked psychomotor retardation, depressive delusions or hallucinations, or life-threatening physical exhaustion associated with mania; when the risks of other treatments outweigh the

risks of ECT; given a history of poor medication response or good ECT response in one or more previous episodes of illness; and in accordance with the patient's preference.

ECT should be considered for secondary use, that is, after one or more medication trials, in the following situations: in cases of treatment resistance to antidepressant medications - for depression, that means after one or more antidepressant trials; for mania, after one or more mood stabilizer trials with adjunctive atypical antipsychotic treatment; for clozapine-resistant schizophrenia; and for lorazepam-resistant catatonia; or in instances of inability to tolerate the adverse effects with pharmacotherapy that are deemed less likely or less severe with ECT; or if the deterioration of the patient's psychiatric or medical condition creates a need for a rapid, definitive response.

Other recommendations suggest that if response or remission is achieved, antidepressants, including lithium augmentation, should be started or continued to prevent relapse. ECT should not be recommended for an individual with moderate depression who has not responded to a previous course of ECT, and a comprehensive informed consent process should be undertaken prior to the initiation of ECT treatment.

I'd like to end this section which reviews published systematic reviews, meta-analyses, and practice guidelines by citing the Surgeon General Report on Mental Health. Though published in 1999, this report

remains the only comprehensive review of mental health by the Surgeon General's Office. With regard to ECT, the report concludes, "On balance, the evidence supports the conclusion that modern ECT is among those treatments effective for the treatment of select severe mental disorders, when used in accord with current standards of care, including appropriate informed consent."

I'll now turn my attention to the independent FDA effectiveness review. The systematic review and meta-analyses conducted by FDA identified randomized control trials for the following indications and comparisons: Trial designs examining depression included ECT versus sham, ECT versus placebo, and ECT versus antidepressants, as well as a group of more recent studies examining variations of two treatment parameters, electrode placement, primarily bilateral and unilateral and varying energy dosage. There were also studies examining variations in frequency of treatment during a course of ECT and alterations in pulse width of the electrical stimulation.

For each of these indications and trial designs, I will now present the results of the FDA systematic review and meta-analysis. The FDA systematic review of 11 studies examining ECT versus sham comparisons for depression demonstrates that in the acute phase, immediate post-ECT, there is sufficient evidence to conclude that ECT is more effective than sham. At time periods one month and longer, there is no evidence that ECT

is superior to sham. Five of the eleven studies are included in the meta-analysis. The meta-analysis using a random effects model, and combining studies examining a two and four week endpoint, estimates that the ECT group had an average improvement of Hamilton Score of 7.1 points greater than the sham group, with a 95 percent confidence interval ranging from -0.1 to 14.2.

The forest plot of the meta-analysis for the ECT versus sham comparison for depression is represented in this slide. Forest plots of the other meta-analyses will not be shown in this presentation but are available for review at the Panel's request. This forest plot demonstrates the study specific treatment effects from each of the five studies included in the meta-analysis. The estimated treatment effects for each study is represented by the boxes above. These boxes here. The diamond at the bottom of the plot shows the overall estimate of improvement in Hamilton Score for ECT relative to sham. The difference in improvement on the Hamilton between ECT and sham is given on the X axis. As you can see from this notation at the bottom of this slide, the findings towards the right of this plot favor ECT effectiveness over sham.

DR. BROTT: Excuse me, Dr. Park. Dr. Ellenberg has a question. We're trying to hold them to end, but it has been quite a few slides.

DR. PARK: Yeah.

DR. BROTT: Go ahead, Dr. Ellenberg.

DR. ELLENBERG: Would you mind going back one slide? The 5 point, 6.5 point increase in the HRSD, is that clinically important?

DR. PARK: That's a very good question. There are many different ways to answer that question. One of the ways to look at it is to compare it to other treatments, and so if we look at treatments for antidepressant medications, there have been different ranges in the literature with regard to what the average effect size is for antidepressants, and those estimates range from about 1.8 up to 4 points on the Hamilton.

DR. ELLENBERG: Thank you.

DR. BROTT: As long as we're on that, we'll let you go, but with these presentations, we've heard the number of studies but never heard the number of patients, unique patients. Can you tell us or give us an idea here, since you've chosen this as the one that you choose to show, how many unique patients are we talking about?

DR. PARK: This is 5 studies, and we're looking at a total of approximately 150 for an overall sample size.

DR. BROTT: I'm instructed by our Federal Officer that we can't do this anymore. We do have our slides, you know, our slide sets with us. So if you can just use that as a guide to mark your questions so that when we get to them, we can go to the specific slides when we're done with the presentations.

DR. PARK: And one final comment. Each of these different

analyses are presented in the Executive Summary in somewhat more detail.

So now we're on to the comparison of ECT versus placebo for depression. For this systematic review, we identified six randomized control trials, and this data demonstrates that in the acute phase, immediately post-ECT, there is conclusive evidence that ECT is more effective than placebo. Long term, six months or greater, post-ECT, one study demonstrated that ECT was more effective than placebo. None of the six studies yielded meta-analyzable data. Therefore, meta-analysis could not be conducted.

Systematic review of the 18 randomized control trials examining ECT versus antidepressant comparisons for depression demonstrates that the acute phase to 1-month post-ECT, there's conflicting evidence with a majority of studies, 7 out of 13, demonstrating no significant difference between ECT and antidepressants but 5 five studies incorporating a sample size of 310 showing ECT as superior to antidepressants and 1 study showing that an antidepressant, imipramine, is superior to ECT. At greater than one month post-ECT, there is sufficient evidence to conclude that ECT is more effective than antidepressants. Eight of eighteen studies are included in the meta-analysis. The meta-analysis estimates that the ECT group had an average improvement on the Hamilton Score of about 5 points greater than the antidepressant group, with confidence interval ranging 0.8 to 9.1.

Examination of the effect of electrode placement looked at 22 randomized controlled trials, examining groups varying electrode placement

and energy dose. This review demonstrated that immediately post-ECT to two weeks, there is no significant difference in effectiveness between bilateral and right unilateral or bifrontal and right unilateral placement. One study demonstrated that unilateral ultrabrief pulse stimulation was significantly more effective than bilateral ultrabrief pulse stimulation. In the medium term, two weeks to three months, there is conclusive evidence that there is no significant difference in effect between bilateral and unilateral electrode placement.

This is a little bit of a repeat, but just going onto the meta-analysis bullet, 5 of the 22 studies were included in the meta-analysis. This meta-analysis which examines studies that compared bilateral and unilateral electrode placement but did not specify energy dose estimates that the bilateral group had an average improvement in Hamilton Score of about 4 points greater than the unilateral group with confidence interval ranging from -0.6 to 8.6. These studies are generally older studies that did not specify the energy dose.

In studies varying energy dosage, systematic review demonstrated that high energy stimulation may be more effective than low or moderate dose stimulation. In addition, in pre- and post-comparisons, there's conclusive evidence that all groups receiving ECT at any energy dosage demonstrated significant improvement up to six months ECT. One study shows this improvement out to the six-month time point. Meta-

analysis of 4 studies examining bilateral low and moderate dose treatment, compared with unilateral high dose treatment, estimates that bilateral low and moderate groups had an average improvement in Hamilton Score of about 0.2 points greater than the unilateral high dose group with confidence interval ranging from -2.2 to +2.6.

Systematic review of the six randomized control trials, examining two times per week versus three times per week ECT, demonstrates that one to four weeks post-treatment, no significant difference is seen between groups while significant change from baseline scores are seen across all groups. From these studies, it can be concluded that three times per week treatment is associated with more rapid improvement in symptoms but is associated with more severe memory problems. Three of these six studies were included in the meta-analysis which estimates that the three times per week group had an average improvement in Hamilton Score of 1.1 points greater than the two times per week group with confidence interval ranging from -5 to 7.2.

Randomized controlled trials comparing brief pulse and ultrabrief pulse stimulation are just beginning to be reported in the literature. At the current time, two studies conducted randomized controlled comparisons of brief pulse and ultrabrief pulse stimulation and yielded mixed results.

One study which examined right unilateral high dose ECT

versus bilateral moderate dose ECT, using brief pulse and ultrabrief pulse stimulus, demonstrated that ultrabrief pulse bilateral ECT is less effective than the other three groups. The other study examining bilateral low dose ultrabrief pulse stimulus compared with unilateral high dose ultrabrief dose stimulus showed at one and six weeks no significant difference between depression scores between groups, though the unilateral ultrabrief pulse group required fewer treatments to achieve response and remission. Meta-analysis was not conducted due to lack of meta-analyzable data.

Systematic review of the 10 randomized controlled trials examining ECT versus sham comparisons for schizophrenia demonstrate that in monotherapy, ECT is not superior to sham immediately post-ECT to eight weeks. In adjunctive therapy, with antipsychotic medications, ECT is not superior to sham at any time. However, some evidence suggests that ECT may increase the overall speed of response. Three of these ten studies were included in the meta-analysis. The meta-analysis estimates that the ECT group had an average improvement in Brief Psychiatric Rating Scale score of 2.3 points better than the sham group with a confidence interval ranging from -3.7 to 8.3.

Systematic review of the six randomized controlled trials examining ECT versus sham or ECT versus lithium comparisons for acute mania demonstrate that ECT is significantly better than sham and as effective as lithium immediately post-ECT. Meta-analysis could not be

conducted.

The summary findings of the independent FDA review of effectiveness are presented on this slide.

For depression, in the acute and subacute phase, ECT is more effective than sham or placebo. After one month post-ECT, ECT is more effective than antidepressants. High dose unilateral ECT may be as effective as low to moderate dose bilateral ECT. No significant difference was seen in effectiveness between two times per week and three times per week ECT, although three times per week ECT is associated with faster response.

For schizophrenia, ECT does not appear more effective than sham or antipsychotic medications.

For mania, limited evidence suggests that ECT is superior to sham and as good as lithium.

Two primary considerations in the determination of whether a device should be classified as Class II or Class III are the identification of key risks and potential mitigating factors. Key risks are defined as substantial risks of device use that could significantly influence the risk/benefit profile of the device. Mitigating factors may potentially serve as regulatory controls to adequately reduce the risk of device use such that a reasonable assurance of safety and effectiveness can be demonstrated for the device.

Like the determination of potentially significant adverse events discussed in the safety review, the identification of key risks is based

on similar criteria, that is, they are substantiated by a comprehensive review of all sources of data, there is sufficient evidence of significant frequency and severity, and there's evidence of being associated with ECT device use.

As previously discussed by Dr. Georgiopoulos, she presented this initial list of potential reported adverse events, FDA identified key risks from this list. The key risks of ECT are presented in this slide and reorganized into three different main categories.

The first category, medical and physical risks includes adverse reaction to anesthetic agents and neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, death, dental and oral trauma, pain and discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, and stroke. The other two main categories include cognitive and memory dysfunction, and device malfunction.

The Panel will be asked to keep this discussion in mind in their deliberations on the question regarding identifying the key risks of ECT requiring mitigation.

Again, here's the list of proposed key risks. The Panel will be asked if this is a complete and accurate list of the key risks presented by ECT and asked to comment on whether you disagree with the inclusion of any of these risks or whether you believe any other risks are among the key risks presented by ECT.

I'll now present an examination of each key risk and potential mitigating factors by reviewing this table which goes over the next three slides.

Adverse reactions to anesthesia are rare but potentially severe complications associated with ECT. These reactions are related to the use of anesthetic agents and neuromuscular blocking agents to which patients may have rare but potentially severe reactions. Potential mitigating factors may consist of pre-ECT assessment, including pertinent medical and surgical history, family history of reaction to anesthetic agents, physical exam, as well as appropriate procedure monitoring and clinical management to any reaction that may arise.

Alterations in blood pressure are common but typically benign complications associated ECT. Hypertension as well as hypotension may be associated with ECT treatment. Potential mitigating factors include pre-ECT assessment of medical, particularly cardiovascular status, appropriate procedure monitoring, and clinical management.

Cardiovascular complications are uncommon but potentially severe complications of ECT treatment. They most commonly include arrhythmias and/or ischemia. Cardiovascular complications are one of the most frequent causes of morbidity and mortality associated with ECT. Potential mitigating factors for cardiovascular complications include pre-ECT assessment which may include blood pressure assessment, pre-ECT

electrocardiogram, echocardiogram or Holter monitoring, appropriate procedure monitoring, and clinical management.

Death is a rare but severe outcome of ECT treatment. It is a result of various complications of ECT such as reactions to anesthesia, cardiovascular complications, pulmonary complications, or stroke. Potential mitigating factors include those proposed for each of these key risks.

Dental and oral trauma including dental fractures, dislocations, lacerations, and prosthetic damage are uncommon complications of ECT and are generally of mild to moderate severity. Potential mitigating factors may include pre-ECT dental assessment, removal of prostheses, as well as the use of mouth protection or bite blocks during the procedure.

Pain and discomfort are common but generally mild to moderate complications of ECT. They are typically treated with the use of as-needed analgesic medication.

Physical trauma associated with ECT, they include fractures and soft tissue injury. Physical trauma usually occurs as a consequence of significant muscle contraction during the treatment. Though more prevalent in previous years of ECT use, in current practice, this key risk is uncommon. Potential mitigating factors to prevent or reduce the severity of physical trauma include the use of general anesthetic agents and neuromuscular blocking agents.

Prolonged seizures are an uncommon and moderate to severe complication of ECT. Status epilepticus may ensue if prolonged seizures are not properly treated. Potential mitigating factors include an appropriate pre-ECT neurological assessment as well as EEG monitoring during the procedure and the availability of rapid treatment of prolonged seizures should they occur.

Pulmonary complications, such as prolonged apnea or aspiration, are rare but potentially severe complications of ECT. With cardiovascular complications, they represent one of the most common causes of morbidity and mortality associated with ECT. Potential mitigating factors include appropriate pre-ECT assessment of pulmonary function, pre-ECT tests such as chest x-ray and pulmonary function test, and appropriate monitoring and clinical management before, during, and after the procedure.

Skin burns are uncommon and typically mild complications of ECT. They most commonly occur when there's poor contact of the electrode with the skin surface resulting in high impedance in the electrical circuit. Skin burns may be mitigated by proper skin preparation, electrode contact, including the use of conductivity gel.

Stroke is a rare and potentially severe complication that may be associated with ECT. Potential mitigating factors include pre-ECT assessment of risk factors for stroke, including possible neuroimaging or

cardiovascular and neurovascular assessment when appropriate, appropriate procedure monitoring, and clinical management during the treatment.

The issue of inadequate informed consent processes and/or forced treatment has been raised in the public docket, in the MAUDE database, and in the published literature. Critics of the informed consent process claim that if individuals are inadequately or inaccurately informed of the risks of ECT, the risk/benefit assessment is altered.

One potential mitigating factor for inadequate consent is the requirement of a more rigorous informed consent process. Such a process would help to ensure that the patient is making a fully informed decision about receiving treatment. The process would consist of outlining a more rigorous consent process in the user labeling of the device that would require the use of an additional checklist in addition to standard written informed consent procedure. This checklist would contain all known risks of device usage, the likelihood of occurrence, and the potential severity.

During the process, the treating physician and patient would be required to review each item with both parties signing off to acknowledge discussion of the item. This checklist could then be kept with the standard written informed consent documentation, and the criteria for patient capacity to consent to treatment and perform the acceptance of risk through this process would remain unchanged. Acceptance of risk checklist may be a useful special control for addressing the risks of ECT device use.

Within FDA, there's precedence for requiring such additional informed consent requirements.

Please keep this discussion of key risks and potential mitigating factors in mind in your deliberations of the following question regarding whether the medical and physical risks of ECT can be adequately mitigated.

Adequately mitigating by employing regulatory controls such as restricting ECT device use to physicians with specific training and/or experience with the administration of ECT; or with physician labeling recommendations for pre-ECT assessment and ECT procedure monitoring, the appropriate use of general anesthesia, neuromuscular blocking agents by a licensed anesthesiologist during the procedure, pre-ECT dental assessment and the use of mouth protection, EEG monitoring, and adequate skin preparation and the use of conductivity gel during electrode placement; or patient labeling requiring the use of a checklist of all known risks of ECT with each item to be signed off by both patient and physician prior to initiating treatment; or the requirement for further premarket studies, either preclinical, bench or animal testing, or clinical studies for significant changes in device technology or new indications for use. And we'll ask the Panel to discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the medical and physical risks of ECT.

A second area of key risks associated with ECT use is cognitive and memory dysfunction. The FDA review found that ECT is likely associated with immediate general cognitive and memory dysfunction. Cognitive dysfunction is represented by disorientation. Disorientation appears to be transient and generally resolves in a matter of minutes after the procedure.

Memory dysfunction in general largely resolves in the days to weeks after the completion of a course of ECT. However, in certain domains, particularly in anterograde verbal memory and retrograde autobiographical memory, deficits may be more prominent and/or persistent. While anterograde memory deficits may resolve in the days to weeks after ECT, autobiographical memory deficits may be more persistent. Per Dr. Como's and Dr. Krulewitch's presentations, at one to two weeks post-ECT, there is evidence that suggests that autobiographical memory performance is approximately 76 to 77 percent of baseline performance for right unilateral treatment and 58 to 67 percent for bilateral treatment. Limited evidence suggests that ECT memory deficits may approach baseline at six months.

In terms of mitigating factors, studies have demonstrated that potential mitigating factors for reducing the occurrence and risk of memory and cognitive adverse events might include exclusive use of square wave, direct current, brief pulse stimulus, use of ultrabrief pulse, 0.3 milliseconds stimulus, exclusive use of unilateral nondominant electrode placement, use of bifrontal electrode placement, or limiting ECT administration to twice per

week.

When the onset of memory and cognitive function are noted during the course of ECT, other mitigating strategies may include switching from bilateral to unilateral treatments, decreasing energy dose or employing ultrabrief pulse stimulus. Identification of safe stimulation parameters in the device labeling to inform practitioners of safe device use may serve as an additional mitigating factor.

Please keep this discussion in mind in your deliberations of the following Panel question regarding mitigating the risks of adverse cognitive and memory adverse events, by employing physician labeling recommendations for exclusive use of brief pulse, that is 1 to 1.5 millisecond waveform stimulus; use of ultrabrief pulse, 0.3 millisecond stimulus; exclusive use of unilateral nondominant electrode placement; use of bifrontal electrode placement; limiting frequency of treatment to a maximum of twice weekly during a course of ECT; and monitoring cognitive status prior to ECT and throughout the course of treatment.

Also patient labeling requiring the use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment or requirement of further premarket studies, either preclinical, bench or animal testing, or clinical studies for significant changes in device technology or new indications for use.

Please discuss each of these potential controls and whether it,

either alone or in combination with others, adequate mitigates the cognitive and memory risks of ECT.

My only device malfunction was identified as the third category of key risks of ECT devices. The proper functioning of all devices, not only ECT devices, is typically mitigated by generally accepted manufacturing and safety standards. These include general controls, such as good manufacturing practices and quality system regulations as described in the Code of Federal Regulations, as well as through adherence in international safety standards of medical devices such as the International Electrotechnical Commission, for example, IEC 60601-1-1 for medical electrical system safety requirements, and electromagnetic compatibility.

In summary, the objective of this Panel meeting is to gain expert recommendations on the question of whether ECT devices should be classified as Class II or Class III for each of the currently cleared indications. To review the classifications, Class II devices cannot be classified into Class I because general controls themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and there's sufficient information to establish special controls to provide such assurance. Class III devices are those for which general and special controls cannot be established and therefore provide reasonable assurance of the safety and effectiveness of the device, and therefore premarket approval is required.

The determination of a reasonable assurance of safety and effectiveness rests on the balance between the probable benefits and risks to health. Throughout the FDA review, we have attempted to accurately characterize the effectiveness of ECT, identify the keys risks of ECT, and offer consideration of potential mitigating factors of those risks. We hope that this analysis will be useful for the Panel in their deliberations of the following question.

Currently cleared indications for use for ECT devices include the following: depression, both unipolar and bipolar; schizophrenia; bipolar manic and mixed states; schizoaffective disorder; schizophreniform disorder; and catatonia. Please provide your overall recommendation for the classification, Class II or III, of the ECT device for each of the above indications.

This concludes the FDA prepared remarks for the Advisory Panel. Thank you.

DR. BROTT: Thank you, Dr. Park.

We'll take a short break, 15 minutes, and we haven't been too good with getting back on time. So let's try to get back here before 20 of 4:00. Thank you.

(Off the record.)

(On the record.)

DR. BROTT: Before we proceed with questions to the FDA, we

have a scheduled speaker who was not able to make it for this morning's session, and we would like to invite her to the podium, Kitty Dukakis, and, Ms. Dukakis, you'll have five minutes. When you get to one minute left, the light to your left will turn from green to amber.

MS. DUKAKIS: Thank you so much for allowing me to speak out of sync, but I have been 48 hours traveling here from Los Angeles.

My name is Katherine Kitty Dukakis, and I live in Brookline, Massachusetts, except during the months of January, February, and March when my husband and I live in the westward section of Los Angeles, and he teaches at the winter quarter at UCLA.

Nearly 30 years ago, in the early 1980s, I began experiencing recurring cycles of depression for no apparent reason. They would hit me every eight or nine months and last for some three or four months, and I could only describe them as being some of the most painful experiences I've ever had. I was treated with therapy, and it would seem to be one unending series of antidepressants after another. Nothing seemed to help, and each cycle produced a depression deeper and more painful than the last.

Finally, after some 17 years of this, Dr. John Matthews of the Massachusetts General Hospital suggested that my husband and I talk with the hospital's ECT specialist, Dr. Charles Welch, about the advisability of undergoing a series of ECT treatments when I was next hit with another of these depressions.

My ECT treatments started 11 years ago, and I would usually have 5 or 6 treatments each time my depression returned. I am now and have for the past 11 months been on ECT maintenance and receive a treatment once a month under Dr. Welch's supervision in Boston and Dr. Ruben Espinoza's in Los Angeles.

It is not an exaggeration to say that I doubt very much that I would not be alive today without ECT. The treatment has been a miracle in my life and for my husband, our three children and their spouses, and our eight grandchildren. In fact, I feel so strongly about the importance of ECT as a treatment for severe depression and other mental and emotional illnesses that I have spoken to grand round meetings in hospitals in close to 30 states and coauthored with Larry Tye a book on the subject entitled *Shock: The Healing Power of Electroconvulsive Therapy.* It is a book that many doctors recommend that their patients read if they are considering ECT.

I have often been asked by physicians to speak individually to patients who are suffering from serious depression but are frightened by the prospect of the treatment. In fact, Larry and I wrote at the end of our preface in our book, "ECT is the only remedy in mainstream medicine that is expanding in use, receiving increased attention and research, and offering lifesaving hope to tens of thousands of people even as some of the public believe it is extinct."

I have a real fear, as have so many of us who have been helped by ECT, that changes some groups are advocating will affect the very positive strides that many of us have made. What is really troubling for the thousands of us, who thanks to ECT are leading healthy and happy lives, is the possibility that ECT will not continue to be made readily available to us and to so many others who could be helped by it.

As both a patient and an advocate, I want to urge you, the Panel, in the strongest possible terms, to reclassify ECT devices into Class II and make it possible for thousands more to benefit from a form of treatment that has transformed our lives. Thank you.

DR. BROTT: Thank you. At this time, the FDA speakers, Drs. Como, Krulewitch, Komiyama, and Dr. Park, and do we have questions for the speakers. Yeah, let's start with the question from the webcast, and it's from Dr. Stebbins, and the question is to Dr. Como. So, Dr. Como, could you come to the podium. Thank you.

And it says, could you ask the Chair to ask Dr. Como the following: Since memory is a biological function, how would you interpret the biological basis of short-term memory deficits at zero to six months followed by potential return to baseline levels at greater than six months? Is there a proposed biological mechanism that could account for these findings?

DR. COMO: Peter Como, FDA. The answer to that question is I

don't think that there's any evidence in the scientific literature much like what the neurobiologic mechanisms for the effectiveness of ECT might be. I think the same issue remains unresolved in the cognitive and adverse memory events literature for reasons that I think one can speculate what the punitive neurobiologic mechanisms might be from, you know. All the things that you heard Dr. Komiyama refer to in terms of direct and indirect mechanisms that might occur as a result of seizure termination will likely have an effect on clinical parameters such as cognitive functions. What that direct mechanism is or indirect mechanism is, is unknown, and why they may get better or improve out to six months, I think, is also unknown.

The only other potential sources of evidence, as I alluded to in my remarks, is that we continue to face this somewhat dilemma in that when you're depressed and have significant symptoms, you're likely to also have cognitive problems that can be both subjective and measured on formal cognitive testing, and when depression resolves, through any type of treatment, not just ECT, people typically report that their thinking is better and formal neuropsychologic testing also indicates that there's been a change from pretreatment levels.

DR. BROTT: Thank you. Dr. Goodman, before you begin with your questions, I think Dr. Ellenberg had a slide.

DR. ELLENBERG: I'm not ready.

DR. BROTT: You're not ready. Okay. So let's start with

Dr. Goodman.

DR. GOODMAN: This is Wayne Goodman. I have several question about effectiveness, although I'm not surprised that your overall conclusions based upon the review of the literature, the FDA's own meta-analysis comes out showing efficacy, particularly acutely for ECT. For depression and some of the other indications you have examined, I think I'm somewhat surprised that the magnitude of the effect wasn't larger. So I'm trying to understand a little bit more why that's the case. Based on my own clinical experience and what I thought I knew about the literature and ECT, I expected a stronger signal separation. So I wonder, not only for my benefit, but I think this would be useful for the committee, too, to go into a little bit more detail about the design of some of the sham-controlled studies that went into the meta-analysis and maybe why we didn't see anything, you didn't see any difference between sham and ECT after four weeks, something about the characteristics of the patients that went into the study, concomitant medications. So a little bit more details on the methodology in order for us to understand how to interpret the results. I wondered if that would be possible.

DR. PARK: Just a clarification. This is Larry Park. Are you specifically talking about the meta-analyses then?

DR. GOODMAN: I'm talking about the meta-analysis, but you can address my question whether looking at the meta-analysis overall or

picking out one of the studies, one of the five studies that contributed to it as representative, as a way of illustrating some of the questions I had in terms of the entry criteria, that the management, concomitant treatments, the times of observation, the standard methodological questions that goes into the design and interpretation of clinical trial.

DR. PARK: If you'll just excuse me, I'm trying to find the right graphic for that.

DR. CLAUDIO: Perhaps we can proceed to the next question, and then when Dr. Park finds his graph, he'll pull it up.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: From many other devices or procedures, we're able to determine different risk factors, and so in thinking about informed consent, I'm thinking if they knew what the risk factors were for the people who don't seem to resolve as readily or as quickly from their cognitive dysfunction, I was wondering in your review of the literature if you found any risk factors that would help someone better understand, you know, this percentage of people, 77 percent have memory problems post-procedure, you know, 30 percent 3 months out, 10 percent 5 months out, and rarely 99 percent resolved by 6 months. However, since you've had a head injury, you know, you're more likely to have persistent memory difficulties. I know we've done this for cardiology, for heart surgeries. We've done it in kidney and dialysis. We've done it in several other medical procedures where we

can predict who's going to fare better or worse with their cognitive outcomes.

DR. COMO: Sure. Peter Como. I'll try and answer that question. The short answer is that the literature doesn't identify the risk factors for a lot of reasons. One is in the earlier days, pre-cognitive assessment was typically not performed, and in some cases that may still be true today. Number two, a standard cognitive battery, regardless of which test you want to pick, hasn't been consistently employed. So we don't have the really large-scale studies with sufficient power, sample size to really answer that question, but in general, there really is not data in the literature as to what the predisposing factors towards cognitive impairment following ECT might be.

DR. BROTT: Dr. Kim.

DR. KIM: Dr. Como, your review of the reviews of the biographical or let's say just retrograde memory problems, I was a little bit surprised in two senses. One is that it seems like you only really emphasize personal memory over, you know, impersonal. And also I think there was a paper in 2000 that showed it's actually impersonal memory that's worse even as far as two months out, and that particular study I think had a control group, which was a little bit unusual. So is it the emphasis on the personal, it's because that's what people have looked at, the instruments, or is it actually each time they compare and then that's what they found?

DR. COMO: Yeah, I think a lot of that, and I'm not an author of any of these papers, of course, but the only thing I can speculate is that as subjects undergoing ECT began to report this type of adverse event and it seemed to focus on my inability to recall past personal events, researchers, if you could call up slide number 61, just -- and I know the Chair had asked for some numbers. Just to give you an illustration, if you actually look, this is our review, the FDA review of the personal memory. You can see that in the subacute period, there's 14 studies involving 1,456 subjects. So I think as a result of the fact that individuals were complaining of this, people then began to look for scales in the literature that could at least objectively quantify this deficit. So the Autobiographical Memory Interview and some of its iterations really began to emerge in the literature as the primary measures studied.

To address your other question, I think the assessment of "impersonal memory" is a little tricky and problematic because it really is dependent up on how you assess it, and if you ask people to recall factual or historical information, then you're beginning to have all sorts of confounds like education, other kinds of cultural and other biases so that if a person does not know who was president during the Civil War, it may have nothing to do with the effects of ECT or anything else but may just have to do with their limited education. So I think that data is a little confounded just by the nature of how you go and assess that, where as the Autobiographical

Memory Interview I think is a little bit more specific because it really does take people through a very careful interview.

DR. BROTT: Dr. Ross.

DR. CLAUDIO: Perhaps we can return back to the answer.

DR. BROTT: Dr. Park -- could you restate, Dr. Goodman, succinctly your question?

DR. GOODMAN: More information about the sham-controlled studies that went into the effectiveness meta-analysis in terms of design and methodology.

DR. PARK: I'm actually going to start at the end to directly answer your question but then work our way backwards to see what the logic was.

So this was the forest plot that we showed during the presentation. As you can see, there's five studies here, Wilson 1963, Lambourn 1978, Johnstone 1980, Brandon 1984, and Jagadeesh 1992. So these five studies, and actually our statistician, Dr. Schroeder, did this analysis for us. If you have specific questions about the analysis, I would probably direct my questions or answer to him. So those are the 5 studies, and they involve 202 subjects, and the range was *n* of 12 to an *n* of 72. And basically we looked at all studies where there was analyzable data where the score was the Hamilton Score in terms assessing depression change, and again to review those results, the estimated improvement of this meta-

analysis was 7.1 points, and based on a random effects model, and as you can see, the fixed effects model, the estimate improvement was 4.8.

Okay. So then to go back a couple of steps -- slide up please. I apologize for this slide. This slide is a chart that's in the back of the Executive Summary. All of the studies are in charts in the back of the Summary and they go over each one of the analyses. So this chart is a chart for randomized controlled trials included in systematic review of effectiveness, ECT versus sham, for depression. That's Table 8. Let me see if I can tell you what page it is, 110, and it continues on 111. It reviews all of the studies that we looked at, and I believe there's 11 of them today.

DR. BROTT: Did these studies have pre-specified sample sizes? I know these are old studies. If they did, did they reach their sample size?

DR. PARK: By and large, they did not. So one of the things that you note, Dr. Brott, is that a lot of these studies are the older studies. The years that they were done range from 1958 all the way up to 1992, but they're an earlier era of study, and I can't say for sure whether they didn't do a sample size estimation. Most of them by and large did not report a sample size estimation or power analysis.

DR. GOODMAN: Do you know if these patients were treatment resistant by any standard that's similar to what we might employ today?

DR. PARK: Usually if they specified, you can see that in the

third column, subjects. So if there was an indication that the patient was treatment resistant, then we would have made that notation there. Generally speaking, again given the older era of studies, patients or subjects in these studies suffered from depression. I do not feel confident saying that these patients that were enrolled in these studies would actually meet criteria for what we think of today as major depressive episode.

DR. GOODMAN: There's one last question I had. And were these all inpatient?

DR. PARK: Not necessarily.

DR. GOODMAN: Not necessarily. And you point out, I forget the exact wording, but that there wasn't clear evidence for efficacy beyond four weeks. Is that because of the limitations of the study or they didn't find what they were looking for? In other words, what is the endpoint of these studies? How many weeks?

DR. PARK: The majority of the endpoints were within a one-month timeframe, but there are some studies that did go beyond that, and you can see that in the sixth column as to where the time endpoints are, and those studies generally had a negative result at the later times.

DR. GOODMAN: And last question around methodology. How about the use of concomitant medications in trying to see how, you know, comparable to how we might do ECT today?

DR. PARK: This is just from my recollection, but I do believe a

fair number of these studies were looking at ECT in monotherapy, that is, without concomitant medication use.

DR. BROTT: Dr. Good.

DR. GOOD: There is one, I believe the Wilson study from 1963 that used imipramine and ECT versus imipramine and sham. So there were actually four arms, but I don't see any of the others that include the medication in it.

DR. PARK: And for the Wilson study, thank you for pointing that out, we only used the groups that were pertinent for each of the different analyses. So for this analyses, we used the sham placebo group and the ECT placebo group.

DR. BROTT: Dr. Peavy.

DR. PEAVY: I have a question for Dr. Como. Mostly because memory loss is such a frequent complaint, I'm concerned about what memory loss means to people. I think there's probably a lot of variability in patients and family members that report memory loss. I'm wondering if you have some thoughts as you've gone through the literature about getting a little more specific about actually what memory loss is, either subjective reports or using objective tests. For example, to some, I looked but didn't see much on this, do some of the reports differentiate say between retrieval ability and recognition memory and that type of thing?

DR. COMO: Sure. Actually that's a good question. One of the

things that also, and I didn't mention in my presentation, that limits the methodology used, the way by which memory is assessed, especially in some of these earlier studies, they fail to include a recognition trial for delayed recall. So if you just ask a subject to recall as many words as they encoded a few minutes ago, but then don't give them a multiple choice or some type of recognition, you're getting an incomplete assessment of memory so that you may have a person that recalls nothing but then recognizes the original material, so that their memory score is different from someone who would do poorly on both tasks. So that's very inconsistent in the literature because the early studies did not employ both a delayed recall and recognition parameter.

To address your first question, I think the literature is very, very clear, and I think you heard from the public testimony this morning that the key memory finding does seem to lie around this issue of the ability to recall both personal events or events that occurred just before ECT treatment and then in some time period following, and that tends to take on a very personal flavor for the individual at hand, whether it's remembering where you left your keys or remembering a key anniversary date. So I think the literature, first of all, there's the most amount of studies as I showed in the earlier slide, and number two, I mean I think that's what the literature really consistently tends to find. When you start to really parse out some of these other aspects of anterograde memory and how that's assessed, it gets

a little muddier.

DR. BROTT: Dr. Gordon.

DR. GORDON: This question is directed to Dr. Park. You listed several potential mitigation factors, and many of them I would consider just information collection attempts. What I really would find much more helpful would be specified thresholds of safety or danger or risk, and as I go through the list of several, probably 10 or a dozen mitigating factors, I do not see thresholds for risk or risk tolerances.

DR. PARK: I would agree. We did not specify risk tolerances for probably any of the potential mitigating factors. I think a lot of that has to do with the fact that in the literature, it is noted that those are difficult to specify. So that's why they're not included.

DR. BROTT: Dr. Good.

DR. GOOD: So two of the most important tables here, going back to the tables that you have, are Table 8 which we just looked at I believe and Table 9 which is ECT versus placebo, and I want to focus on the outcome measures for these studies. These are mostly old trials. If you look at the *n*'s, the *n*'s are fairly small, and some of these trials talk about clinical assessment, you know, the outcome measure is "clinical assessment." So without drilling down further, that's somewhat bothersome to me. These are trials from the '60s, '70s, and we talked about the HAM-D as being probably the most consistent efficacy measure, but a lot of these don't even

use that. Some do. So I wonder if you can just comment on that. I guess maybe it's an obvious sort of a statement, but any comments.

DR. PARK: Yes, I think that your observation is accurate. As you can see, there are several studies where the efficacy measure is noted as clinical assessment, and generally that clinical assessment is some sort of score by the clinician or patient on a 1 to 5 scale, kind of a predecessor to our clinical global impression scale.

Those studies were systematically collected. We did include them in the systematic review. However, those studies were not included in the meta-analysis and, you know, as we undertook this project, I think it was a matter of discussion and an eventual matter of consensus from the group that we only use one measure in order to reduce the heterogeneity of the meta-analysis. So of all of these studies that we identified, randomized controlled trials, only the ones that used the Hamilton were included in the meta-analysis.

DR. BROTT: Dr. Domino.

DR. DOMINO: I have a question for Dr. Komiyama, and this question, there are actually two questions. One is related to the deaths that you describe in Nuttall et al. in 2004. You mentioned they weren't related to the treatment, and then I heard later on that many of them seemed to be anesthetic or patient comorbidity complications. I wonder if you could tell me what these 18 deaths were.

DR. PARK: I think maybe if I could answer that question. My recollection from reading that paper, and in order to be completely accurate, I would have to go back to it -- I believe that paper is included in the bibliography, and if it's not, we certainly can provide it -- but I think the reason that the authors concluded that many of these mortalities were not related were that they weren't related to anesthesia or related to any neurological complications. I believe in some cases there was some period of time before a cardiovascular event, or I think maybe there was even an accident that --

DR. BROTT: Do you know what time period we're talking about? Was it less than 30 days, a year, or --

DR. PARK: What did the slide say? I think it said within a month.

DR. DOMINO: Thirty days on the slide.

DR. BROTT: What's the denominator?

DR. DOMINO: 2,279 patients receiving a little over 17,000 treatments and there were 18 deaths within 30 days of the last treatment.

MS. CARRAS: Excuse me. This is Michelle Carras. I have that paper up in front of me if anyone would like me to read any of the information.

DR. BROTT: What's the first author? I've got it here, too.

MS. CARRAS: It's Nuttall, N U T T A L L. I was actually going to

bring that one up myself.

DR. DOMINO: I did have another question while --

DR. BROTT: I would just say as we look into it, I'm involved, and Dr. Good just reviewed a study of 2,500 elderly patients, and 30 day mortality and, you know, 18 deaths in 30 days, you have to take that pretty seriously. So maybe we can come back to that one. I can maybe e-mail it over to you. Did you have a second question?

DR. DOMINO: Yes. I was looking at some of the histopathology stuff, and the question I had as you were talking about primate studies and you were saying there were some older rodent studies, and I'm just curious with repeated electroconvulsive shock -- I don't want to call it treatments. I mean they're not really treatments, and assuming you're oxygenating these animals beforehand so they're hypoxic during the period of time, is there any histopathologic evidence of any brain damage in these species of animals?

DR. KOMIYAMA: Sure. I guess I'd like you to tell me what you mean by brain damage. Are you meaning loss as well as proliferation?

DR. DOMINO: Whatever you think as a neuropathologist.

DR. KOMIYAMA: Okay. So, yes, there were -- I think that is in your Executive Summary. There were studies that did find loss of neurons specifically in the hippocampus, in rats as well as mice. On the other hand, there were about an equal amount of papers. Could you bring up my

reserve slides? I'm not sure which number it was. Hold on for just one second.

So there are papers by Zarubenko and Cardoso, and there are a few papers by Cardoso from that lab that demonstrate neuronal loss in the hilus on the right-hand side. Nonetheless, in the left, in Zarubenko et al., there was a significant decrease in certain portions of the hippocampus as well, which is noted in the black bar.

On the next slide, there was also noted neuroproliferation in rats after electroconvulsive shock, and you can see this, and I think the papers have been provided to you in Malberg et al. 2000, Madsen et al. 2000, and Hellsten et al. in 2004, and similar results to what I showed in the Perera study.

DR. BROTT: Dr. Ross.

DR. ROSS: I'd like to ask a question to follow up on this, and then I have a question about cognition. In these rodent ECS studies, are the animals oxygenated the way humans are done, or is the shock done without any attempt to maintain oxygenation?

DR. KOMIYAMA: I will look that up and get back to you on that.

DR. ROSS: Because that could make a big difference.

DR. KOMIYAMA: Sure.

DR. ROSS: And then a question about cognition, I think this is

such an important issue and such a major concern, my impression is for most patients, it's a relatively limited concern, but there are some patients, and we heard some of them today, for whom memory problems are really a major and very disturbing side effect. I'm just wondering if there's any way to identify the patients who have those more disturbing complaints? For instance, do they have cerebrovascular risk factors? Do they have anything else that can give one a sense of who might be at higher risk? I think this is related to the question Jane asked, but I just want to make sure we're getting a good discussion of that.

DR. COMO: Thank you, Dr. Ross. I think that's a very important question. In reviewing the literature, that was one of the things that I was specifically searching for because I think a key issue is are there risk factors before the initiation of treatment that's going to predispose you to the later development of cognitive or persistent cognitive problems or maybe reduce the likelihood that you might return to baseline or improve.

Unfortunately, that hasn't been a topic that researchers have really looked at. I mean there are mentions in the literature, usually the older literature, and some of the new literature, although they didn't study it in their discussion sections, they draw out the usual cast of characters, age, previous history of neurologic injury, head injury, the usual cast of characters in which if you sustain these types of problems or these demographics, you're probably at a likely risk, but evidence-based data for

that just doesn't exist at least in our review of the literature.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Regarding the slides you have up here and other evidence that ECS or ECT might induce neuroproliferation, and answer to your question is that brain damage or not, certainly it's an indication of possible brain changes, but generally speaking, that would be interpreted as a possible clue to the mechanism or therapeutic mechanism of action of the treatment, and similar kinds of neurotrophic effects have been postulated to be the mitigating factors of antidepressants as well. So this may be a clue to how it works rather than indicative of damage.

DR. KOMIYAMA: Yes, you're correct. I think possibly that the terms neuropathology or neuropathological changes should not be so closely tied to brain damage. I think one is possibly the other and the other one is possibly separate.

DR. BROTT: Ms. Carras.

MS. CARRAS: Thank you. I just wanted to respond on a couple of things. I think Perera in 2007 lists an alternate hypothesis for the neuroproliferation, saying that it could be a response to cell death. So I think that should be kind of out on the table as well, but I also wanted to point to the fact that it seems like we're talking about, with regard to the memory loss and patients' subjective experience of it, that there may be a subgroup of patients for whom it is a devastating experience to undergo

ECT, and we don't seem to know who might have those devastating results and who might feel like it saved their lives. So I wanted to bring up, if people could keep in mind how ECT might be delivered in practice might affect the decisions that we make about what we recommend to the FDA in terms of their regulation decision.

DR. BROTT: And related to that, maybe, Dr. Park, you can answer this. I'm still, as a neurologist, a little confused because we called it electroconvulsive therapy, but the studies that have been cited, you're looking at how you're delivering the current to induce the seizure, and it seems to me that, or we haven't heard evidence, and I did my homework, I tried, and I was unable to get much of a connection between the stimulus and the seizure, and we heard data about delivery methods in terms of the electrodes and strength, but if I were reviewing the papers, I would, you know, wonder how long was the seizure? What were the measures of the seizure? And is that just not available?

DR. PARK: There is an earlier literature that we did not review. I would say to summarize that literature, initially when ECT first originated in the late 1930s and 1940s, of course, the question was mechanism, like what's going on and how does this all work? And through a series of these older studies, it was determined that the therapeutic part of the treatment is actually having the seizure. Actually before 1938, a lot of people were trying to treat depression or other psychiatric illnesses not using

electroconvulsive therapy but a chemical convulsive therapy. So they would offer pro-convulsant agents to patients. They would have a seizure that way, and at least in the literature, that was reported as a much more dangerous way to have a seizure when compared to electroconvulsive therapy. So I think that --

DR. BROTT: But that had to do with hypoglycemic coma, didn't it?

DR. PARK: Well, insulin coma therapy is a type of therapy that is often thought to be related to ECT. However, my understanding of that is that actually insulin coma therapy, people think that the important part about that treatment is the hypoglycemia and not necessarily the seizure, and so when you look at differential effectiveness, some papers and some researchers have reported that it's not the seizure that's the important part of insulin coma therapy. It's really the hypoglycemic episode.

DR. BROTT: Well, in this instance then, do we know or do we have evidence? Is it the electrical stimulus or is it the seizure or should this be studied?

DR. PARK: I think it's both. So the earlier body of literature told us, and I think fairly conclusively, that it's really having the seizure that's the important aspect of the treatment.

Now, the newer literature is trying to understand it even more. So it's not just having a seizure. There was a period of time when

they were looking at sort of the dynamics of the seizure, the characteristics, the length, and I think generally the conclusion from those studies would be that it had to be a generalized tonic-clonic seizure and had to involve both hemispheres of the brain. It had to demonstrate a certain morphology, meaning pretty deep spike in wave activity and symmetry on both of the hemispheres and last 30 to 60 seconds. So the research has been trying to hone down more and more, and I think that's where it gets us to this issue about, is it the stimulus? Well, it is also probably some aspects of the stimulus which we don't know if it's just the stimulus itself or whether increasing stimulus may affect the seizure and some characteristic that we've not yet identified.

DR. BROTT: Dr. Kim.

DR. KIM: Yes, Dr. Park. I just wanted to go back and follow up a little bit deeper into what Dr. Goodman was asking about, the sham comparison, because that's our, I guess, such as it is, the best data in terms of effectiveness, I guess, because those are the only sham studies we have. And I guess I would like for you to comment further since you know this literature better. It's obvious that what they were doing in those studies is very different from what people do today, and I think it would be helpful for us if you could enumerate some of those differences. I mean just from perusing this, it's clear that, you know, bilateral, unilateral, doses, different pulse delivery, even using individual thresholds to gauge doses and so forth,

and what effect those differences from today might have on how we think about, does it mean that they underestimated the true effect size or did they -- do you see what I'm saying? So if you could comment.

DR. PARK: Well, let's walk through this. I'm not sure in the end what the final calculus is going to be, but the first thing I would note from these studies is this patient population or the subject population. So in current studies, we have a much clearer idea of some diagnosis as to what the subject population is, and here we do not for many of the studies. They're just saying they're schizophrenia or depressive illness, depressive syndromes, symptoms of depression. You can go down the chart and you can see. So it's not entirely clear as to whether it's the same population or different population than what we would be studying today.

If you look at the next column, looking at the sample size, I believe Dr. Goodman said this, but I would echo the comment about these are generally smaller studies, and it's not clear from many of the studies whether they were adequately powered.

In terms of the comparisons, so these are sham studies, and when we say sham, we've included a number of different comparative treatments. So those treatments can be something like having general anesthesia but not having a stimulus. One of the other or maybe several of the other studies had the comparator where they applied a subconvulsive stimulus after the induction of general anesthesia. There's one study that

actually gave the sham group one real ECT to initiate the course and then sham treatments afterwards. So there's a range of different sham conditions, and I think this was a topic of conversation before, as to what the blinding of that was, and again generally speaking, we don't have very good blinding analyses for these studies to know whether participants in the trial would know whether they were getting the real treatment or not the real treatment.

So having said all that, I think it's very difficult to kind of put an estimate or to say which direction those types of effects would have versus, you know, what we would see today.

DR. BROTT: Okay. Dr. Eydelman.

DR. EYDELMAN: And in light of Dr. Goodman's and Dr. Kim's comments, I just wanted to point out that the current clearances do not limit the use necessarily to parallel what you believe the current practices are. So, hence, the summary, the comprehensive summary as performed is really parallel to what the currently cleared devices allow one to do.

DR. KIM: I didn't get that. It sounds like a regulatory statement more than a scientific one. So --

DR. EYDELMAN: Okay. Let's try one more time. Both of you referred to current clinical way of using ECT. While there may be an APA guideline or some other clinical guideline, that does not parallel the current regulation of the ECT devices. So the effectiveness analysis as performed

really parallels what the FDA cleared devices allows one to do with these. Did that make more sense?

DR. BROTT: Dr. Goodman.

DR. GOODMAN: I know what you're saying, but I'm not sure it makes that much sense from a clinical standpoint. I understand from a regulatory standpoint but, in fact, there are some major differences, we can go through them, between the way those studies are conducted and the way we would practice with the device currently.

DR. EYDELMAN: Right. And that's why tomorrow we'll be asking specific questions as to whether you believe the use of ECT devices should be limited to those particular ways. So there's a rhyme and reason to this.

DR. BROTT: Right now we're asking you the questions. Dr. Komiyama, I did try to do my homework, in trying to determine myself from the material that we were given in terms of whether or not we have evidence what this does or doesn't do to the brain. You mentioned I guess the S-100 and enolase. You know, for the heart, we've got troponin. It's very sensitive for cardiac injury. Any hospital in this metropolitan area, if you have anything close to chest pain, maybe pain in the jaw, you'll get troponin, and it's remarkably reliable. It's got standards. The markers that you mentioned, none of them have been shown to be reliable. All of them have been shown to be unreliable. That's why they're not used in the

hospital down the block or anywhere in the country to measure brain injury.

We also have MRI scans that we use. We've got DWIs with acute seizures. It's not infrequent to see changes, and we also have the EEG that's going in the device, and with 100,000 people a year, you know, as a neurologist, I'm asking, you know, how many people have had MRIs to look at the structure of the brain? How many people have had serial EEGs to look at potential changes in the EEG? And how many people have had neuropathological examinations which would be appropriate to judge whether or not this device impacts the structure of the brain? And I tried to look and I saw very little, and I concluded that the evidence is not there to really address the question either way, and I'd like to hear how you would respond.

DR. KOMIYAMA: Certainly. I agree with you. I think biomarkers can be a useful tool. However, lack of there being any changes or any evidence that they peak when there's been -- post-ECT doesn't necessarily mean that there's no damage certainly. You're mostly referring to the human studies, correct? MRI biomarkers.

DR. BROTT: That's what we're asked to decide.

DR. KOMIYAMA: Certainly. You're right. I do believe I presented today more of the non-human, non-primate, sorry, the primate data as well as the human data. I think there is quite a bit of rodent data that demonstrates lack of lesions and gross neuronal loss. However, the

human data appears to be not perfect.

DR. BROTT: Dr. Good.

DR. GOOD: So a couple of comments to follow up on this. It seems a little amazing that systematic MR imaging hasn't been performed on people who have had the ECT. I guess that's the case. I didn't do a search myself, but I'm assuming you didn't find anything but what you've already presented with hippocampal volume. Is that right?

DR. KOMIYAMA: There is another paper I mentioned but I did not show the slides for. It's Nobuhara et al. in 2004. It's titled "The Effects of Electroconvulsive Therapy on Frontal White Matter in Late-Life Depression," and that's using a diffusion tensor imaging study, and what they found was that there was a significant increase in frontal white matter following ECT treatment. That publication has been provided.

DR. BROTT: Again, the hippocampal study is 12 patients. This study is 8 patients. You know, I've got it here on my computer. I'll look at it carefully this evening, and the other one as well. Dr. Goodman, or Dr. Good.

DR. GOOD: One other point. The neuroproliferative changes, this is in the hippocampus, right? Isn't this where these were? I'm sorry. I missed part of that, the slide you had up here.

DR. KOMIYAMA: Yes, those were in the hippocampus.

DR. GOOD: So that's quite common. It isn't necessarily negative, that's right, and actually neuroproliferative changes in the

hippocampus has been described just with seizures, and if you're giving seizures with ECT, that's another possible explanation.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I just summarized the deaths that you had queried earlier because I thought that was key for us to be able to review, and of those 18 deaths, 2 were suicides; 1 was neuroleptic malignant syndrome; 5 were in a nursing home, and although the nursing home said unknown, the description of the patients were end stage dementia, end stage Parkinson's, on oxygen for severe end stage COPD, and stroke; 3 were cancer, lung cancer, colon cancer, and pancreatic cancer; 4 were cardiovascular related, and 2 of those had end stage renal failure, 1 was pulmonary fibrosis, 1 was hepatic cirrhosis. So these were from very sick folks. There's multiple comorbidities.

DR. BROTT: Ms. Carras.

MS. CARRAS: Michelle Carras, Patient Representative. As a former medical librarian, I have some concerns about how the data were presented, and this Nuttall study is a good example of that because we were told by a couple of different speakers that the 18 deaths weren't related to the ECT, but 2 of them were suicide, and that has been brought up as a potential key risk, I believe the term is. So that is something I think we should consider.

Another thing is that we were given an enormous amount of

literature to review as a Panel and, Dr. Park, when you did your review of the sham literature in depression, there was a slide, hold on just a moment please, there was a slide on page 59, the effectiveness summary slide, that reported only the positive findings for ECT versus sham, whereas on the detailed slide on page 54, we're told that there's no evidence that ECT is superior to sham at one month or longer. And these kinds of ways that things are reported, I find it a little more difficult to draw conclusions when I feel like I have to sift through a lot of conflicting ways of things being reported.

DR. BROTT: Do you wish to respond, Dr. Park?

DR. PARK: Thank you for your comment. I guess for the first issue regarding the Nuttall study, there were two suicides, but my recollection was according to the paper's authors, they did not think that they were related, and as we know, suicides can be related to depression as well. So from the FDA perspective, we weren't able to analyze more than that. We weren't given any more information than that.

With regard to the presentation of the data, I didn't completely understand you, but I thought that we had presented in the ECT versus sham information that there was no data for evidence of effectiveness after one month.

DR. BROTT: Dr. Ellenberg. Dr. Ellenberg asked to show these slides, and we felt that it was worth him doing it. Go ahead.

DR. ELLENBERG: What I'd like to do is try and get some guidance from FDA for our deliberations tomorrow, and I'd like to go through both the data sources for safety and the data sources for efficacy. If I'm taking too much time, I can split them in half or what have you.

My sense from the MAUDE reporting, which I assume is equivalent to theirs and the other reporting elements to FDA, side effects, that it's basically anecdotal, voluntary, and there's no denominator data. So when we look at the results from MAUDE, well, obviously looking at frequency of side effects, especially if they're very bad side effects, and seeing changes over time or what have you is extraordinarily important. In terms of judging the safety profile for a particular device, it leaves a lot to be desired. The reporting bias, I would guess that there are fewer reports than there really are, but I'm sure someone else could argue that there are more reports than there really are.

We don't have any reporting of the CI infractions, and one of the papers that was presented I think by Dr. Park, but I'm not sure, indicated that it was non-trivial, but again we don't have a requirement that people report side effects from the ECT.

It may be that in terms of the mitigating factor, if this were to go forward, might be that we would have required reporting, and then at least some timeframe we would know that all of the reports, all is an overstatement, but many more reports might come in and we would have a

much better denominator. Right now, if you take the number of reports, and we've seen 500, 700, 1200, we don't know the denominator for that number. So we don't know if that's frequent or infrequent. We don't know the usage. We don't know whether the usage is the first time -- or it's the third ECT. That data is simply not available.

So this raises the larger question for everything we've heard today. We've seen data that's been anecdotal, both from the audience and from the literature, and we've seen data all the way up to the theoretical gold standard in terms of randomized controlled trials. So there are multiple sources of data designs, that we use to collect various information that we've seen, and I think it would be very helpful to me certainly, and perhaps the committee, to try and understand what FDA expects from us in terms of the evaluation of this data.

DR. BROTT: Before we leave the slide, Dr. Ellenberg, reporting of CI infractions, Dr. Ellenberg is a biostatistician. Oh, my goodness. Could you translate that for all of us.

DR. ELLENBERG: It should be IC. Excuse me. That's a social preference. It should be informed consent, not confidence intervals.

DR. BROTT: Thank you. Dr. Eydelman.

DR. EYDELMAN: Yes, you're absolutely correct in everything that you have said. The data sources that we presented --

DR. BROTT: I can't believe that really.

DR. EYDELMAN: The data that we presented to you does indeed have a wide variance of accuracy or producibility. Having said that -- hence the dilemma. So we convened this meeting with the hopes that you will utilize your clinical expertise, or your statistical expertise in your particular case, to help us put all of these data together and answer the questions tomorrow.

DR. BROTT: And I just wanted to make a comment. We had another panel yesterday, and I had to review my own papers from 1983 and 1985, and one of them was published in *JAMA* and the other one was published in *Stroke*, and I must say it was shocking. And I think we really do need, all kidding aside, to appreciate the challenges of comparing studies from different eras, and when the studies are positive and practice is affected, then it makes the studies that we like to see today much more difficult to accomplish. Dr. Goodman.

DR. GOODMAN: Yeah. The question has come up several times in this discussion about are there any neurotoxic effects of ECT or ECS, and it seems to me, I'm not an expert on this, but at least in animals, if you take some of the animal studies you reviewed looking at ECS, that try to replicate how it's done carefully in the clinical environment, appropriate oxygenation, similar kinds of proportionate magnitude, that you can, unlike the case in the human, do very invasive studies. Lots of studies are done in traumatic brain injury, assessing the effects of oxygenative stress, apoptosis.

You don't have to wait until you see something on the MRI or the CSF. You can homogenize the brain and look for evidence that there's been neurotoxic damage.

So in your review of that literature, I've been trying to do it here as I sit, and I can't find any evidence that ECS acutely in animals induces any more toxic effects. although there are a number of reports that particularly repeated ECS induces neurotrophic effects that are similar to what are seen with chronic antidepressant treatment.

DR. KOMIYAMA: I'm sorry. What was your question?

DR. GOODMAN: The question is did you find any evidence in your review of using ECS in animal studies of neurotoxicity, you know, meaning of the kind that you might see if you gave methamphetamine or you induced traumatic brain injury, some evidence of oxygenative stress, so glutamate, you know, the usual suspects in the chain leading to cell death, from cell injury to cell death.

DR. KOMIYAMA: I think the majority of the papers similarly looked at did stainings and looked at loss of neurons or loss of volume in specific portions of the brain. Fewer looked at actual neurotoxicity based on -- you're thinking of doing immunohistochemistry stainings to look for particularly neurotoxicity, I assume. I did not come across those I know of, no. I can look into my research or my review and look for those.

I want to answer the question from earlier. I think you asked

about oxygenation. The primate studies did have oxygenation for the ECT treated animals.

DR. BROTT: In terms of our timing, we will have to adjourn at 5:00 tonight because of transportation challenges.

One thing with the models, you know, it is tough to truly model diseases like stroke where the average age is basically around 68, 69. What's the average -- because we use teenage rodents is what it amounts to. What's the average age? Do we have data on the average age and the age spread, like interquartile range, you know, mean interquartile range, something like that to describe the population undergoing ECT?

DR. PARK: This is Larry Park from the FDA. We do not have that data readily available, but over the evening tonight, maybe we can come up with some information with regard to that question.

DR. BROTT: Thank you. So we've got 15 minutes left for questions. We haven't heard from Dr. Duff for a while. Dr. Duff.

DR. DUFF: This is a follow-up on a question that Dr. Peavy had started earlier. One of the more consistent findings that come from cognitive literature seems to be this autobiographical retrograde amnesia or memory loss. And I think it's probably because losing personal information is very personal. It's something at you can really identify very clearly, and I'm wondering if there's in the literature any specific information about what types of autobiographical information gets lost for individuals that undergo

ECT? Is it, you know, what they did or had for breakfast the morning of the ECT or the day before, or is it like some of the personal comments made that they're losing chunks of their lives from much earlier on, you know, well before they had the ECT treatment? I'm wondering if you could comment on the specific types of autobiographical information that seems to be lost.

DR. COMO: Sure. It really hinges on -- Peter Como, FDA. It hinges purely on the components of the Autobiographical Memory Interview, or the AMI, which is probably the most commonly used one, and there's a short version and there's a Duke version of it as well, and basically it's just broken down, and what patients typically do is the metric is the percent of events that you recalled from your baseline assessment. So it's broken down into, you know, personal events and various personal recollections that are recorded prior to treatment, and then after treatment, they ask the same question again, and the metric is a calculation of the percent recalled. We could probably pull up the Autobiographical Memory Interview to look at the specific content if you want, but it does cover what you said, the gambit of recalling key personal events, you know, anniversaries, birth dates, those kinds of things. It also does include a section like you mentioned of recollection of things that were done prior, you know, within the past few days or so, but we can get that scale for you if you want to look at it.

DR. BROTT: Dr. Peavy.

DR. PEAVY: I think one of the questions that you might be referring to is where's the distress. I don't know where you would get that information exactly, but do you have any thoughts about that?

DR. COMO: You know, without sounding cavalier, I mean the distress is clearly autobiographical. For person A it may be extremely upsetting that you can't remember where your keys are, and for person B it may be even catastrophic to not remember your daughter's birthday. And I think I mention that in the limitations of the studies is that there's such a tremendous amount of individual variability, in cognitive tests, performance in general, regardless of the type of scale you're using. So, you know, one person's keys may be more important than another person's birthday, you're right.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Yes, Francine Stokes McElveen. Without a doubt, we know that the treatment itself is invasive, and I've read a lot of literature, but what I'm looking for specifically, and maybe you can help me, what factors can you consider prior to the implementation of the treatment that would limit the duration and intensity of the energy level to induce a seizure?

DR. PARK: Larry Park from FDA. Just as a point of clarification, do you mean per individual or --

MS. STOKES McELVEEN: Per individual. Are there any gold

standards or something specifically you can look at, factors that might contribute?

DR. PARK: In limiting specifically --

MS. STOKES McELVEEN: The energy level.

DR. PARK: -- cognitive.

MS. STOKES McELVEEN: Yes. We know that there's a range of energy, energy range level that may be used, but are there better factors to consider, if you want to limit the amount of energy used?

DR. PARK: Well, I guess I would have two responses to that. One is the data that we know about modifying the energy dose, my summary of that would be that dosage does appear important, and higher doses appear to be related to greater cognitive and memory deficits. That's particularly true of unilateral treatment and may also be true of the bilateral treatment. So, you know, one issue is that we would want to try to use the minimally effective dose of that.

The second response I would have is similar to one of Dr. Como's responses about can we tell, do we know what the risk factors are for cognitive and memory deficits for people undergoing ECT? And, generally speaking, that literature is not as well developed, though we do have some clinical practice which, as Dr. Como mentioned, really looks at the age of the person and also the presence of any underlying neurological, organic pathology before the treatments.

DR. BROTT: Dr. Ross.

DR. COMO: I found the information that Dr. Duff asked about.

DR. BROTT: Okay.

DR. COMO: I found the information that Dr. Duff was asking for. Is this the appropriate time?

DR. BROTT: That's fine. Could you repeat his question?

DR. COMO: Sure. Dr. Duff, I believe, I don't want to paraphrase you, but you wanted to know what the components of the Autobiographical Memory Interview were?

DR. DUFF: Yeah.

DR. COMO: Okay. And this is in your Executive Summary on page 136. So it was developed at Columbia University. The reference is Kopelman et al. 1989. It contains two sections, autobiographical incidence schedule and a personal semantic memory schedule. Each schedule contains questions from three time blocks, childhood, early adult life, and recent events, and then there's some information about its validation which I don't need to go into now unless the Panel wants that.

DR. BROTT: What was the first author again?

DR. COMO: The first author is Kopelman et al.

DR. BROTT: C --

DR. COMO: K O P E L M A N. I believe it's in your CD that we've sent you of the bibliography.

DR. DUFF: And, I'm sorry, but also more relevant to that was which of these areas seems most affected by ECT.

DR. COMO: It's really dependent on the study. There's no consistent block or events that seem to be more impaired than another.

DR. BROTT: Yeah, I don't see it in the CD. I did see it in the reference list. So maybe it's there, but I don't see it. It might be good to get it. We haven't heard from Dr. Gordon for a while.

DR. GORDON: All right. I am really surprised that these small sample studies show differences in safety as well as efficacy. I would be interested in some bigger picture questions of safety that could only be addressed with *n*'s of 20, 40, 50 thousand, where you have a denominator that has untreated and treated, and I'm thinking maybe Medicare databases, group practice databases, but in your search of the literature, did you find these studies? I mean large administrative databases. What we'd be interested in is incidence of trauma in an ECT group, and you could calibrate it with regard to exposure and timing, for instance. A Medicare database would have that. You could look at nursing home admissions, comorbid conditions, many more questions than can be answered in these small safety and efficacy studies.

DR. BROTT: Would you like to respond, Dr. Park?

DR. PARK: Sure. Well, I would agree. I think there's a dearth of those types of studies available in the literature at the present time. The

only study that your remarks call to mind is the study where we were looking at I believe it was, I think it was the Nuttall paper, where they were looking at, it was the Nuttall paper or the paper before that, where they did look at complications, but the main complication they looked at was cardiovascular complications. I think that, you know, it would probably be challenging to think about how you might make that study and be able to look at cognitive and memory problems in that large sample size.

DR. BROTT: Yeah, we might just ask our psychiatry and neuropsychology colleagues to think about that a little bit in preparation for our addressing the questions tomorrow. Certainly with procedures, other procedures, such as carotid surgery, coronary artery bypass graft surgery, appendectomy, you know, there are in-hospital audits, systems and, you know, these things are looked at all the time, and so we might think about is that feasible or not. Dr. Ross had a question.

DR. ROSS: Yeah.

DR. BROTT: We've got six more minutes.

DR. ROSS: This will take just a few seconds. I just wanted to follow up Dr. Goodman's question. If we're being asked to comment about this question of brain injury or brain damage, I think it would be useful if we could get some more systematic review of the rodent literature with oxygenated seizures and also the human MRI studies such as they exist.

DR. BROTT: Thank you. Ms. Carras.

MS. CARRAS: Just a quick question for Dr. Park. You had mentioned that there were mitigating, I'm sorry, that there was a precedent for development of a checklist that would be used for informed consent. Can you go into a little more detail about that?

DR. PARK: I'll defer that question to Dr. Eydelman.

MS. CARRAS: Thank you.

DR. EYDELMAN: So as Dr. Park alluded to in his presentation, we have had two precedents where for particular devices where we felt that it was imperative for the patients to be very, very clear about particular risks associated with that device, that we constructed a specific checklist, and that checklist delineates the adverse event and has two columns, one to be initialed by the patient and one by the physician. So this is what Dr. Park was referring to.

DR. ROSS: What devices were those?

DR. EYDELMAN: So, currently, the two devices are breast implants and the implantable miniature telescope, which is a device for end stage macular disease.

DR. BROTT: I have a question, Dr. Park. Frequently guideline statements from the American Heart Association, American College of Cardiology, you know, the American Neurological Association, those guidelines might be about a particular procedure. Very frequently they include suggestions for future research or what needs to be done, you know,

the holes in the knowledge. You've mentioned I think you went through two or three guidelines in detail. I think I looked at one of them last night, but I didn't focus on that aspect of things. What have the APA and the European groups suggested in terms of what they think needs to be learned about ECT?

DR. PARK: Thank you for the question. In our review of those practice guidelines, you do point out the fact that we didn't discuss what future directions the guidelines recommended. So, again, from my recollection, part of the research that they recommended really kind of reflects a lot of the questions that are going around the room right now. So really one of the questions is effectiveness and looking at the effectiveness of specific indications; also this issue that the effectiveness seems to be demonstrated only very short term and what happens long term and if there's a relapse there, and if there is a relapse, are there ways to prevent relapse, looking at different stimulation parameters or different ways to administer ECT to minimize cognitive and memory side effects as well as other side effects or also adjunctive treatments to try to minimize side effects as well. So those are the ones that I recall in terms of what the specific recommendations are from the treatment guidelines.

DR. BROTT: Thank you. We've reached 5:00 p.m. We've been asked to adjourn an hour early because of the traffic. Dr. Eydelman, is that acceptable to you?

DR. EYDELMAN: Yes.

DR. BROTT: Then we will call these proceedings to an end for today, and Dr. Eydelman, when should we reconvene tomorrow morning?

DR. EYDELMAN: 8:00 a.m., please.

DR. BROTT: Thank you. And thanks to the members of the public and to the members of the Panel. Thank you very much.

DR. EYDELMAN: Thank you, Dr. Brott.

(Whereupon, at 5:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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