FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) MEETING

Morning Session

Wednesday, February 3, 2016

8:03 a.m. to 11:58 a.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

Thomas A. Grieger, MD

Maryland Department of Health and

Mental Hygiene

Thomas B. Finance Center

Cumberland, Maryland

David Pickar, MD

(Acting Chairperson)

Adjunct Professor of Psychiatry

Johns Hopkins Medical School

Uniformed Services University of Health Sciences

Gabriel Sciences, LLC

Chevy Chase, Maryland

Murray B. Stein, MD, MPH

Professor of Psychiatry and Family &

Preventive Medicine

Anxiety & Traumatic Stress Disorders Program

Department of Psychiatry

University of California San Diego

La Jolla, California

TEMPORARY MEMBERS (Voting)

Dwight Dickinson, PhD, JD

Staff Scientist

Psychosis and Cognitive Studies Section

Clinical and Translational Neuroscience Branch

National Institute of Mental Health (NIMH)

National Institutes of Health (NIH)

Bethesda, Maryland

Jennifer Higgins, PhD

(Acting Consumer Representative)

Director

Compliance and Quality Assurance

Center for Human Development

Springfield, Massachusetts

Charles Hinkin, MD

Professor-in-Residence

Department of Psychiatry and

Biobehavioral Sciences

University of California Los Angeles School

of Medicine

Los Angeles, California

Dawn Ionescu, MD

Assistant in Psychiatry

Depression Clinical and Research Program

Massachusetts General Hospital

Instructor, Harvard Medical School

Boston, Massachusetts

Francis J. McMahon, MD

Chief

Human Genetics Branch

Intramural Research Program

NIMH, NIH

Bethesda, Maryland

Rajesh Narendran, MD

Attending Psychiatrist

Resolve Crisis Network

Western Psychiatric Institute and Clinics

Associate Professor in Radiology and Psychiatry

Psychiatric Molecular Imaging Program

University of Pittsburgh

Pittsburgh, Pennsylvania

Natalie Compagni Portis, MFT, PsyD

(Patient Representative)

Oakland, California

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Robert R. Conley, MD

(Acting Industry Representative)

Global Development Leader and

Distinguished Lilly Scholar, Neuroscience

Eli Lilly and Company

Baltimore, Maryland

GUEST SPEAKER (Non-Voting)

Madhukar Trivedi, MD

(Morning Session Only)

Betty Jo Hay Distinguished Chair in Mental Health

Department of Psychiatry

University of Texas Southwestern Medical Center

Dallas, Texas

FDA PARTICIPANTS (Non-Voting)

Robert Temple, MD

Deputy Director for Clinical Science

CDER, FDA

Deputy Director (Acting)

Office of Drug Evaluation-I (ODE-I)

OND, CDER, FDA

Tiffany R. Farchione, MD

Deputy Director

DPP, ODE-I, OND, CDER, FDA

Mitchell Mathis, MD

Director

Division of Psychiatry Products (DPP)

ODE-I, OND, CDER, FDA

Aeva Gaymon-Doomes, MD

Medical Officer

DPP, ODE-I,OND, CDER, FDA

Wen-Hung Chen, PhD

Acting Team Leader

Clinical Outcome Assessments Staff

Immediate Office

OND, CDER, FDA

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P R O C E E D I N G S

8:03 a.m.

Call to Order

Introduction of Committee

DR. PICKAR: Good morning. First piece of business, I want to remind you to turn off your cell phone, put it on silence, or any other devices that you might have like that. I'd also like to identify the press contact for the FDA, Sandra Walsh. I'm not sure if Sandra -- hi, Sandra. Okay. There you go.

My name is David Pickar. I am the acting chairperson of the Psychopharmacologic Drug Advisory Committee, and I will be chairing this meeting. I wish to call the Psychopharmacologic Drug Advisory Committee to order. We will start by going around the table and introducing ourselves. We will start with our colleagues at the FDA with Dr. Temple.

DR. TEMPLE: Bob Temple. I'm deputy director of ODE-1.

DR. MATHIS: Mitch Mathis, director of

Psychiatry Products.

DR. FARCHIONE: Tiffany Farchione, deputy director of Psychiatry Products.

DR. GAYMON-DOOMES: Aeva Gaymon-Doomes, medical officer.

DR. CHEN: Wen-Hung Chen, acting leader, clinical outcome assessments staff.

DR. NARENDRAN: Raj Narendran, psychiatrist, University of Pittsburgh.

DR. STEIN: Murray Stein, psychiatrist at the University of California, San Diego.

DR. IONESCU: Dawn Ionescu, psychiatrist at Massachusetts General Hospital.

MS. BHATT: Good morning. Kalyani Bhatt. I'm with the Division of Advisory Committee and Consultant Management.

DR. PICKAR: David Pickar, psychiatrist, Johns Hopkins.

DR. HIGGINS: Jennifer Higgins, acting consumer representative.

DR. COMPAGNI PORTIS: Natalie Compagni Portis. I'm the patient representative today.

DR. DICKINSON: Dwight Dickinson. I'm a neuropsychologist at NIMH.

DR. CONLEY: Rob Conley. I'm a psychiatrist. I'm the acting industry representative, and I work at Eli Lilly where I'm a distinguished scholar and head of late-phase neuroscience.

DR. PICKAR: Okay. We have a very interesting two sessions today. For times like this, there's going to be a lot of opinions, some of which might be quite strongly held. That's why we're going to have an advisory committee, to offer opinions and our best thoughts to the FDA. We want it to be an open and fair forum for discussion of these issues and individuals can express themselves without interruption.

Thus, a little gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a very productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you very much.

Let me now pass on to Kalyani Bhatt, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: Good morning. The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict

of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of the committee 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 purposes of 18 USC Section 208, their employers. Their interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

During the morning session, the committee will discuss cognitive dysfunction in major depressive disorder. This is an evolving concept, and experts in the field have not yet reached consensus as to whether cognitive dysfunction in MDD is a distinct entity. The committee will consider the clinical presentation of cognitive dysfunction in MDD, as well as methods for assessing this condition.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Robert Conley is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Conley's role at this meeting is to represent industry in general and not any particular company. Dr. Conley is employed by Eli Lilly.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by this speaker is essential. The following interest is being made to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Madhukar Trivedi has acknowledged that he has received consulting fees from affected entities, including Allergan, Bristol-Myers Squibb, Cerecor, Eli Lilly, Forest, Lundbeck, Merck, Naurex, Nestle Health Science, Otsuka, Pamlab, Pfizer, and Takeda within the past two years.

We would like to remind members and temporary voting members that if the discussions

involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussion. Thank you.

DR. PICKAR: I see that there are two members who have joined us. Perhaps you could introduce yourselves. Dr. Hinkin?

DR. HINKIN: Charlie Hinkin.

DR. PICKAR: Push the button there.

DR. HINKIN: Hi. Charlie Hinkin. I'm a professor in the Department of Psychiatry at UCLA School of Medicine, as well as the director of neuropsychological services at the West Los Angeles VA.

DR. PICKAR: Thank you. Dr. Grieger?

DR. GRIEGER: Hi. Tom Grieger. I work for

the Maryland Department of Health and Mental Hygiene. I'm also a professor at Uniformed Services University.

DR. PICKAR: Thanks so much, Tom. And there's another gentleman walking up now who looks like Dr. McMahon. Do I have that right?

DR. McMAHON: Yes, you have it right. I'm Francis McMahon.

DR. PICKAR: Push the button there, and you're in good shape.

DR. McMAHON: Francis McMahon from the National Institute of Health. I head the human genetics branch in the NIMH IRP.

DR. PICKAR: Perfect. Thank you.

Okay. We are now ready to proceed with the first introductory comments by Dr. Mitchell Mathis, director of Division of Psychiatry Products.

FDA Presentation - Mitchell Mathis

DR. MATHIS: Okay. Thank you. Thank you for coming to discuss with us a topic that we consider very important, cognitive dysfunction in major depressive disorder. We're actually going to

have two advisory committees today, this morning, one session, and then the afternoon session. We'll have the same panel but different sessions.

That was intentional because the morning session, we hope to have a good discussion about cognitive dysfunction in major depressive disorder: where we see it, how we measure it, and how to sort it out from the core symptoms of major depressive disorder.

The afternoon session will examine a specific drug with a specific drug development program, where the goal was to treat -- to identify, and treat, and show a drug difference for cognitive dysfunction in patients with depression.

So this is a relatively new area, cognitive dysfunction in depression, for the division. As you'll hear today, it had been our policy for many years that cognitive dysfunction was a part of MDD and couldn't be separated from it. In other words, it would be what we call pseudospecific to isolate a particular part of MDD as a syndrome and then treat it as an individual drug target.

I think a lot of people still believe that cognitive dysfunction is part of major depression and that it gets better when you make the core symptoms of major depression better. But there's a fair amount of evidence that cognitive problems persist even after the mood problems have been addressed by medications and other forms of therapy. And these symptoms, of course, are very disabling for our patients.

So this morning, we will engage a discussion with our panel, and here are the three discussion questions that we have. We're going to, again, discuss whether cognitive dysfunction in major depression is an appropriate drug development target. If so, which cognitive domains are affected by the dysfunction and what's the best method to measure to assess them.

Then, we specifically have an interest in knowing what the committee thinks are acceptable primary efficacy endpoints for treatment of cognitive dysfunction in MDD as claimed.

As a third point of discussion -- and we

can, of course, discuss other things -- we thought we'd ask what the committee thinks about whether a functional assessment is necessary as a co-primary endpoint; the idea there being when you're not quite certain what your primary is measuring but you see a statistical difference, is there a reason to have a functional endpoint that goes along with it to reassure you that it's a meaningful change.

So that's all I have, and I think you'll enjoy what we've put together for you; and it should be educational for everyone, especially the division. I'm going to ask that the division's deputy director, Tiffany Farchione, come up and start us off.

FDA Presentation - Tiffany Farchione

DR. FARCHIONE: Good morning, everybody. I'm going to just present to you a brief introduction into the way that we as a division have viewed cognitive dysfunction in major depressive disorder; how our perspective has changed over time, from where we started, as Mitch was saying, with the idea of pseudospecificity; all the way up where we

are today.

Just to begin, what is pseudospecificity? We throw this word around a lot and not a lot of people really know what it means. The term itself was coined during one of these meetings, during an advisory committee meeting back in 2001. And the topic at that time was whether or not agitation was an acceptable clinical target for development of intramuscular antipsychotic products.

Tom Laughren, who used to be our division director -- back at the time of this meeting, he was a team leader for Psychiatry Products -- he wrote the memo for the division during this meeting.

So he outlined basically the two types of clinical entities that are appropriate targets for drug claims, one being specific diseases or syndromes, which are the usual focus of drug claims, but then also nonspecific signs or symptoms that aren't unique to a single disease or syndrome and they kind of cut across disorders. And those would be things like pain or fever. So both of

those would be appropriate targets.

Now, the problem comes in when you try to say that a nonspecific sign or symptom is -- when you try to make a claim for that in the context of a specific disease or syndrome, and that's where you get into this concept of pseudospecificity. And that's pretty much what Tom -- what he outlined, the way that he defined it in his memo for the division.

The gist of it is, in this original context, we were talking about this narrow focus of a nonspecific sign or symptom, making a claim in a specific disease. But it's been explained a little bit since then just to generally mean any claim that is artificially narrow.

So some examples would be if you want to have a claim for treatment of depression in women or post-traumatic stress disorder in men. In that case, you would have to convince us that this particular demographic subgroup responds differently to your product than the other demographic subgroup. To say we're not going to

give you an indication to treat depression in women if your product also works in men, that would be pseudospecific. The same applies to comorbid conditions. So post-stroke depression, why is that any different than any other form of depression?

Back to the idea that nonspecific symptoms, something like back pain, would be an example of pseudospecificity, why would a medication treat just that one particular kind of pain? Wouldn't any analgesic work for back pain, headache, muscle pain, et cetera?

Then we get to the idea that we're talking about today, whether you can parse out a specific symptom or symptom cluster from a DSM-5 defined syndrome and make a claim for that.

So one example would be if you think you can treat just hallucinations in schizophrenia. Wouldn't you be treating the whole psychotic illness? How are you only treating that symptom? And then, the issue that we're going to be talking about today, does cognitive dysfunction in major depressive disorder fall into this category? So

the big question is why we would even consider cognitive dysfunction in MDD to be pseudospecific to begin with.

What we have listed here are the criteria that you're all familiar with, nine different symptoms for major depressive disorder. You have to have five of them for two weeks in order to get the diagnosis, et cetera. But just one of these actually -- just one of them falls into the category of cognitive dysfunction. So diminished ability to think or concentrate, or indecisiveness, is the only symptom in the diagnostic criteria that actually applies to what we're talking about here.

The division's position, up until this point, has always been that if you're treating major depression, you are treating the entire syndrome. So if your mood is improving, if you're sleeping better, if you're less fatigued, you should also have better ability to think and concentrate. Everything should get better together. The rising tide lifts all boats, that kind of idea.

But over time, the academic community and industry investigators have continued to explore this issue, and it turns out that maybe that's not always the case, that evidence has really been mounting recently in the past few years that maybe the current treatment that we have, while they might improve mood symptoms, don't always address the other components of depression, such as cognitive symptoms. Maybe a rising tide doesn't lift all boats. Maybe cognition doesn't come along for the ride.

But all of this was happening in the background, and FDA hadn't really been presented with this data yet. So we were going along on our happy little way, thinking pseudospecificity, and then we have this turning point.

That brings us to June of 2014 at the American Society of Clinical Psychopharmacology annual meeting. There was a workshop there that was entitled Cognitive Deficits in Depression: What are they? Are they independent dimensions? Are they targets for treatment?

This workshop was put together by some of these academics that I was talking about earlier , who were doing all of the research in this area. And the topics were things like clinical characteristics, what this looks like out in the real world, methods of assessment of these cognitive symptoms, effects of treatment, very small samples but still good preliminary data, and whether or not this had any impact on functional outcomes.

So I was invited actually to be a discussant at this meeting during this workshop. And I have to admit that I did kind of go into the meeting with the idea in my head that, oh, yeah, I'm going to have to deliver the pseudospecificity party line and all of that. But as the discussion went on and as I was watching the presentations and listening to the data, it got to the point where I said, well, maybe the answer isn't no. Maybe now it's kind of maybe.

Needless to say, once that door was open a little crack, everybody got really interested.

There were a few additional workshops after that point. They were put together to really educate the FDA on the current state of the evidence. One of these was put together by the folks at Massachusetts General and their psychiatry academy, and that was held in Silver Spring so that all of our FDA folks could attend. There was also an Institute of Medicine workshop on the topic.

At the end of each of these workshops and discussions, we kind of always reached the same conclusion, that, well, this seems like something that's reasonable to consider, but, and then there were all these caveats: how do you define it, and how do you assess it, and what are the best outcome measures, and on and on.

There were just lots of questions. But nonetheless, we realized that we had kind of opened Pandora's box at that point and had invited -- basically, we knew that we were inviting applications for a potential claim that we hadn't yet decided how to deal with, so we knew we needed to get up to speed pretty quickly.

At that point, after the Institute of Medicine meeting, the division started to -- we began a collaboration with our federal partners over at the National Institute of Mental Health. The reason we chose them was because we were looking for people who had expertise but who didn't have financial conflicts. And we felt like this project, this idea that we were exploring, was a good fit with the RDoCs group.

Now, the RDoCs, that's short for research domain criteria, and this is a relatively new group over at NIMH. They're working to put together a translational framework for studying mental disorders. So this idea that everybody talks about from bench to bedside, they're looking at everything from genetic markers, to patient-reported outcomes, to really define the spectrum of behavior, both normal and abnormal.

These are the folks that are trying to move us forward from syndromal definitions of psychiatric illness to actually understanding pathophysiology. And the idea that perhaps this

element of an overall syndrome could somehow be separate fits in this model pretty neatly.

When we met with the NIMH folks, we had a whole bunch of questions that we were trying to resolve: what domains of cognition are the most relevant in depression, and what are the best tools for assessing those domains?

If you have changes in these neuropsychological tests, does that translate into a clinically meaningful change or do you need a separate functional measure in order to assess whether this matters to people; if you've got objective and subjective measures.

So neuropsych tests versus patient reports, those can be divergent for a number of reasons. Is one more reliable, more relevant, if you need both, how do you reconcile the disparate ratings?

So we had a lot of questions, and we were trying to resolve all these issues. But the primary goal that we had with this whole project is that we want to develop a framework for our regulatory decision-making without being overly

prescriptive. So we don't want to get to the point where we say, if you want an indication for a cognitive dysfunction associated with major depressive, you need to do this endpoint, and this endpoint, and have this period of time, and so on and so forth.

We want to basically develop a set of instructions for the folks in industry so that they know how to frame their rationale for the endpoints they've chosen and for the length of treatment that they've chosen for their trials, and so on. Just like I said: a set of instructions for how to interact with us and how to justify their application.

Now, that we have this nifty little document from our folks at the NIMH -- and Jenni Pacheco is going to talk to you a little bit about the information that they provided to us -- now, we need to incorporate all of that into our regulatory decision-making. And the things that we need to decide for ourselves in the division is what kind of information do we think can be gleaned from

different study designs?

If you've already got folks who have been treated for depression, their mood symptoms are better, they still have cognitive problems, that seems like a no-brainer that you're going to want to do an add-on study and maybe get an adjunctive claim. But what do you do if you want to start from the beginning and see that your product just works better generally?

So what can a monotherapy study tell us? Is superiority to placebo enough? Probably not because of that whole pseudospecificity issue. But do you just need an active comparator in the study? Is numerical superiority good enough or do you need to be statistically superior to an active comparator? Do you need a functional co-primary, like I was saying, to ground this in clinical meaningfulness?

The appropriate design in any given case is probably going to depend on a whole bunch of different factors, including your proposed mechanism of action for the new drug. So a company

might come in and justify their design and say we think that we're treating this domain because of this action at this receptor. That's probably never going to make it into a label, at least not any time soon.

But the idea being when I say mechanism of action, I'm thinking more like if your product is an antidepressant and you come in -- that means that you're probably going to come in with a monotherapy study because you want to treat depression and cognition at the same time; or if your product is something that you think is a cognitive enhancer in some way, you've already treated the mood symptoms, you want to add this on, that's what I'm talking about when I say mechanism of action, informing the study design.

So that brings us today and the difficulty that we've come up against. And as I was saying, when we opened Pandora's box, we knew we were going to start getting applications, and lo and behold, we have one. So we were still considering all of these issues and hadn't quite come up with our plan

for dealing with them when we got our first supplemental application seeking a claim for cognitive dysfunction in MDD.

Now, in order to properly evaluate that application, we need to understand the current state of the evidence that's going to inform our decision-making not just on that application, but on any application, obviously.

If we're going to change our approach and say maybe this isn't pseudospecific, we're willing to entertain these claims, we need to have this discussion in a public forum so that not just this single company, but every company, every academic researcher, understands what we're thinking and how we want folks to approach drug development in this area.

So this morning's session is -- like Mitch was saying, it's a separate AC for a reason. But everything that we talk about this morning is clearly going to inform our discussion that we have this afternoon. So that's pretty much the end of what I've got. I think at this point, I'm going to

be handing it over to Jenni Pacheco from the NIMH.

DR. PICKAR: I think it's Dr. Zarate who will be speaking next.

DR. FARCHIONE: Oh, it's Dr. Zarate next. Oh, yeah, you're right. You're right. I'm sorry. We rearranged it somewhere in the middle there.

DR. PICKAR: Okay. We welcome Dr. Carlos Zarate, chief of Experimental Therapeutics and Pathophysiology Branch, intramural research, NIMH.

Presentation - Carlos Zarate

DR. ZARATE: Thank you so much for this invitation. I will be reviewing cognition neuroimaging and depression, what is a brief overview. This is my disclosure, which was already discussed. I work at the intramural program at NIMH.

What I'll be providing is more of a broad overview in my talk about the imaging studies that have been done in the context of cognition and depression. Our next speaker will get a little bit more into detail, Dr. Madhukar Trivedi, on what are the effect sizes of the different cognitive domain

disruptions in depression. And then our next speaker, Jenni Pacheco, will get into a more granular -- she will get into more describing what are the different domains affected and how we measure them. So I will provide a very brief overview.

This is the outline. I'll be focusing on the triple network model intrinsic connectivity as a potential unified framework of cognitive dysfunction in depression. I'll next review the aberrant cognitive domains in depression. The reason why I'm focusing on the triple network model is at times, it's not so simple to focus on region experts [indiscernible], and is why we need to take into account that this is really a complex network, and we can simplify it along three different networks, also referred to as intrinsic connectivity.

Then you'll see that most of the studies done have been in very small sample size, and they're affected with medication or comorbidity, or medical conditions. So I'll focus predominantly on

a meta-analysis of studies, which are probably going to be more informative in terms of identifying what cognitive domains are affected. The third point will be reviewing resting state rather than using the models that cause activation or deactivation that are task-based. I'll be looking at resting state as a better way of understanding intrinsic connectivity in higher cognitive function.

This is a triple network model that has been proposed by several, not only for depression, but for, in this case, post-traumatic stress disorder, and this is kind of where the field is heading. We have, in general, three networks. One is the salience network here. We have the default mode network and the central executive network. This is what takes into account the different domains and puts them in these different networks.

For example, here in the central executive network, we can see the area predominantly affected is the dorsal lateral prefrontal cortex involved in working memory, planning, executive function,

attention, which is going to be, I think, a focus of today. We could have clinical markers. So if you have a problem there, that would be manifested as impairments of attention and working memory. There are therapies. One could use cognitive remediation as used in, for example, psychoses, and then there are other interventions.

Towards the left, we have the default mode network, which has been well studied. And it's inter-receptive process, a sense of self, and involved in social cognition, and autobiographical aspects as well. The treatments of course would be therapies that are self-reflective in terms of function medications or certain neural devices might have effects.

Then you have the salience network. Here, we see dorsal anterior cingulate cortex and insula that has to do with organizing or directing behaviors towards a specific goal. I'll talk a little bit how these interact. But one can see that these do not function in isolation. They're highly integrated. There's a nice interplay

important in that, and I'll give some examples at the end.

This is how I divided the focus on the alterations or aberrations of cognitive function domains. These are largely task-based procedures, and I'll discuss it. We divided into the following: looking at effective processing. I'll talk about attention. I won't focus so much on working memory and executive function because our next speakers will go into that, and then reward processing.

Centers of affective processing, we generally see that there is a bias towards negative stimuli and depression, and most of the studies have been very consistent in showing that. In terms of negative stimuli, one might use faces. One might use images. One might use words or autobiographical forms to tap into that bias. The bias is towards negative stimuli or away from positive stimuli.

As I mentioned, I won't get into specific studies because when you do, data is all over the

place. When you get into meta-analysis, it's kind of useful here. These are functional studies, 14, looking at PET, positron emission tomography studies, and 24, looking at functional MRI studies.

For the most part, focusing on the salience network, we see that there's a hyperreactivity of the salience network. Remember, these are predominantly in the areas I mentioned. This is at the amygdala. This is the dorsal cingulate anterior cortex and insula here. It's towards the negative and away from the positive stimuli or the neutral control; whereas, you see the contrary in terms of the executive network, you see hyporeactivity in the dorsal lateral prefrontal cortex. So you can see this ying-yang and interplay.

Another study by Groenewold pretty much showed the same thing, and so this is consistent. This is another meta-analysis involved in 44 functional MRI studies. You can see looking at, for example, the salience network, that there's

hyporeactivity in the dorsal cingulate cortex towards negative emotions and away in positive emotions. Consistent with the previous meta-analysis, you see hyporeactivity in these studies and mainly in the central executive network; once again, the importance of these networks and how they act in concert.

The other area that has, for the most part, shown fairly consistent results in the same direction is attention. And there are many, many different ways of tapping into attention circuits and some clever ways. One can use dot probe task. One could use distractor stimuli, and I'll give some examples.

This is a study by Wang looking at the attention process and network. What generally one does is you can use a task. In this case, one can use a control, which may be a square. And the other is that you use the -- you ask the individual to focus on a circle, which would be called the odd-ball task.

So that is getting attention, but what

happens is that sometimes emotions get in the way. So what you do is use a distractor, in this case, a sad face. And we already talked about that that biases and pulls away the individual's attention toward the negative stimuli, and then you're more able to tap into that attention circuit. That's the typical design of the study, and you see, generally, differences between major depressive disorder and controls.

More specifically, you see the following. If you focus towards the left, this is the salience network, which I described, and towards the right, this is the central executive network.

Towards the left, you see these darker colors, which are the controls and these warmer colors are the patients. When you see that -- you use a distractor, you see, in controls, an increased activity when you use a distractor, which in this case is sad faces, compared to the target to the neutral condition in healthy controls; whereas in major depression, you see the opposite pattern. You see decreased activity in anterior

cingulate cortex and insula in this salience network.

Now, this is in the salience network, so what would we expect to happen in the central executive network? The contrary. So we see, in general, in the dark colors, healthy controls, we see a decrease in hyperactivity in the pre-front regions in controls, and in depressed, we see more increased activity in these regions. So again, these studies, at least in meta-analysis, larger studies, this is 20 subjects with depression and 20 controls. We see that it's fairly consistent.

Now, you may be familiar with the dot probe task. This is another way of pulling attention away, distracting individuals to get more at the specific circuit. This is referred to as a block design or face block design. Here, you pair two faces. One is neutral and one could be angry or happy. In this case, it's angry; here, it's supposedly happy. Then immediately, these faces are removed, and you use a dot. That's referred to as a dot probe test.

The dot could either match with one of the faces, the neural condition, or it might be more the emotion, in this case angry. You can't see it from here, but this would be considered an incongruent trial because that is matched with a neutral condition, and here it would be considered a congruent condition because it's matched with happy. You do these in blocks while an individual is scanning [indiscernible], then you can identify the circuits that might be implicated.

This is one of the studies we are doing. You see the main effect of emotion in the reward areas. And here, striatum's affected, so that supports the use of this task. If you look at the salience network, I already mentioned dorsal cingulate is involved, you can see activation here. And towards the right, you see the default mode network, parahippocampal and also amygdala not seen as clearly, but you would see activation. So this does show that there is a main effect of emotion, and that's what you want.

The next step would be to see if there's an

interaction of emotion with group interaction, and you do see that here. You do see that the superior and middle temporal cortises, there's a cluster here that's activated. You also see -- I can't really see from here. Sorry. But we do see that prefrontal cortex extended activation of this cluster to the insula, and that does show that there is an emotion by group interaction.

In the interest of time, I won't get into working memory and executive function, but typically there are N-back tasks, delayed matching tasks, and our next speakers will go a little bit more into it.

Another area that is receiving more attention in terms of cognitive domain is reward processing. I've just given a general overview and examples. Here, one can use gambling tasks or money incentive tasks to tap into the circuits. The example I do provide here is anhedonia, since it's a key cardinal symptom in depression. And the dysfunction -- so anhedonia is one of the main symptoms involved in the criteria of depression.

There are different types of anhedonia. You have anticipatory anhedonia. For example, you start thinking that you want to get a reward. Then there's the motivational aspect; okay, you get going to get that award. And then there's a consummatory. You got that pepperoni pizza and you enjoy it. Those are the different components of anhedonia, and one can tap into that with specific tasks.

More, the anticipatory is referred to as the wanting, where the consummatory eating or some other pleasure is like an aspect of it. In the wanting, which is the anticipatory, generally involves the orbital frontal cortex, anterior cingulate, and nucleus accumbens, whereas, the consummatory aspect would be, for example, ventral striatum, dopamine mediated.

Here, we see a study, looking at the different aspects of consummatory anhedonia, the lack of interest or pleasure. We see that there is, in general, a hyperactivity in the striatum in patients -- I'm sorry, in healthy controls, where

there is not so much of an increase in the patients, but more of a decrease. So that's the consummatory anhedonia.

The anticipatory anhedonia, the more initial aspect does involve an increased activity in healthy controls at dorsal cingulate and a decrease in patients. And as would be expected, we see a decrease in emotional processing in the anterior cingulate as well. This is one example of another cognitive domain one might tap into. And remember, these are all activity-based tasks.

Now, here we are looking, for example, at a task we're developing, very simple. And I think it's important that if one were to go to mass skilled, that you come up with simple tasks that are reproducible and aren't very expensive.

Here is a task that looks at liked activities or disliked activities in healthy controls versus patients with major depressive disorder. If you look at the liked activities in those who are healthy, it's higher than patients, and the disliked activity, you can see it's less in

healthy controls compared to patients.

Now, how does this map on to existing scales of anhedonia? Here, these are different in anhedonia. You can see that, generally, the correlation is fairly good. This is in preparation of developing an imaging paradigm. We see the liked activity, a negative correlation with anhedonia. The more you like something, of course, it goes in the opposite direction of anhedonia. And you see a nice correlation between disliked words in anhedonia total scores; so another way of looking at it. This is in preparation.

Now, I introduced this because it's very important in depression and mental health. It's suicide, some refer to as suicidal cognition. It's a complex behavior. And more recent data is functioning on anhedonia, lack of pleasure, and suicide. You can see how you can start linking tasks that are being developed for reward processing and for other domains. One might want to consider that in research portfolios.

Suicide is also involved in impulsivity and

mood -- also has aspects of impulsivity and mood lability. You can tap into that with other tasks. It's really not well studied and not very well understood. This is a study that gives an example of functional imaging, positron emission tomography.

Here, we look at blood glucose, the surrogate measure for glutamine. We see that in area 25, which most everybody is familiar with, infralimbic cortex, that the greater the cerebral blood flow in this region, the greater the relationship with suicidal thinking. So that would be an example. One can link with anhedonia and develop tasks along those domains or interventions.

What I talked to you is about -- I mentioned the task base. You activate, you deactivate, based on the dot probe or something else. Here, I'm talking about resting state, which means you just lie still and you focus using crosshairs or you just close your eyes and lie still.

What happens in healthy individuals, some of you may be, for example, daydreaming with my talk

here and your mind might be elsewhere. Others might be planning, thinking what I'm going to have for lunch or my vacation; I'm heading out of here in a few hours. So this is just resting.

You kind of think of it as a way of getting at the circuits, at the triple network, without interfering with our tasks. It's another way of looking at things. And what happens in depression, you do the same thing, eyes closed or crosshairs focused there, and this is the difference with our patients. I'm not a success story, thinking of how they want to kill themselves, or that I'm a horrible person, and I can't get it out of my head. And this goes on over and over again. If you think of it, this is rumination that has to do with the default mode network we talked about. I'll give an example in a few minutes.

Getting back to the triple network, what we have here is the default mode network. We talked about salience network, and then this is the executive control network. You can see here that there are clusters of activity. But when you look

within a specific network -- for example, salience network, here, we have dorsal anterior cingulate cortex and insula -- generally the activity is in the same direction, for the most part, in the central executive -- the activity of these nodes or these clusters are in the same.

So they go in synch, one with the other, and that's important because you'll see that there are differences from one network to another. Sometimes they go in opposite directions. But within the same network, they go in the same direction for the most part.

This is an example of the triple network model, coming back to this. Just to review again, we have the salience network, default mode network, and the central executive network. Here, you can see in terms of the salience networks, self-referential thinking we talked about. We talked about social processing, other aspects. Generally, you see there's increased activity of this network over the default mode network, which dampens the activity of the self-referential

thinking here.

What happens here, this has to do more with the activity. So in this case, you might have an individual who has -- we see that rested state -- ruminations, thinking of how to die, whereas over here, this has to do with the salience network with more initiating or directing behaviors towards the action.

So in this case, the action could be you act on the ruminations of thoughts of dying; you take your life or you could walk away. These are some examples here. Then, of course, you have the relationship between the default mode network and the central executive network in a negative way, decrease in activity.

This is an example. What I showed you was bold imaging fMRI studies resting state. That looks at one aspect, but you can also use magnetic encephalography that gets more into real time in a real way, the activity, these intrinsic -- these networks, intrinsic connectivity networks. And pretty much in our study using magnetic

encephalography, MEG, you see bilateral insula temporal activation, very consistent with the salience network, so we talked about that.

There are different modalities now being explored and how with treatment, one might see, for example, a decreased connectivity in this area in the patients compared to healthy controls. And with treatment, you may even decrease the connectivity more to either normalized or go to a lower state.

This is a slide summarizing the different domains, as we'll be talking about. The next speakers will talk in isolation about the amygdala and, for example, striatum, and maybe some functions. But what you see here is how these regions start mapping onto these networks very nicely.

So these two, for example, an emotions process maps nicely to salience network, executive network. When you get into alterations and reward processing, it could be the dorsal cingulate and striatum. Those are the regions involved in the

salience network. When we get into self-directed cognition, all the three networks are involved, salience, executive, and default mode network, representing the regions of amygdala and subgenual ACC, so putting all this together.

I think this might be the last slide. This is model. It's a work in progress. But to really keep in mind that as we present a separate task we thing might be related to a certain brain region, it's much more complex. So one will be able to come up with better treatments if you think along this paradigm.

Down here, we talk about the default mode network, DMN. We say that it's involved in the rumination, poor autobiographical memory. For example, some of these things might be more amenable to certain psychotherapy, self-referential thinking rather than specific medications.

Up here, impoverished cognition, working memory, attention might be more amenable to other types of treatment. So one can start considering combination treatments, depending on the

dysfunction of the network.

Then you have this network. We say it's involved in behaviors directed towards perceived or important action, the salience network. But in itself, it's influenced by these boxes. You can see, from a bottom-up approach, it might be a sensory stimuli.

There's limbic information, the limbic cortex involved in influencing the salience network. But also, we can see how they interact with each other, this network with this, and how they affect the other two networks. So it's really a nice interplay dynamic.

In summary, the triple network model is one direction that people are pursuing. It seems to be a very important way of integrating or providing a framework for cognitive function, not only in depression but for other psychiatric disorders. This is important because most of our patients with depression have comorbidity, so that's something to keep in mind.

Within this framework, one can be able to

dissect it using certain drugs or certain therapies. Then eventually, once we have that information, we may be able to tap into specific networks, selecting the treatment ahead of time. They may be doing better with medication, or better with therapy, or the combination. Thank you for your time.

Clarifying Questions

DR. PICKAR: Thank you very much, Carlos. We're going to take questions --

DR. ZARATE: At the end.

DR. PICKAR: -- yes, if that's okay.

DR. ZARATE: Yes, sure.

DR. PICKAR: We actually have a couple of minutes. Does anybody have a specific question for Carlos right now? Francis?

DR. McMAHON: Carlos, this is very interesting. The previous speaker emphasized, at the level of DSM symptoms, one particular cognitive domain. That is decreased concentration that is one of the cardinal diagnostic symptoms of depression. But if I understand what the thrust of

your talk is saying is that, actually, cognitive dysfunction is underlying most of the symptoms that are at the surface go into the diagnosis of depression.

Is that a fair conclusion?

DR. ZARATE: Well, when we say cognitive dysfunction -- let's say we say distractability, poor decision-making as an example. It is within depression, but it's fairly nonspecific, and you might see it in other disorders. So we can agree there. But even in patients who remit from the depression, they might have these residual symptoms that could potentially be a target of specific therapies.

The one problem there, and I think our next speakers will address in more detail, is that in distractability or poor decision-making, there could be other residual symptoms. So there could be fatigue, apathy. That could be the result of insomnia. So my point is, without understanding the totality of what's going on -- is it poor decision-making because you didn't sleep all night

or is it something separate and in a specific cognitive domain? So I think it's something that needs to be parceled out in further research.

DR. McMAHON: Right. So there's a range of sort of chicken and egg problems built into that. Is someone thinking poorly because they're sleeping badly or are they having trouble enjoying themselves because of a fundamental problem with anhedonic processing?

DR. ZARATE: Yes, apathy -- yes, exactly. So some people have tried to discern that, but it's not that easy.

DR. McMAHON: Thanks.

DR. PICKAR: We have time for just a couple questions. We're going to stay on schedule, and then we're going to have questions at the end, Carlos. So be ready.

Any other questions now for anybody before we move on?

(No response.)

DR. PICKAR: Okay. Carlos, thank you so much, and there will be more coming. We move to

our next speaker, Dr. Trivedi from the University of Texas Southwestern in Dallas. Welcome.

Presentation - Madhukar Trivedi

DR. TRIVEDI: Thank you very much. Good morning. This is an exciting issue. I think one fundamental issue, this is not new information, that cognition and cognitive dysfunction is a major component of major depressive disorder. I think we have not as a field really spent as much effort in studying this over the last 30 years or 20 years, and that is why this question comes up.

Two other things to think about as we start figuring out what is the role of where does this all fit in terms of depression. One thing is we all talk of -- and Tiffany showed, and I will show you the slide on the diagnostic criteria for major depressive disorder. We all forget one important parameter, and that is functional impairment is required for the diagnosis of major depressive disorder.

So you cannot actually make diagnosis of major depressive disorder, even if you have all the

nine symptoms in its most severe form, if you don't have functional impairment. What is the role of cognition in that functional impairment? It's something we as a field have not paid attention to.

If you then flip back on understanding cognition and its role in psychiatry, I think we always think of models like ADHD, Alzheimer's, and even schizophrenia, where we actually accept that that is a major concept, and we have talked and studied it enough.

The one big caveat to think about, again, there, and it dovetails with the dysfunctional impairment issue, is that the severity and the components of cognitive dysfunction we are talking about in something like Alzheimer's or schizophrenia are very different. In fact, if you look at the functional measures used in those conditions, they're asking about the activities of daily living, can you find your shirt and can you catch your keys, or can you balance your checkbook.

In functional impairment and depression, we are talking, really, work impairment and a number

of other different components of domain. So I think that we have to be careful so that it's not all lumped into one and we miss the boat.

Talking about boats, I think Tiffany's sort of point that is this really these cognitive symptoms, really, where a rise in tide raises all boats, the research domain criteria aspect -- and I am assuming Bruce Cuthbert might be amused with my reductionist view of it. But it is an attempt to try to actually say that all rising tides will not raise all boats because not all symptoms and behaviors are reflective of the same brain pathology. And therefore, we have to be thinking about it in a more nuanced way.

So having said that, what my task is, is very straightforward. Given that I've already confessed that we have not studied this as much, I'm going to give you a little bit of the sense of where the literature is in terms of what has been studied in terms of cognitive dysfunction and depression over the last 20 years. These are my disclosures, and you have that in your booklet, I

think.

I'm going to try to talk about something -- at least give you the data on what we know about assessing cognitive function; what is the prevalence and characteristics of cognitive symptoms and depression; what are treatment considerations. And I think this is where we have the smallest amount of database. We have not actually spent enough time trying to predetermine and, a priori, focus our attention on how best to treat it. So I'll give you what we at least have in the literature.

What are the functional consequences of cognitive deficits in depression is a really big interesting component; what is the mismatch between changes in symptoms that we call core symptoms of major depression and changes in cognitive dysfunction; and some idea of where I think we should be going as a next step in the field.

So a very quick review, although I'm going to skip a little bit of this because it's really -- this is a crowd that actually accepts

depression as an illness, and is really severe; and it's very chronic and very early onset, et cetera. So I'm going to not spend too much time on this but to say that for most patients, depression is chronic and/or recurrent.

Again, that has an impact on functional impairment. And it starts in second or third decade of life and impairs work productivity quite significantly over the lifetime. In fact, I'll show you some of the data on persistent cognitive impairments in people who have full remission of their core symptoms.

The other issue is we all -- when you read about literature on depression, we don't always talk about just the symptoms but also the disability associated with it. And we know by 2020, depression is predicted to be the second leading cause of disability. In fact, there's now increasing data that it may have already reached that. In the United States, disability associated with depression has increased 40 percent over the last two decades.

Again, talking about the criteria, we know that diminished ability to think, concentrate, or to be indecisive is a core symptom, but this again doesn't cover all the domains of cognitive dysfunction, as I'll show you. And I think that we all lump it all in one criterion, but it is not always true.

One of the big challenges I think for all of us, and you as the advisory group, is going to be the following. Not everybody has cognitive dysfunction if they have major depressive disorder, and not everybody who has cognitive dysfunction and depression necessarily has it to such an extent that it really is significantly impairing. So therefore, that doesn't mean that we should therefore say since it is not seen in everybody, it is not a worthwhile symptom.

I think that where you fall on that, how do you figure that out, thankfully, I don't have to be on that side.

So it is an interesting question that I'll, again, show you, that unlike some of the other

cognitive disorders, that we call cognitive disorders, this may be the kind of thing we have to as a field think about. Cognitive function is frequently observed in depression in the following domains: attention, verbal learning, nonverbal learning, memory, executive function.

I think that, Francis, your question on whether this therefore is at the root of all symptoms, and at least the presentations, is a very intriguing question; not always true, but it has some implications that we ought to be thinking about.

Carlos already addressed this, but I think that one of the other -- and that is that the domains or the circuitry associated with cognitive dysfunction and in fact how the emotional symptoms impact on cognitive performance really covers a wide range of circuitry in the brain. And most of the assessments done don't cover all of this. So therefore, you look at which part of the elephant and therefore sometimes really miss the boat in terms of what is really the nature of the cognitive

dysfunction in that particular subgroup of patients.

This is an example of that just to give you an idea. This is really looking at impaired cognition through objective measures. And you can multiple domains are studied and controls are different from both endogenous -- this is an older paper. As you can see, the definition of depression is divided into endogenous and neurotic. But nevertheless, controls are different from neurotic as well as endogenous depression.

More interestingly, DSST, which measures attention, working memory, and processing speed, is quite significantly different between endogenous and controls. And Trails A that measures attention and Trails B that measures shifting mental flexibility are the three domains, which are clearly significantly different for controls versus endogenous depressed patients.

So there is not a doubt that these separate domains have a separate degree of differences between subgroups of depression and healthy

controls. As the research domain criteria become even more explicated and we study it -- this is still a theoretical model. As we study it, this kind of fine grain clarity is I think going to come about, and Dr. Pacheco may address some of that.

One additional thing is, traditionally, we have thought of cognitive dysfunction as much more relevant for bipolar disorder than unipolar depression. And therefore, people think that with bipolar disorder you are more likely to find this cognitive dysfunction whereas not with unipolar depression. It may be true for some domains. Like alertness, you can see the percent impairment there for bipolar disorder is much higher than for unipolar depression, but that is not true for all of the domains of cognitive function.

So information processing speed, this IPS, is clearly where at least it's comparable, if not slightly worse actually, with unipolar depression than with bipolar disorder. So again, to assume that bipolar disorder has the cognitive dysfunction with not so much a component of unipolar depression

is, obviously, something to think about.

The other piece -- and this, again, dovetails to, Francis, your question. We all know that there is a significant impairment in processing speed or attention in processing speed. And therefore, all other cognitive performance tasks are really sort of an effect of having poor processing speed, so therefore, you're making all the other errors.

This meta-analysis actually quite elegantly shows that this gray line is the processing speed in these studies that while not profoundly extremely different, other domains of cognitive function are still present beyond the accounting for processing speed with modest effect sizes but still there, suggesting that it is not just the issue of processing speed but more than that.

I'll give you a little bit of the same thing, but different domains of this cognitive function. So this is psychomotor speed, and you can see psychomotor speed. Not all studies, as you will see -- and this is, again, both the positive

and the question that we have to figure out, and that is it depends on patient selection, to some extent, I bet. But there is a consistent effect of processing speed difficulty in people with major depressive disorder.

The same thing with -- well, my memory still works.

(Laughter.)

DR. TRIVEDI: The same thing -- I apologize. So the bottom line is this meta-analysis this kind of consistent finding for cognitive dysfunction in all the domains, including psychomotor speed, working memory, that is beyond just processing speed difficulties.

(Pause.)

DR. TRIVEDI: I think the next slide shows the same thing, that with psychomotor speed you will see the consistent finding with variability, obviously, across studies, the same degree of variability you see with attention and working memory, or slide number 14, with verbal, visual, learning, and memory.

So this is an area -- again, before it became fashionable to think about cognition, this meta-analysis includes studies that are really quite wide-ranging from a long time over the last 20 years. Slide 15 really shows mean differences in cognitive function between patient groups and controls.

Should I wait or go? Tiffany?

MS. BHATT: You can keep going.

DR. TRIVEDI: Keep going. Okay.

As we are talking about this, I think one of the places where this may help you in your deliberations to think about how to see the role of cognitive dysfunction is in this question of treatment effects. And we'll come to that, and I'll have slides on it.

But I think in that group of patients who have significant improvement, either with the medication or, for that matter, with just time, they have now, symptoms reduced or even almost symptom free, continued to have significant impairments in their functioning. And if you then

carefully evaluate those patients, they have as a major component three things: lack of motivation, cognitive dysfunction, and sometimes sleep or anxiety as the most common residual reason for their impairments.

I think there again -- any luck? Keep going. All right.

If you look at slide number 15, you see the differences in cognitive function between patient groups and controls. And as you can easily see, there is not a profound --

DR. PICKAR: Excuse me. Why don't we take a couple of minutes break.

DR. TRIVEDI: Okay.

DR. PICKAR: Those slides are great. We want to see them. And give them a chance to put it together.

Murray, Dr. Stein, what do you think?

DR. STEIN: Yes.

DR. PICKAR: Okay. I follow Dr. Stein's orders on this.

DR. TRIVEDI: Thank you.

DR. PICKAR: A five-minute break. You think we can get it up and going by then?

DR. TRIVEDI: You're making me feel good. You're saying slides are good.

DR. PICKAR: Bathroom break. It's a quick one. We've got it all under control, Kalyani.

(Whereupon, at 9:12 a.m., a recess was taken.)

DR. PICKAR: We'd like to reconvene the session. I think our slides are all squared away, and I turn this right back to Dr. Trivedi.

DR. TRIVEDI: Thank you very much.

So I think that we were starting here, and then I talked about the slide. So I won't repeat too much, but the fact that psychomotor speed has this consistent finding in this meta-analysis; same thing with attention, as well as working memory, and verbal, visual, and learning memory.

This is where I was talking about, is that if you look overall, differences between major depressive disorder, generalized anxiety disorder for that matter, bipolar 1 and 2 disorder and

controls, there are some differences, but they're very quite modest. One of the reasons is, which is what I keep on talking about, that if you start looking at the same data in box plots, you can see that patients with depression -- actually, not all of them, but there is a sizeable proportion that has significant effect.

That is really the key thing that we will have to try to understand, because in these patients, if you ignore it, these are the very patients who are going to have continuous, significant dysfunction, even if you take care of the symptoms.

This is the kind of group that reminds me of the patients I -- some of you know I'm a big proponent of measurement-based care, so in clinical care, using measurements generally ends up being, as usual in research, measurement of symptoms.

So my patients, they measure their symptoms routinely. And one of the things that always comes back and something that you have to address is that the patient says, "Doc, I know you're asking me to

measure these symptoms. They are better, significantly better, but I still can't function." And that's when you start asking about the residual symptoms, and that is when these aspects are uncovered if you don't prospectively do it, which we don't often routinely do it, except ask them are you able to concentrate, are you able to attend to tasks, et cetera.

Same thing. If you think about it, if you're looking for 3 standard deviations away like we do in Alzheimer's, or 2 standard deviations away, you can see that the numbers that account for those with 2, 3, or 4, or 5 standard deviations away is smaller, but it's still there.

I think one of the things that we as a field don't yet fully understand is that even this group that is 1 standard deviation from normal in people who are working, how much of an impairment that really leads to. And I think that is something that -- at least I'll show you some little data. But I think that is the thing that we have to struggle with, that even this smaller amount of

cognitive dysfunction can have an upsize effect on their clinical care.

Determinants of cognitive deficits, somebody asked me about age. Age is obviously a factor; age at onset; educational attainment. We often don't pay attention to this, but that 1 standard deviation drop may not actually seem insignificant for somebody who has a very high educational achievement and is in a high position, but it still has an impact on their impairment.

So do these symptoms change I think is the central crux of the question about whether this pseudospecific or not, and what happens with the residual symptoms is an important question. Several treatments have been associated with improvement in cognition. And in fact, in a group of patients, if you monitor patients with major depressive disorder and use any of our standard treatments, their symptoms, if they do improve, they will also be associated with improvements in cognitive function.

How much and how closely that happens is

really the main question that we have to think about, one caveat being very few studies have used cognition as a primary outcome. So if you do a PubMed search on randomized control trials with primary outcome measure as cognitive dysfunction for major depressive disorder, you're not going to come up with too much.

That is really the unfortunate state of affairs for our field. Many studies, preliminary and more, obviously are needed. In the interest of full disclosure, my life is in academics, so therefore more studies are needed is a fact. That just continues my career.

(Laughter.)

Pre-post cognitive changes in several domains are being noticed. And you can see this, which is what I was talking about, is that, again, what Tiffany started with is whether these symptoms improve, and therefore cognition also improves. And that is indeed true, that cognitive function in various domains, when you measure it objectively like with continuous performance tasks or

finger-tapping, or Wisconsin Card Sort, you can see that before and after treatment, there is improvement, higher numbers of improvement. And you can see that.

Obviously, there's some degree of practice effects, and that is a major question. And hopefully, Dr. Pacheco will address some of that, is that when you are doing measurements of cognitive function, there are several things we need to be considering.

Cognitive function is indeed a common residual symptom. Studies indicate that there remains cognitive dysfunction as residual symptoms. The biggest, really, interesting finding is even when you look at patients who are fully in symptom remission, and I'll show you a series of studies on that.

This is with patients in the STAR*D trial. As most of you know, STAR*D was the large multicenter clinical practice trial in primary care and specialty care. And that group of patients, we did not use objective measures of cognitive

function. We used symptom rating scales like we traditionally do.

This is a group of patients who achieved response as well as people who were in remission. And as you can see, obviously, with people who have only achieved response but not remission, there remains moderate symptoms of concentration and decision-making difficulties. And obviously, a milder version of that symptom is seen in a large proportion of patients.

What is interesting is even in people who are fully remitted, these symptoms persist not in the mild version and very little in the moderate to severe. So this group of patients who have these persistent symptoms, and they were in full remission -- so if you look at the standard way of telling the patient, you would say, "Ms. Jones, you are now all well." And Ms. Jones says, "But what about this?" And that is the challenge we have to be thinking about.

What are the most common symptoms in non-remitted responders? This is that group

earlier that had some improvement or significant improvement, but not in remission or remitters. And you can see all these symptoms at baseline, and then at post-treatment, they continue.

One of the other things that we have not, again, done a significant enough understanding on is what is the treatment emergent cognitive dysfunction that occurs with our psychotropic medications. And that work, actually, there's been a lot of paucity in that.

This is from a self-rated rating scale developed by Maurizio Fava, CPFQ. And you can see residual physical and cognitive deficits in people who were responders to antidepressant treatments. And you can see mild/moderate severity in terms of the distribution of these symptoms. Nothing dramatic on these, but you can see that word-finding difficulty is indeed a significant residual symptom for these patients.

This is an interesting slide. It's a little busy, so I'll take a minute to describe to you. But this is describing the proportion of time

patients who meet DSM-4 criteria for major depressive disorder, and then they are better non-MDE, major depressive disorder, episode on the right side. Not surprisingly, for example, patients who are in the middle of major depressive disorder, all of them have -- all of them have depressed mood or diminished interest required for the diagnosis. But you can see cognitive dysfunction is quite common in these patients. What is most dramatic is about 44 percent of the patients will have residual cognitive dysfunction even when they're in full remission.

This study actually is quite interesting because this highlights the fact that not all symptoms totally go away even when you get to remission. But the bottom line being cognitive dysfunction is more often seen as residual symptoms than, say, worthlessness or guilt, or eating problems.

Suicidal ideation, for example, is all but gone. This tells you that even when somebody is not in a depressive episode. When they were in a

depressive episode, these symptoms were present, but that is actually not surprising. It's when they're not in the episode, they still have these symptoms.

I'm going to skip this in the interest of time. So what are the functional consequences? As I started with, major depressive disorder should be diagnosed with the idea that there is functional impairment. In fact, in 2011 or '12, there was an ACNP task force report for on remission from the American College of Neuropsychopharmacology.

John Rush is the first author. It describes the idea that making the definition of remission based only on symptoms is incomplete. We need to be adding two things: sustained remissions, so that these remission symptoms are not just one valuation but sustained, and make sure that functional impairment is included in the definition of remission.

So we have not only DSM-5 criteria asking for us to include functional impairment, but post-treatment remission from ACNP recommending

that we should be doing that. The areas of impairment I've already said include physical, psychosocial, occupational quality of life functioning. And it's important to identify the contribution of cognition to the functional impairments.

Cognition mediates function is not very surprising, at least in -- and Carlos actually elegantly showed that not only that, but you can objectively show that in neuroimaging tasks. But increasing evidence is associated with this.

There's no consensus, unfortunately, to date on specifying the relationship between particular domains, as in if you have difficulty with working memory, what is the impairment as opposed to if you have just processing speed difficulty. But we have more data on work impairment and occupational functioning.

We know that on an average, depression adds approximately 4 hours per week to health-related lost productive time, and one-tenth of the workforce reports being depressed. The question of

how much of this should be objective and how much of it is self-report is a big question. In an area of my interest, I've tried getting work productivity data objectively from an employer; very hard, and therefore often we end up depending on self-report.

There's a very large study done by Ray Lam in Canada. And you can see clinically, in terms of self-report, the amount of interference that patients report from their difficulty with concentration is very much comparable to a number of other symptoms; obviously not the main core symptoms but a number of other symptoms of major depressive disorder, suggesting that at least with self, referentially, they see the difficulty they find, face, in terms of functioning because of concentration difficulty.

Functioning correlations have been seen many times. This is an interesting data set, again, where the remission with no residual symptoms were compared with people who had remission but with some residual symptoms. If you look consistently,

a number of domains are functioning on the social adjustments rating scale, patients with remission below residual symptoms compared to patients with remission with residual symptoms, a small study, but still very consistent findings. Those with no residual symptoms function better than those with the residual symptoms.

Measurement, this is the big challenge for us. We do a literature review on this like I did to get ready for this. Most of our rating instruments that we use for defining outcomes use things like MADRS, HRSD, PHQ-9, and QIDS-SR.

The number of items that are scored for cognitive function in these are much less. In fact, QIDS-SR was developed by John Rush at our institution, and that actually goes into much further detail on sleep than on cognitive function, recognizing, for example, in that rating scale that sleep assessment is much more important. Similarly, I think we have to do better with our outcome measures for cognitive function.

Are the depressive symptoms and cognitive

symptoms correlated? The short answer is yes. The longer answer is poorly. So if you look at each of these symptoms and look at correlations with memory or recall, or focus/sustain attention, you can see that all of these symptoms actually are correlated but vary weekly, again suggesting that cognitive function or cognitive performance has an independent presence in patients with major depressive disorder.

So what about targeted treatments? That has been already mentioned at the beginning, that not much has been done on it and how do you incorporate measures into definitions of remission. I will give you a very small example from a very small study we did that is non-pharmacotherapy to, again, highlight this idea of the effect of treatment on cognitive function. As you know, exercise has been shown to be beneficial for cognitive function.

We did a study with high-dose exercise versus low-dose exercise. The primary study, which was the efficacy study, was very small as you can see and showed some benefit for the high does, but

the effect size was not dramatic for the sample size. But we did cognitive function in that study and the CANTAB that measured attention, visual memory, executive function, set shifting, and set planning. This is a sample, so a small sample, 39 patients, 20 in the low dose and 19 in the high dose. And there was no significant correlation between depression symptom severity and improvement on cognitive tasks on that.

When we looked at specific performance on the CANTAB -- so these are just to orient you. These are errors that people make on the 4-box task, or 6-box task, or 8-box task. And the fewer errors you make, the better obviously.

So you can see that the high-dose group consistently performed better than the low-dose group in this study, suggesting that if you have the right dose of exercise that it can have a positive improvement on cognitive function over and above what you see with symptom change.

So we know remission should include improvement in function, work productivity, and

cognition. Traditional outcome ratings do not measure cognition adequately. Functional recovery, obviously I've said enough about it. But I think with the return to productive work and social functioning, it should be something we have to start thinking about.

Whether we do that by doing clinically significant change analysis or normative comparison is going to be the task for us to really start thinking about this to know if it is good enough improvement or not. I do think that we need not only statistically significant but clinically significant effects.

Other group organizations like the CANMAT group in Canada have started recommending to their regulatory agencies that measurement-based care or evaluation of outcomes for new treatments should include functional outcome measures. So we are not the only one in the world thinking about this.

In conclusion, I think what I'm going to say is that for at least half, or 40 to 50 percent of patients, cognitive dysfunction, either subjective

or objective, is a big significant problem. This is associated with greater illness, severity, and poor functioning. Patients with cognitive dysfunction are less likely to improve with placebo than major depressive disorder. Target functional recovery, including cognitive dysfunction, should be something we should be thinking about.

We should evaluate specific impairments across domains and then the more trickier things like greater satisfaction with life. We should assess it for an adequate period of time. Whether you can do that over one assessment or more is something that we as a field will have to decide. I'm going to stop here. Thank you.

Clarifying Questions

DR. PICKAR: Thank you very much. We have time to take a few clarifying questions, and then we'll bring all the speakers back and have more opportunity to discuss with them.

Does anybody have a -- Dr. Stein has a question.

DR. STEIN: Actually, I have two.

Hi, Madhukar. Thank you for the talk.

DR. TRIVEDI: Hi.

DR. STEIN: No doubt it's really important to focus more than we have in the past on functioning in depression. But it's true, is it not, that you can meet diagnostic criteria for major depression on the basis of distress. So for example, you can have somebody who is just absolutely miserable and in pain but functioning pretty well, and they still meet diagnostic criteria for major depressive. I think you had said it was all about -- you needed functional impairment.

Is that -- what's the case?

DR. TRIVEDI: Right. If you are significantly stressed with that and you don't have any functional impairment, I'm not sure if that is something I see clinically. But you're right. It could be that you could have just significant distress associated with all your symptoms but no functional impairment.

DR. STEIN: So in that way, it's not that

different than certain kinds of pain that we treat, where usually --

DR. TRIVEDI: Correct.

DR. STEIN: -- they are associated with functional impairment. But in this case, we're also treating emotional pain sometimes.

I agree with you completely about the need to focus more on cognition and depression. You made a lot of points about cognition, cognitive dysfunction being worse in people who are not remitted. And I'm just wondering, many of the points that you made about cognitive dysfunction, could I have substituted the word "insomnia" and come up with kind of the same set of conclusions?

Are the things you said specific to cognitive dysfunction or are there other symptoms that go along with non-remission and poor functioning? What's special about cognition I guess is the question.

DR. TRIVEDI: Absolutely. There are two things that are true. One is not all symptoms are as often seen in the residual status even when

somebody achieves remission. But it is not exclusively cognition, so you're absolutely right. And sleep, anxiety, and cognition are the three most commonly seen. And if you want to include four, then lack of energy or apathy are the four.

So you're absolutely right. That is not the only symptom, but the large majority of other symptoms disappear. And I showed you the ones that disappear. But you can also still find patients who are fully remitted and still have significant anhedonia. So it isn't like this is exclusively cognition.

The question of any of these residual symptoms and its effect on distress of the patient -- because that sounds like what you are really interested in -- is actually much more commonly seen with cognition than you see with sleep or with other things, but still work needs to be done.

DR. DICKINSON: Thank you, Dr. Trivedi, for that talk. I have a question about cognition. We've really been talking about cognition sort of

with a capital C, but then woven into the discussion are mentions of different domains of cognition. It struck me from the meta-analytics evidence that you showed that there aren't really impressive differences in the magnitude of the depression-related cognitive impairment across these different domains.

Can you comment on that?

DR. TRIVEDI: You're right. That's what I started with, that the magnitude of cognitive dysfunction we see with depression, it will not match the magnitude you see with Alzheimer's, and that is a fact.

DR. DICKINSON: But this impairment is really a generalized impairment. It doesn't seem like it's specific to memory or specific to working memory.

DR. TRIVEDI: Right. So most of the data shows it is processing speed, working memory, and executive function, but there is other dysfunction, as I so showed you in the specific tasks.

DR. DICKINSON: I guess what I'm asking is,

is there domain specificity of the cognitive impairment in depression, or is it really a generalized sort of all cognition is impaired kind of an impairment?

DR. TRIVEDI: So the short answer is it's very difficult to disentangle each domain in cognition, period. So it's not a unique problem to depression. But if you look at the magnitude of the dysfunction, then the most often seen, highest magnitude effects are in processing speed, working memory, and executive function.

DR. PICKAR: Dr. Ionescu?

DR. IONESCU: Thanks so much for your talk. A quick question. Regarding stimulant augmentation to antidepressants in patients with depression, is there any evidence that we know of that the stimulant augmentation can improve the cognitive domains? Like for example attention, we know that it improves in patients with ADHD even if it's not improving the depression per se in patients with depression.

DR. TRIVEDI: Wonderful question, and I

think that this dovetails, again, to the earlier question about domains and the magnitude. We don't have a large plethora of evidence in all this. So with lisdexamfetamine, Vyvanse, there is a trial that is published in Neuropsychopharmacology that shows cognitive function impairment in people with residual symptoms who were treated with it versus placebo.

Different studies, unfortunately, you do different domains of cognitive function, and therefore, there is some evidence that stimulant use in that group of patients does improve cognitive function. Whether it's the same exact domains or not is a question because we don't have the data.

Similar to this, we don't have large epidemiological databases to find out what is the general population level of cognitive dysfunction in people with major depressive disorder. Most often, these are convenient samples that we use in randomized control trials, studies, et cetera, and obviously more needs to be done to try to

understand that.

DR. PICKAR: Other questions? Dr. Conley?

DR. CONLEY: Thanks again for your presentation. This is kind of taking off from these other two questions. I thinking about developing treatments, which is part of the question in front of us, I think what I took away -- but I would like you to kind of underline this as true or not true -- is that, first of course, there can be people -- I mean, depression isn't necessarily just one thing. There can be people who are mostly depressed because there's some cognitive dysmetria that turns them into that. Maybe other people are extremely upset, whatever. I mean, there are differences.

But here importantly for outcomes, what I think I'm hearing you say is that there are some people who have persistence in cognitive symptoms despite the fact that they've had change in their depression. And you've seen at least some evidence through small studies that some things might help. Is that true?

DR. TRIVEDI: So that is -- so the first part is absolutely true, that there is persistence of cognitive symptoms in people who have improvements of various degrees, including who would be declared full remission and, in fact, in long-term studies who have been outside of a major depressive episode for some time. Better treatments, per se, addressing those can and change that cognitive function is the emerging literature, and we don't have all the data out.

That's what the earlier question on stimulant addressed. There are some indications from studies that are beginning to show that those measured cognitive functions can show improvement with treatment. But that is really a new field, and I wouldn't say that we already have that as a standard or an accepted component. And I assume that's something you will discuss in the afternoon.

DR. PICKAR: You mentioned earlier that, typically, the neuropsych variables do not correlate well with recovery or change in depression. Do any of them? Because they're not

all the same. And one of the things we're going to be looking at are specific ones. That's the challenge of this and the fun of it. But are there specific ones that correlate better and others that really function on an independent path?

DR. TRIVEDI: I think that is a very good question, and I think it dovetails to Dr. Stein's question. And that is, if the symptoms improve, which when you look at a responder group or a remitter group, that means there are symptoms that improve, in that group of patients, there are a core set of symptoms that correlate very well both in terms of at the end as well as the change over time. And that includes sad mood, anhedonia, lack of energy, worthlessness, guilt, et cetera. The symptoms that don't are the ones Dr. Stein mentioned: anxiety, sleep, and cognitive function. They do not correlate well.

So there is a core group that do, and there is a group that doesn't. And when you have response or remission, as Dr. Farchione mentioned at the beginning, that idea that everything will

improve, is true for a core group of symptoms but not true for these typically residual symptoms that everybody has talked about in the past. And sleep, for example, for the longest time was the focus of that in depression for a long time. Those symptoms don't seem to correlate as well.

DR. PICKAR: Dr. Hinkin?

DR. HINKIN: Yes, if I may elaborate on that, too. I think one of the issues in that lack of correlation is often the way affective symptoms or somatic symptoms -- depression -- are measured differently than cognitive symptoms.

If you rely solely upon patient self-report, I think there is usually a reasonably good degree of correlation. But if you're relying on patient self-report for symptoms of emotions, sad mood, and using psychometric measures with hopefully some better degree of precision and sensitivity, there, clearly the correlations totally fall apart.

DR. TRIVEDI: I think that is a central issue and thank you for bringing that up. That wasn't the focus of my presentation; probably

you'll get into it with Dr. Pacheco or in the late afternoon have you measure what is the contribution of self-ratings, what is the contribution of objective ratings, all that is an issue that needs to be addressed, absolutely. For example, as you mentioned, rightly, self-ratings are quite often impacted by the level of symptom severity. So therefore, if you are not feeling better, you will say you're not concentrating better.

DR. PICKAR: We're going to move on. Thank you very much, and we'll have an opportunity to ask all three of the speakers some questions. We now move to Dr. Pacheco from the National Institute of Mental Health.

Presentation - Jenni Pacheco

DR. PACHECO: Thank you. I enjoyed that discussion about cognition because that's what I'm going to be talking about. Yes, I'm at the National Institutes of Mental Health. I work with RDoCument [ph]. My talk won't be focused mostly on RDoC, just cognition in general and how we assess that. I'm happy to answer any other questions.

My talk is really in three parts, first, what is cognition, which we kind of just touched upon, that we might need to all agree on what we're talking about. How do we measure cognitive function? And then importantly, how we do we determine cognitive improvement, which is probably what we're interested in if we're talking about treating cognitive dysfunction.

Cognition is a multifaceted concept that encompasses several constructs and processes. The subprocesses that fall under cognition are supported by higher level brain functions and are crucial for interaction with the world.

This list here is not meant to be all inclusive, but it's just to point out that cognition is really big. There's a lot going on. So you have things like attention, decision-making, flexibility, inhibition, knowledge, language, memory, perception, performance monitoring, planning, reasoning, and working memory, and other things. And the boundaries between these are kind of fuzzy, and they all overlap.

You can cut down on this word cloud a little bit if we talk about executive function, which is really just an umbrella term for the management of cognitive processes, and that includes things like decision-making, flexibility, inhibition, planning, reasoning, and working memory. But even still, that means executive function is pretty broad and there's a lot going on there as well. But it does make our list a little less overwhelming.

When we talk about the cognitive dysfunction in depression, primarily we're talking about things like memory, attention, and executive function that are the domains that are most commonly identified as impaired in individuals with depression, and that's where I'll focus a lot of this talk on today.

The impairment with memory is for explicit memory, not implicit memory, so your memory of places and things and people, and what was just said and not any kind of conditional learning or subliminal memory. It happens in both recognition and recall tasks, and from a neural standpoint,

memory is really the coordination between medial temporal lobe structures like the hippocampus, entorhinal cortex parahippocampal gyrus, and the prefrontal cortex.

Some examples of tests that can be used are delayed match to sample, paired associates learning, pattern recognition memory, and story and list learning. So as a quick example, I'll talk about the Rey Auditory Verbal Learning Test, which is a list learning that has both an immediate and a delayed component.

For this task, the participant is read a list of 15 words out loud, and then they're just simply asked what was on list A. And that's repeated again and again for five times. And after that, the participant is read a second list with 15 words and then asked what was on this list B. And after that, they're asked again what was on list A, the first list that was read several times. And then, finally, after waiting 30 minutes, they're asked again what was on list A.

For this task, it takes approximately

10 minutes to administer. Of course, you have to build in that 30-minute delay. And from this, you can get measures of learning, so how many words could you remember after the first time you heard the list; how many words could you remember after you heard it five times. You get some susceptibility for interference from distractors, and you get this idea of how well the memory lasts over 30 minutes.

With attention, the effects that we're seeing in depression are for this effortful attention; again, not any kind of implicit processing. And attention is really the coordination between other limbic structures, so things like amygdala, the hippocampus, or the basal ganglia with the prefrontal cortex.

Examples of these tests include choice reaction time tasks, digit symbol coding, sustained attention tasks, and continuous performance tasks. I'll walk through a continuous performance task, or CPT, which measures both sustained attention and selective attention.

There are a lot of different varieties of CPT. Each of them has a slightly different administration time and trial set, but the one I'll show you today just has a simple simile set of 1's and 2's. So the subject will just see 1's and 2's kind of show up on the screen, and every time they see a 1, they have to push a button.

There can be two different types of trials in this task. There can be a high demand trial, which will have a lot of 1's and very few 2's. So by this, we're asking the participant to maintain constant focus and to be ready to put on the brakes when they see a 2 and not push a button. So again, a lot of 1's will come up. They'll be pushing the button, and when they see that 2, they have to refrain from pushing the button.

This will give you errors of commission, so times that they push the button when they saw a 2 and they shouldn't have. It measures sustained attention and has implications for impulsivity. In contrast, a low demand trial would have a lot of 2's and not many 1's. And here we're asking a

participant to focus on the relevant stimuli and to try not to drift off but to really maintain their attention.

So they're seeing lots of 2's possibly on the screen, and when a 1 pops up, then they have to remember to push the button in response. This will track errors of omission or times they forgot to push a button when the 1 showed up. It measures selective attention and has implications for destructibility.

Lastly, executive function, it encapsulates many higher level cognitive functions, specifically planning, inhibition, problem solving, processing speed, and set shifting. This is really the coordination between the prefrontal cortex and several non-frontal structures that allow for the integration of information in order to perform these tasks.

Examples of tests that are used are Stroop, Wisconsin Card Sorting Test, the Trail Making Test B, Tower of London, and Spatial Span. As a quick example, I'll show the Trail Making Test A and B,

which measures processing speed, mental flexibility, and task switching. Generally, we start with Trail Making A, which is just a simple connect the dots. We ask the subject to connect the dots in order, as fast as they can. Then we give them part B, which involves letters and numbers. In this case, we're asking them to connect the dots in order of number then letter, as fast as they can; so like 1A, 2B, 3C.

This is pretty quick to administer. It probably takes about five minutes to get through both parts. Part A generally uses a measure of just plain processing speed, how quickly can you move through 25 dots. The extra time or the difference between the two is generally attributed to the executive function load are then needed now to switch tasks and kind of maintain where you are in the letters and the numbers.

So that's what we're talking about when we're talking about cognition in general. But how do we really measure cognitive functioning in terms of kind of a clinical trial or a research study?

There's a big debate as to whether or not a single test is valid or if we need a whole battery of tests. Of course, there are many benefits to having a stand-alone cognitive test. It's easy and fast to administer. There's less burden on participants and study staff. And there is a simplicity of data analysis in that you only have really one result to look at.

But the question remains is one test enough. My belief is that the answer is not really. The entire multifaceted and heterogeneous nature of cognition is really hard to measure with one task. We have a slight task impurity problem, so most of these tests aren't really a pure measure of any one construct of cognition.

So if we think about the Rey Auditory Verbal Learning that I showed, yes, it's a memory task, but of course there is some level of motivation and even auditory perception that's needed. So if you're not very motivated and you're not paying attention to the lists, you're certainly not going to remember the words. If you can't hear the lists

very well, you're not going to remember the words. We have this problem with these tasks and with all the cognition being so interrelated that it's hard to have one task really being a measure of anything purely.

Additionally, individuals might score poorly for different reasons. So think about if we tried to boil down all of are you healthy or are you a fit individual by how fast you can run a mile, sure, that's a good indication, but there's a lot of different reasons why people are fast or slow at running a mile, and that one metric just may not really be enough to determine somebody's fitness level.

Additionally, the multiple measures can provide converging validities. Every test that you use has unique psychometric properties, that you're now going to use to measure the whole cognitive domain. So then your conclusions about the cognitive domain are kind of relying on those unique psychometric properties. With multiple tests, you can kind of converge some of those to

get a little bit more valid or reliable information.

Obviously, as I'm promoting the idea of a battery of tests, we can talk about a couple of test batteries that are available or have been made. The two that I'm going to talk about were developed specifically for research of schizophrenia. The MATRICS Consensus Battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia developed a standardized battery for use in clinical trials of cognition enhancing interventions for schizophrenia research.

The test battery is founded on traditional neuropsychological tests. It covers cognitive domains. It includes overlapping and converging measures for some of the domains, and you get a specific score for each domain and then an overall composite score.

The seven domains are speed of processing, attention, working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition. No similar test battery standardization

has been developed for depression, however, this MATRICS battery has been used in clinical trials of pharmacological treatment of depression as well as some studies of bipolar disorder.

The tests in this battery were selected for their psychometrics rather than their specificity in terms of brain related systems. For that, they're a little bit messy. There's overlapping processes required to perform each test, and it results in significant part to whole correlations. So the scores for each domain are highly correlated to the overall composite score. So you're not necessarily getting a specific process with any of these domain scores that you get. The time to administer this battery is about 60 to 90 minutes.

This is just a listing of the cognitive domains and the tests and a short description that are involved in this battery. Alternatively, the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia consortium, or CNTRACS, assembled a list of tasks that assess a more narrow cognitive process and they demonstrate

associations with activation in specific circuits, and disruptions of those circuits are important for patients with schizophrenia.

These tasks were further developed and optimized, and the scores on these tests are modestly intercorrelated. So unlike the MATRICS battery, there's not as much overlap or intercorrelation between the domains and these tests, which suggests that they're assessing more discrete cognitive circuits and processes. For the CNTRACS tests, these are the four cognitive domains that they have: goal maintenance, relational encoding and retrieval, gain control, and visual integration, and the tests that are included here.

Those are some ways that we can measure cognitive function, but how do we really determine cognitive improvement? And this was touched upon a little bit in the questions after Dr. Trivedi's talk in to what extent does improvement on a clinical or lab-based task indicate observable life gains? If I'm able to perform Trails B 10 seconds faster, have I gotten a better job? Am I happier

with my life? Am I doing better out in the world? Probably not.

Functioning is multiply determined, so although these scores are associated with ratings and functioning, they account only for one-third approximately of the variance associated with the functioning of individuals.

There is currently no empirically based threshold to determine the degree of change on a cognitive test that predicts a meaningful change in everyday function. So if not 10 seconds, is it 12 seconds? We don't really know how those changes really relate to everyday functioning.

So how do we assess everyday functioning? Can we just ask a participant if their functioning has improved? The unfortunate answer is probably no. For individuals with bipolar and schizophrenia, there's a strong inverse relationship between depression severity and self-ratings of functioning. So the worse their mood symptoms are, the worse they're going to say that their functioning is.

Kind of following that, treatment of the mood symptoms can improve these self-ratings of function without any actual improvement in cognitive ability. So they're feeling better about the world. They feel better about themselves. They're going to rate themselves a little bit better regardless of how they're actually performing.

There's evidence that ratings of functioning made by either a high contact clinician, a close caregiver, or family member are more accurate and maybe more reliable. Obviously, those are a little bit more difficult to obtain, and not every person is going to have someone who can give that kind of rating for them.

There are some novel methods of passive data collection, so wearable devices or ecological momentary assessments may help resolve the discrepancies between self-report and actually functioning. But it is kind of a big question, and I am also glad I'm on this side and not on that side to figure out how we know if functioning has

improved.

Here's just a sampling of some data that was presented for patients with bipolar disorder. The darker blue bars are patients with cognitive complaints, and the green bars are patients without cognitive complaints, and the lighter blue are the controls.

In this study, they did a whole bunch of tests. I'm just giving you an example. But pretty much, the trend was that there was no difference at all between the patients who expressed cognitive difficulties and those who did not. So again, their self-report or their inference on how they're doing is not great.

In that case, is a clinical objective measure more informative than a self-report? Since self-report can be dependent on mood state, it can be a little bit unreliable and kind of vacillate back and forth. But I guess the big question there is, is cognitive improvement that's detected only by a test and not noticeable to the patient an acceptable outcome? So again, if you make me do

Trails B faster by 10 seconds but I don't really notice it, am I better? It's something that probably they'll need a little bit of self-awareness about to feel like they've gotten any improvement.

There aren't many studies that show data that indicate the extent to which improving someone's subjective sense of their cognitive abilities is really due to any kind of actual improvement in functioning. But there are a couple of studies, specifically on schizophrenia, that show that their misestimation of ability was the strongest predictor of real-world functioning. So patients who were not able to accurately estimate their own functioning or their own ability were shown to have less real-world functioning.

What that means is that that might be a target or a place for intervention, where if you can get patients to be a little bit more accurate with the understanding of their own limitations, they might actually then be functioning in the real world better. Even if their performance on the

tests are low, if they are aware of that, their real-world, everyday functioning might actually be better. If they don't have that awareness, then it seems like their real-world functioning is a little bit worse.

So another important thing to think about as we're talking about how to address cognitive dysfunction in depression is how much impairment can we actually detect with these tests. Cognitive impairment in other mental disorders, such as schizophrenia, can be severe, so about 1 to 2 standard deviations below healthy controls.

As Dr. Trivedi said, too, cognitive impairment in depression, while it can be impactful to the patient, it may be less obvious on some of these tests, which could be deemed to easy so that they're kind of having these ceiling effects and performing too well, and you won't actually see much of the impairment.

So the tests that are chosen to assess those should be sensitive enough to detect the slight changes in cognition and potentially should have

procedural modulations that you can make them harder or more sensitive as needed for your participants.

I said it was only three parts, but I feel like I've kind of led us down this dark road of despair. So we can put it all together, I would be a little bit remiss if I didn't talk about the Digit Symbol Substitution Test. This has been widely used as a broad-band quick and sensitive measure of cognition in depression and other mental disorders as well. So this is just a sample of it.

For this test, each digit has a symbol associated with it, and participants are asked to fill in the associated symbol for each digit in a given time frame. So they get out about 2 minutes, and they get to go as far as they can. And their score is how many correct symbols they were able to put down. It is said to measure executive function, speed of processing and attention, and it is a pretty robust test of cognitive ability.

As I said, it has been widely used, and it could be considered for inclusion as an implicit

comparison to previous studies, but I don't think it's a stand-alone measure for cognition. There's still a lot of variation that we could see. You're not necessarily getting the breakdown of how you're giving them 2 minutes, and you're saying has your cognition -- where do you fall in this 2 minutes. So if we had a couple of other tests that measured other aspects of cognition as well, they should be included in the study.

Particularly, we should maybe focus on some measures derived from cognitive neuroscience, which will assess more narrow aspects of cognition, so you can actually see which areas you're having a deficit and see which areas you've improved, as opposed to the tests that are a little bit more intercorrelated.

The general conclusion here is that there's probably no one test or set of tests that are good for every study of cognition or cognitive dysfunction in depression, but there is a pretty good way to figure out how to select your tests. So appropriate measures should have evidence of

valid behavioral and cognitive function. They should have evidence of impairment in depression. They should have evidence for an implementing neural system. And they should have links to the mechanism of action of the pharmacological agent at hand. So as long as these things are taken into account, then they're probably any number of tests that could serve to help figure out cognitive improvement is happening. Thank you.

Clarifying Questions

DR. PICKAR: Thank you very much. We'll take some questions now, and then we're going to bring the whole group up. But how about questions of Dr. Pacheco? Yes, Dr. McMahon?

DR. McMAHON: Thanks for that really informative overview. You made the point that subjective measures of cognition are affected by mood state, which certainly makes intuitive sense and squares with clinical experience. But are the objective measures also affected by mood state? What are the data on validity of objective measures during a major depressive episode?

DR. PACHECO: I mean, yes, they're certainly going to be affected by the mood state. I don't -- off the top of my head, I don't know what the data -- Dr. Trivedi might have better data about the actual validity of some of the studies. But I think that's part of the big problem, is that it will certainly also affect your objective measures.

If you're having trouble concentrating, your attention's going to be poor. Presumably, then if you're able to address the mood symptoms, some of these may be corrected. So if you're able to address the mood symptoms, then your concentration's better, you might have better attention, and your test scores will improve a bit. So that's all.

DR. GRIEGER: Tom Grieger. I'm kind of struck by slide 24 that only the changes on cognitive testing with I guess objective tests only account for a third of variance in actual functioning. Do you recall what specific patient groups were being studied by Depp and Bowie?

DR. PACHECO: Off the top of my head, I don't. Sorry.

DR. GRIEGER: That's fine. I just wondered if it was mood disorders versus primary psychotic disorders. And I guess the other question goes along with that. Even though it does account for that limited amount of variance in performance, is there a specific aspect of cognition that's most specific to performance? I'm thinking executive function versus memory versus attention level.

DR. PACHECO: I mean, again, I think Dr. Trivedi might have some more experience with this because I don't have as much experience with depression as I do with cognition. But there are certainly -- I believe the memory or even some of the attention deficits that we're seeing with depression, once the mood symptoms are addressed, those kind of remit themselves and we don't see them as much. And some of the executive function or processing speed, working memory issues, those might persist a little bit beyond the treatment of the symptoms.

So I think they certainly are working differently in that some of them will last past the mood symptoms, and some will clear up with the mood symptoms.

DR. GRIEGER: Thank you.

DR. PACHECO: Sure.

DR. PICKAR: Dr. Narendran?

DR. NARENDRAN: I just have a question -- I know like in schizophrenia, you have these two batteries, and in ADHD, you potentially have some battery tests. At least based on schizophrenia and ADHD literature, for a particular therapeutic -- I mean, batteries are good to delineate patients versus controls and those kinds of things. But if you're talking a specific therapeutic, how well -- is the effect size any better in detecting improvement if you use a battery as opposed to using a single test or a few tests?

DR. PACHECO: Yes. I mean, I think there's something to be said; if the tests that you're using is shown to have this impairment in depression and it relates to the system or the

neurological functioning that you think you're addressing, then, sure. I think a more focused test or group of tests rather than a global general battery is probably a good idea.

DR. NARENDRAN: Is there evidence for that? Like, for example, the MATRICS detects 0.4 improvement effect size versus if they just use Wisconsin Card Sorting, 0.15.

DR. PACHECO: I don't have those numbers off the top of my head, so I don't know them. Again, I think that it would just be that you want to make sure that you're assessing enough of cognition to make that claim. So if you can improve the Wisconsin Card Sorting slightly, what aspect of that are you improving and was that due to just they got better at figuring out how to do Wisconsin Card Sorting or are they actually able to shift with the rules better?

I think you have to be sure that the improvement you're seeing is actually what you're claiming it would be. And one test, it's a little hard to make that claim.

DR. PICKAR: Dr. Stein?

DR. STEIN: Thanks. I also appreciated your presentation. So help me understand the statement you made towards the end, or at the end, that no single measure would be good enough for these purposes. I think you used the example of the Digit Symbol Substitution Test. That, for example, is a test that does a pretty good job. It's tapping into processing speed. It's tapping into some aspects of attention, executive functioning.

Granted, there are lots of things that influence that, but at least those functions are covered. It's quick. So if you were going to -- and more complicated isn't always better, right? So we're not always in a situation where we could administer a whole battery of tests. What would be wrong with using a measure like that?

DR. PACHECO: I think if you're trying to say that you're improving cognition, which is a huge overarching thing, and you've improved it by getting a score better in 2 minutes, as something that measures speed of processing, attention,

executive function, all these things, what is your improvement -- you know, what is your improvement based on? It's hard to say from a 2-minute test that measures potentially five different things. It could be due to anything.

DR. STEIN: I guess my frame of reference is how we measure depressive symptoms, which is not --

DR. PACHECO: Not great.

DR. STEIN: -- even as good as that.

DR. STEIN: Right, which RDoC is trying to I think -- and putting cognition into depression, we're talking about two kind of huge, heterogenous behemoths butting heads. It's a hard question, but important.

DR. PICKAR: Dr. Hinkin?

DR. HINKIN: Yes, if I just may expand on Dr. Stein's point. I think one of the crux of these issues is the amount of time invested versus the amount of payoff you get. And certainly, if one only was able to use a single test, because you only had 2 minutes with the patient, then perhaps

something like the Digit Symbol Test would be a fine choice. And now, I guess, if you only had one question to ask a patient to determine if they're depressed, how is your mood is probably the one question you would ask. And it would probably be better than any other single question, but it might not be sufficient to really capture all the components of it. That's kind of the trade off that I guess we'll be talking about this afternoon.

DR. PICKAR: Dr. Conley?

DR. CONLEY: Just one thing, and thanks. This kind of touches on what we're talking about right now, is that for the MATRICS and other batteries in schizophrenia, some thought was put in to what could a person with schizophrenia actually reasonably do.

DR. PACHECO: Right.

DR. CONLEY: And that's kind of what I'm wondering here for a battery. I mean, you're an expert in the area, so do you have some idea of what's reasonable, not so much as single tests. I mean, that's kind of the easy question. But is it

15 minutes of examination, 30 minutes of examination? My worry is with a depressed person, there's something about just the challenge of completing 90 minutes that is not only going to be a challenge to actually do, but it's going to be terribly correlated with their depression itself. So any idea about that?

DR. PACHECO: Yes. I think it's hard to pick exactly -- just for reference, in my dissertation study, I was working with older adults with either healthier dementia, and I did a 90 to 120-minute test battery on them. And it was long, and we had to take breaks, but they sat through it just for 10 bucks or something, whatever I was giving them to participate in my study.

So it is a burden to sit through something that long. No one probably wants to do it, but I don't think it's going to be detrimental or impossible. I think someone with depression, cognitively, their impairment is going to be less than someone with dementia, so it's going to be a little bit easier to get through some of this.

Certainly, if they're not terribly motivated or having trouble concentrating, it will be a little difficult. I'm not suggesting that we put people through a 2-hour battery by any means, but certainly 15 minutes, half an hour, should be doable for a participant.

DR. CONLEY: One thing, just to follow up on that -- thanks for thinking of this because I know it's not easy.

DR. PACHECO: No.

DR. CONLEY: But also, the thing with cognitive tests, you're talking about elderly adults, and I know, in a sense, no one likes these things because you ultimately wind up failing on them no matter how good you are. That's kind of the way you do the test.

So I do wonder if that's also -- do you have any opinion about is that some special burden in depression, where people already have this construct that they don't do well on things and you're giving them a test they ultimately fail.

DR. PACHECO: I'm sure it is. Again,

because a lot of this work I did was with dementia patients, and we had a ton of memory tests, and they're already feeling like they're going to be bad at that, we had to tell them ahead of time that I wasn't allowed to give them any feedback, and they were set up to be hard, and that they weren't going to do well.

I would imagine that a similar type of reassurance before the test -- I mean, again, when you're doing some of these, you can't give any feedback. You can't let them know if they're doing well or poorly, and kind of reassuring them that this doesn't mean that they're doing terrible, or that they're a bad person, or that this is somehow reflective on that, is probably helpful. But sure, I'm guessing that if you're giving them really hard tests for 45 minutes, it's not going to be an enjoyable experience for anyone.

Clarifying Questions of Presenters

DR. PICKAR: Might we have Dr. Zarate and Dr. Trivedi come on up here, and we can open up the questions to all three. And if any of those good

folks want to jump in with any responses to questions that you're hearing, it's all welcomed. It's a tough discussion we're going to have, an interesting discussion we're going to have, about these matters. Ms. Compagni Portis?

DR. COMPAGNI PORTIS: Well, in your presentation -- thank you for that -- you mentioned one really important piece, which is that a high contact individual is going to get better data and better information, and yet we keep talking about how do we do this briefly and what's one test that will show.

I know it's kind of the question of the day, but how do we resolve that? Because I think there isn't -- and I think also, just to add on to that, we also don't know with people who are depressed -- even if we test them when they first come in with depression, we don't know what their premorbid functioning is. And if you're talking about people -- you know, we have letters from people that were highly successful, and they are aware. Maybe they can do the Trails test. Maybe

they can do that, but they know they're not able to do what they did before.

I mean, all these things, we're kind of at crossed purposes because what we need is a lot of time to figure this out from someone.

DR. PACHECO: Yes. I mean, it's a big -- I mean, I think every question we ask comes up with four new questions of how do we handle this and what does that mean. I don't think there's a straightforward answer, unfortunately, right now, but I think -- and I guess that's what your job is, to figure out.

(Laughter.)

DR. PACHECO: But I think that the tendency is to always want to do something that's the quickest, fastest, easiest, cheapest way to do something, and that just might not give you the best answer or the best data. I think especially with something so broad as cognition and so heterogeneous as depression, that if you're getting a bunch of data back and it's questionably valid and going to be conflicting, it may be a bigger

waste of time to have done a 10-minute test and 4 questions than to do a 45-minute test and 25 questions.

DR. TRIVEDI: Just a little to add to this, two or three things. I tend to agree with Dr. Stein that more is not always better, so two major issues. One is, we have to be careful. We are already in our field where we have a research set of assessments that we don't use clinically. So we do a 6-hour assessment battery and find a perfect answer, but it never gets used. So we have to be careful of that.

The second issue is the question on something like a brief assessment tool is not that it is an all encompassing, fully formed answer to the entire set of questions. The idea is if that assessment battery can -- even if it's brief -- give you a good enough -- a very good signal for a component, that is worthwhile thinking about because MATRICS is fantastic.

Schizophrenia is not my field, but I'm not aware of any treatment that has, therefore, been

able to show any effect. So the fact that we have more complete universal understanding doesn't get us that.

Secondly, I think this issue of effort is very complicated. We are not the only field that has to struggle with it. So if you're doing pulmonary function tests, the patient, how much effort they put in actually goes into it, but the pulmonologist doesn't say, well, then I'm not going to use a primary function test. We have to balance that with if we can do that in the preponderance of patients.

So we have to think about that as we move forward; otherwise, we are stuck in this 4-hour, 6-hour neuropsych battery that helps us understand where the deficit is at the neuronal level but doesn't get used. So how do we draw -- which is why she is so generous that this is your headache. But it is something worth thinking about. If we do something that is so elaborate but doesn't get us output -- so --

DR. PICKAR: The question of treatment,

which is so fundamental, Carlos, from the imaging point of view, how much of this is state dependent in the sense of a treatment, related to actual treatment? Is there data there?

DR. TRIVEDI: Can you repeat?

DR. PICKAR: I'm trying to tease apart treatment, looking at these areas. We're looking at the pathophysiology and localization of sites and so forth for these areas of dysfunction. We know mood improves. Does that pathophysiology -- do those models have anything to tell us about their clinical measures, which are really neuropsych measures as well?

DR. ZARATE: No. Good, well-controlled studies are very few just on cognition, and linking cognition and imaging and treatment, very few if any.

DR. PICKAR: Very few.

DR. ZARATE: If any. So in the problem areas of those existing, many are post hoc, so you're taking advantage of a data set, and you look at --

DR. PICKAR: That's right.

DR. ZARATE: It's not the same as you require to go into a trial with cognitive impairment. So here, a lot of times -- here we're talking about the general battery, but it's clear that many specific domains are not affected in depression, and it varies from subject to subject. So you could end up with not enough variance, so you might have to require that prospectively to go into trial. There's very few if any data on that.

DR. PICKAR: Very little data to help us there.

DR. ZARATE: Very little, yes.

DR. PICKAR: Earlier when I asked you, Dr. Trivedi, which of the neuropsych measures co-vary with depression, in general, they don't necessarily. Are there some that are tracked with depression better than others? That's what I was asking you before, whether it's the Digit Symbol, or whether it's Trails, or whether it's any of them. I just don't know that answer. Do any of them track with depression and some stick out?

Wisconsin Card Sorting may stick out. I don't know.

DR. TRIVEDI: As you saw in the pre-, post-treatment as well as those in the episode and non-episode data, a number of -- like DSST showed change in the episode to non-episode. You're then bringing in the treatment aspect, which is where we don't have too much data. So if you then try to factor in a particular treatment or between treatments, et cetera, we don't have that data. But DSST, for example, you saw Trails A does track with depression and improvement.

DR. HINKIN: In response to that --

DR. TRIVEDI: Dr. Dickinson? Excuse me. Dr. Dickinson is up next. We're very formal here.

DR. DICKINSON: Thank you.

DR. PICKAR: Sorry.

DR. DICKINSON: So I guess I'm sort of struck that we're -- there's a little bit of false dichotomy here. It's not a choice between using Digit Symbol, a 2-minute assessment, and a 4-hour neuropsych battery. The question is, how do we

balance validity and test measurement reliability with burden to the patient, burden to the study that we're trying to get done? I think there's an argument to be made that, you know, 15 minutes is better than 2 minutes, and 30 minutes is better than 15 minutes in terms of the testing that you do and the assortment of tests that you use.

So you don't have to jump from 2-minute Digit Symbol to 3-hour neuropsych, and there may be a sweet spot in the middle there, or it may vary from situation to situation. But I just think we need to -- there are other options besides the MATRICS battery on the one hand 90 minutes and Digit Symbol on the other.

DR. TRIVEDI: Absolutely, and I'm glad you brought that up, that we shouldn't make this a dichotomy or false choice. But the point I was making was slightly on a different plane. If a particular shorter test gets you enough domains that you can actually say this a measurable effect that we then can claim or have thoughts of improvement in the patient's clinical status, and

it does not measure some other domains, that doesn't mean that this is not an efficient way to do it.

You could say, then, what about the other domains and whether they improve or not. But that may be important, may not be, but this particular set of domains, if we can see an effect, then at least I think it is worthwhile, even if it doesn't mean it is showing or measuring all the domains. That's all I was saying.

DR. PICKAR: Dr. Hinkin?

DR. HINKIN: Oh, I --

DR. DICKINSON: Let me just follow that a little bit. And I guess the question is, in my mind, do you know that you are seeing an effect? I mean, is this measure, a single measure, a reliable way to get a sense of whether there is an effect or not? And just in a very simple-minded way, to me, it would be much more convincing to see three measures showing an effect than to see one measure showing an effect. So Digit Symbol and the Rey Auditory Verbal Learning Test together is a more

convincing case than Digit Symbol alone.

DR. PICKAR: Dr. Conley?

DR. CONLEY: Actually, if it's all right, I had a question for Dr. Farchione. That was one of the morning talks --

DR. PICKAR: Sure.

DR. CONLEY: -- if that's okay.

DR. PICKAR: Sure.

DR. CONLEY: I had two clarifying things from what she had mentioned this morning. You mentioned in questioning what should we have. You said try to -- and obviously we're trying to address the issue of pseudospecificity; do you need evidence versus placebo or do you need evidence versus an active comparator? The obvious question versus a clarifying one is like here today, we don't really have an active comparator if you think of it as the definition of something that actually works for depression and cognition.

So what on earth would that be is one kind of clarifying -- just to make sure people know what they're asking.

DR. FARCHIONE: It's not an issue of an active comparator in terms of improving cognition. It's a matter of showing that you have one product -- you have two products that are both antidepressants, and yet, while you're improving mood in both situations, now you're showing that this other product then improves cognition on top of the mood symptoms.

So if you have a difference in a cognitive measure, even though they both help with mood, now you've kind of -- it seems like you've addressed some of this pseudospecificity issue.

DR. CONLEY: I can understand -- I mean, that makes it -- I mean, in essence, I could get how that makes your job easy if you have the beating. But not making your --

DR. FARCHIONE: But it is a high bar, though.

DR. CONLEY: That's right, but not -- that's right. It's a higher bar because as we're hearing here, the comment behind it, of course, is that there's a lot of things that can help depression

and cognition, and therefore, any treatment's going to make it more variable. So what do you beat?

But the second question is -- you've mentioned a couple of times seeking a claim. And there's a number of ways of getting things on a label, including the clinical trials section and not a claim. And here, it feels as if we're only talking about a claim.

DR. FARCHIONE: Well, actually, that's why I used that word "claim" as opposed to the word "indication."

DR. CONLEY: Okay, gotcha. So you're thinking of a claim as anywhere on the label is partially a claim.

DR. FARCHIONE: Right.

DR. CONLEY: Okay. Good.

DR. PICKAR: Dr. Temple?

DR. TEMPLE: To go back to the first question, this is a very important part of our consideration. It seems sort of obvious that if one antidepressant has no effect on this function and another one is shown to, you're sort of done.

But if you really believe this has not been fully evaluated in the antidepressant world, then finding out that it works on this component, which may or may not -- this is what everybody's talking about -- which may or may not track the other aspects of depression, conceivably that could also be a good thing to know if you didn't know it before. That's why we're putting that question.

DR. CONLEY: Good. Thanks.

DR. GRIEGER: I think what we're going to get into this afternoon is really an indication for a symptom within a syndrome, which we treat patients with -- we used to only treat syndromes. Now we treat syndromes and symptoms, but usually it's with an agent that wouldn't treat the syndrome. This seems a little different than that.

I guess the question is, if this is going to be a claimed benefit for this drug, is it reasonable only to compare it against one other medication versus all other classes of medication, because you're making a claim for a specific medication of a specific class as though it only

exists in that medication. Granted, the other companies could come in and do the same trials and say, well, okay, now I get that indication, too. I guess the precedent for that is using atypical antipsychotics to treat bipolar depression. There are some that are labeled for that and others that are not.

How does this compare with that? I mean, we're talking about really a different disorder, a different syndrome. Bipolar depression is different than bipolar mania. We're not talking about treating a specific symptom within a syndrome. And I just wonder what is adequate for getting an indication for that from a scientific standpoint. I don't know who could answer that question.

DR. PICKAR: They enjoy the fact that we have to grapple with that. The speakers said that. You really hear that.

What do you think? Could you share a thought on that question? That's one we're going to grapple with.

DR. ZARATE: Do you have any thoughts on that?

DR. TRIVEDI: I think that is why I'm standing and you're sitting.

(Laughter.)

DR. TRIVEDI: I think the issue for me is -- I can't go into the details of whether one product versus the other. I mean, I haven't even seen the data. My sense is that if something can -- and I'll use my exercise treatment study example. If the high dose changes cognitive function over and above what the low-dose exercise did, despite the fact that there is some improvement in symptoms on low-dose exercise also, that exercise effect on cognitive function I see as real.

Now, for products and the question that you're asking -- for the FDA, the question is something that you have to see all the data, so I don't want to overstep my --

DR. ZARATE: I guess, what would you do -- thinking of anhedonia as a symptom or a

syndrome. So would patients with depression who had predominantly anhedonia, what would you do with that? Because you could -- and there's actually research to back it up that you could divide it into different components. I talked about that, consummatory, motivational, anticipatory. So would you give -- and some antidepressants might help with that, others not.

So are you going to require they help with each component, one component? Are you going to compare it to other treatments, require all drugs? So you could end up with -- people now are looking more, RDoC and others, at how to dissect these symptoms and syndromes. Lack of drive and pleasure is linked with poor outcome, anhedonia, with suicide. We talked about that. So how would you address that.

I'll throw it back to you.

DR. TRIVEDI: One backdrop of all this that really we have to recognize, all of us, is that our syndromes, while we think of them as sort of religious texts, are not really based on biology.

And therefore, the fact that that is a syndrome, and why should we pick one or the other would assume -- we're making the erroneous assumption -- a lot of us, I do, too -- that the syndrome is one thing. But the syndrome is made up of committee work and not based on biology. So therefore, if a treatment changes one sent thing like anhedonia, although that has been tried and not successful, whereas cognition -- then that becomes something we have to think about seriously.

That's the issue, because we are behaving as if it's a syndrome, then everything should stand together. And if something else, one of the other things changes differently, that is seen with suspicion, is the question. But the syndrome is not a real entity, although we are living with it.

DR. PICKAR: Dr. Ionescu, this is the last question before break.

DR. IONESCU: I'm curious to know what the three of you think about thinking about cognitive dysfunction in depression as more of almost like a biased mismatch or a biased imbalance. Because

think about cognitive dysfunction, as Dr. Trivedi mentioned, in dementias or psychosis, it's different. It's different.

What we see is patients who have depression can pay attention. They just pay attention to the more negative things. It's almost like there's a mismatch or an imbalance in the pleasure and pain, the happiness and sadness. They can focus on these things. They just, because of the disease, focus on the more negative things.

DR. PICKAR: Any comment?

DR. TRIVEDI: So I agree.

(Laughter.)

DR. TRIVEDI: I mean, I think that the only problem with that, which we all understand and agree, is how do you codify and measure it. Right? I think that's the challenge we have. So therefore, we recognize that there is this negative balance and false bias, or maybe it sometimes true bias because there's data showing that patients with depression actually have a more realistic appraisal of the situation that we do. I think

that bias is something not often measured, and it's very hard to do.

DR. PICKAR: I think we'll leave that as the last comment before break. We're going to take a 10-minute break. We will reconvene at 10:50. And please remember, no discussion. It's hard to, but we really want to keep the discussion in here and very public. It's important. Of the topic during break amongst yourselves, you can talk about anything else. We will resume in 10 minutes. Thank you.

(Whereupon, at 10:40 a.m., a recess was taken.)

DR. PICKAR: Okay. Welcome back. I hope some advisory board members find there way back. It depends on their cognition, I think, Trails B. Isn't that Trails, Rob? I think that is.

We're moving on with the program. Dr. Farchione has some comments she'd like to share with the group.

DR. FARCHIONE: Yes. I think that -- I just wanted to try to pull together and summarize some

of the stuff I feel like I heard from the other speakers this morning, and so to maybe focus the discussion a little bit. I introduced the idea that we're struggling with how we're going to evaluate these applications.

It's not just once an application is in in-house, but if a company comes to us asking about a development program that they want to start, what kind of advice are we going to give them: well, if you look at this in your study; if you look at that in your study; what kind of patients you want to recruit, et cetera.

Just in trying to pull together some of the things I heard this morning, from Carlos' talk, I kind of got the idea that you've got these neural circuits that are involved in emotion. You've got neural circuits involved in depression. In some places, they overlap; in some places, they don't.

When I try to combine that with Dr. Trivedi's talk, what I see is, okay, now you've got some folks with depression, and you see deficits in certain cognitive domains you don't

necessarily see in all the patients. Is there a difference in the neurocircuitry that's engaged? And we don't have that data yet, so we can't really answer that question.

I guess the big issues becomes, with what we know so far, what can we say about the kinds of study designs we want to see for a drug seeking this claim. And then, for the larger field, not just FDA but for the larger field, what kind of information are we really going to need in order to move this forward. So it's a big question for the group, but hopefully we can focus on the regulatory piece of it for today because that's going to be the --

DR. PICKAR: I think that's the critical thing. That's why we're all here, is the regulatory piece. And I thought there was a lot of good information there, but how do we pull it together so we can talk about it and then help you, because that's why we're here today.

You made reference earlier -- let me just for my clarification, the difference between -- and

Dr. Conley was mentioned -- difference between a claim -- and an indication. Excuse me.

DR. FARCHIONE: Right. So for instance, you've got your different sections of the labeling. So section 1 is your indications and usage statement, and that's where you say this product is indicated for the treatment of depression, or it's indicated for the treatment of schizophrenia. But in terms of whether or not a company could get an indication for a treatment of cognitive dysfunction associated with depression, I don't necessarily see that landing in the indications statement until we have some idea that this is a specific, inseparable entity.

But if you go further down the label into things like section 14, where you describe the clinical studies, now you're giving data that supports the idea that this product is useful in that condition, but it's not a specific indication. So folks can still market based on that. They can still --

DR. PICKAR: Actually, that was

my -- Dr. Temple?

DR. TEMPLE: Well, that's what I was going to say. Either place, if it's in section 14, not an indication, you can still present it if it's in there, in advertising and other places.

DR. PICKAR: Dr. Stein?

DR. STEIN: This is a question for my FDA colleagues. Are there examples in the past -- I think I can think of one -- where you did give -- I think it was even an indication, expansion of the indication. The example I'm thinking of is irritability in autism. What was the thinking that led you to be able to do that? How did you get there?

DR. FARCHIONE: Well, the issue with autism is that we don't actually have any treatments that change the core functions of autism. So in that case, we have medications that only treat that one specific symptom. But as far as your social cognition, and your repetitive behaviors, and all of the language deficits that go along with autism, it doesn't really do anything for that. So if it

only affects that one symptom, that's the only thing that you're going to get.

DR. STEIN: So that was actually the indication they received? Because I thought it was an expansion of an already existing indication.

DR. MATHIS: No, that drug had not been approved for anything in autism that was shown to be effective for the irritability of autism.

DR. TEMPLE: We sometimes pull out components of a larger scale. We've given claims for certain drugs for schizophrenia to treat negative symptoms.

DR. FARCHIONE: Well, we -- [inaudible - off mic]

DR. TEMPLE: Well, we've thought about. Sorry.

(Laughter.)

DR. TEMPLE: We could.

DR. PICKAR: So if that was real news, Dr. Temple, that would have been really something. I love that.

(Laughter.)

DR. TEMPLE: The point is, we take a broad scale that has both positive and negative symptoms in them. And we've thought about the negative symptoms as being sufficiently different from the positive symptoms so that we don't always expect them to go all the same way depending, and we've thought of that as not pseudospecific. It's a good example.

You know, you could have an arthritis drug that is labeled a drug that treats people with osteoarthritis that just treats their pain. Well, that's not the only thing that osteoarthritis does. There's disability and all that stuff. But we say, well, if you treat pain, that's okay because it's a pain drug.

DR. PICKAR: Let me read the first question. The panel -- are we back to seeing no discussion? Kalyani wants to make sure we do not discuss this outside of here. We're ready for the first question.

Discuss whether cognitive dysfunction in major depressive disorder is an appropriate drug

development target. So now we're trying to focus on the target issue and the regulatory issue. If so, which cognitive domains are mainly affected by the cognitive dysfunction in major depressive disorder, and what is the best method to assess these affected domains?

The floor is open. I'd like to hear the discussion.

(No response.)

DR. PICKAR: This is not a voting bell. This is a discussion, and we can go around the room as well. I can leave it open for people who want to start it or we can go around the room.

DR. NARENDRAN: Well, it seems to me like, based on the evidence they present, that clearly cognitive dysfunction exists in depression. Now, when you put that in the context of psychiatric drug development and how successful we've been in the past 20 years, not very well, it seems perfectly fine and rational to think -- in terms of what RDoC is doing, it's probably okay to open up a little bit some of these sub-syndromes.

As Dr. Trivedi said, and I agree, none of these symptom clusters are based in biology. They're kind of based on a bunch of consensus that we followed for 40 years. So maybe if we do see some of these things as cognitive dysfunction as a druggable target, or suicidality as a druggable target -- people argue there's plenty of evidence that lithium can reduce suicide, but it was never pursued, so maybe it's perfectly fine. I think your thinking is actually in line with what's happening, an evolving field, is my thought.

DR. PICKAR: Dr. Ionescu?

DR. IONESCU: So I agree that with the data presented today, it certainly looks like there is a cognitive dysfunction. Whether or not using that term is necessarily appropriate I'm still sort of struggling with the idea of cognitive dysfunction in depression being called cognitive dysfunction. But nonetheless, it seems like there's definitely something happening in patients with depression.

My concern is -- and I'm just kind of thinking out loud here, so I'd like to hear what

other people think as well. But if we say cognitive dysfunction in MDD is an appropriate drug development target, then we have to say sleep is a target, interests are targets, guilt is target, energy's target. Each symptom of depression as we know it currently would all then have targets individually in depression.

That's just -- I'm wondering what other people think, like would this potentially be a slippery slope that a drug could get an approval based on one target.

DR. PICKAR: Mitch? Dr. Mathis?

DR. MATHIS: I can tell you what we've thought about that. I think it potentially is a slippery slope, but it's a slippery slope that we can temper with what's important to patients. For instance, the irritability in autism is important to patients. We thought that was a legitimate drug target because it had a lot of impact on the U.S. public health and deserved to be a drug target.

I think it can be a completely slopeless landscape if we say you have to meet everything at

DSM and we're not going to consider anything outside of that to be clinically meaningful. So we're trying to find a balance, a regulatory balance, somewhere between you get what you get that's in the book, and you can't have anything else, or everything is a target. And I think that we can use some rational clinical judgment to come up with those targets.

There's a fair amount of evidence that cognitive problems in depression are a persistent problem, which seems to be phenomenologically to say that even when you use the drugs that have been approved to make the core symptoms better, there's this persistent problem, and it's a dysfunctional problem for our patients.

So it seems like it could be potentially -- and that's what we're here today to discuss -- a legitimate drug target. I don't know that everything else would be, but there may be other parts of the depression syndrome that are.

DR. PICKAR: Dr. Temple?

DR. TEMPLE: Well, that last point I think

has always seemed quite important to us. For the components of one or another tests that all sort of track together if you think they did, then we might have considered and might still consider a claim for one of them pseudospecific. I don't necessarily think that means it wouldn't be of interest to know how each one worked, but that's a different question.

But people have presented data in the past and present that cognitive dysfunction, at least sometimes, doesn't track very well with the other symptoms, that it can persist after they're gone. Well, that alone sort of makes it interesting because it's not true, maybe, that treating the overall disease treats them all if some of them behave differently. I mean, I would bet anything that sleep doesn't respond the same to all drugs, too, but one could get into that.

DR. PICKAR: The drug target question, comment on just what is a drug target to you folks. It has to be defined? It has to -- just help me. I'm not trying to put words in there. But it's

something in this committee that we really need to have real clarity on, A, about the cognitive things. But just help us a little bit with drug target.

DR. MATHIS: So what we mean by drug target is it's something that you should consider reasonable to intervene pharmacologically to make better. It's that simple.

DR. PICKAR: Well, for example, height in basketball is a tough one, but that's not a drug target. You can't change it. The question is, is this hard-wired and not a changeable problem? Retardation, you want to see neuropsych -- things that are not movable. By making this a drug target, we inherently believe that it's a "movable" in quotes -- is that a correct way of thinking or am I off on that?

DR. FARCHIONE: No. I think that you're correct. It doesn't make any sense to develop a drug for something that's not going to move, right? To get to your question, in the past, it's always been a target was some specific disease entity.

And in psychiatry, to call it a disease, it's really more of a syndrome because you've got a cluster of symptoms that we think track together.

Now, we're kind of in this gray area as a field, where because of things like the RDoCs initiative, we're really trying to understand the pathophysiology of the illnesses so that we can move past these syndromal definitions and move into actual neurocircuits, pathophysiology, and so we can understand why is it that a drug might work in one set of symptoms and not another, but we're not there yet.

So I guess that in this particular instance, we have this sense that perhaps there's maybe not cognition as a whole, but maybe elements of cognition. That's why we're asking about the affected domains. Maybe there are elements of cognition that somehow track on different circuits or somehow have a different mechanism associated with that that some drugs would address and others wouldn't. And that seems reasonable to say, that if you think they're different, that that should be

a separate target.

Does that answer your question?

DR. PICKAR: Well, I don't know if there's a simple answer, but that's the --

DR. FARCHIONE: There's not a simple answer. That's why we're here.

DR. PICKAR: -- conversation that we're grappling with.

Dr. Conley?

DR. CONLEY: Well, I like that answer because it's one where it does make some sense about what's clinically relevant and what isn't and also what's targetable and what's not. We have to really recognize where the state of the field is. So speaking from my general knowledge as a drug developer, but also I think something that might help inform the discussion, where the state of the art is right now in depression research that actually isn't true -- to my knowledge -- is that there are PhRMA companies trying to pick off every single symptom of depression and trying to get some special label language for it.

To me, treatment resistant depression, the people don't stay in a persistent remission, what we saw on the slide is that people with depression aren't really getting back to a normal life. Those are important. Suicide is I think important. And to me, the question is, is cognition a component of these people not getting back to normal life and if you help that. Honestly, I don't have a bunch else on the list; maybe sleep, but that's probably not.

So again, actually I appreciate that you're thinking about what should be there or not because from the discovery standpoint, guys, we're not going to look at everything in the world. We just can't. So we do need some guidance as to what's worth it.

DR. FARCHIONE: And to speak to your point about sleep, that brings up a different aspect of pseudospecificity, where we have plenty of drugs that are out there, the sedative hypnotics that work in sleep regardless of what's causing the sleep disturbance.

DR. CONLEY: That was the maybe thing. I

mean, I don't want to say that there's not a sleep component of depression, but it's not really a big target on this area now.

DR. FARCHIONE: Right. But we wouldn't -- we probably wouldn't even consider that indication for treatment of sleep -- treatment of insomnia associated with depression because if you're treating insomnia in that context, you should be able to treat insomnia in any context.

DR. CONLEY: So for the purposes of today's discussion, I hear you. And to me, you really are asking the question about cognition, does that make the list. Right? I mean, that's kind of it.

DR. PICKAR: Dr. Compagni?

DR. COMPAGNI PORTIS: I had one thought, but now I have another. This question -- and I think Dr. Stein brought it up -- about sleep and the cognitive issues and how they go together is really compelling because you look at that cluster of things that don't improve -- sleep and cognition, and I can't remember what the third thing was -- that's a really compelling question; what's

the combination?

I think, absolutely, it's an appropriate target to look at this. We know from the research and we know anecdotally that this is a symptom that continues, and people do continue to suffer from that. We also know, though, that one depression is not like another. That's why we already have so many different drugs for depression, and people often will go through a number of them until they find one that fits. There isn't a heterogeneity about it.

The thing that I start to wonder about and that we also don't know -- and I think it was mentioned somewhere in our materials -- is, is there a drug that does help the cognitive aspects. But also, are there drugs that are hindering the cognitive aspects, and we don't know that piece either. I guess I'm not -- I'm just asking more questions to which we have no answers.

DR. PICKAR: That's one of the themes today, is a lot of questions that aren't all that well answered. Dr. Grieger?

DR. GRIEGER: Yes, a couple of things. One, I'm not sure how clinicians would use this. I mean, would you say -- would this be used as a primary treatment for depression because this patient has horrible cognitive defects, or would this be an augmentation strategy?

Would this be a replacement strategy? I mean, I'm not sure how you would choose because every patient, almost every patient, with depression has some degree of cognitive complaint, if you will. Would you test them and see are they performing poorly on Trails B, and therefore this would be your primary candidate drug for initial therapy, or would you take patients who failed it? That's part of my question.

Then getting back to the second part of the discussion question, I guess I don't know what it means if a product improves one aspect of cognitive function but doesn't impact statistically on the other tests of cognitive function that were administered to the same patient. I don't know what to make of that.

Granted, all these tests go across domains of cognitive function, but I don't understand why it would work on one but not two or three others in a statistically significant manner. Maybe it's not a large population to get that, but I don't know what it means when you get -- it's like studies where you see where the Hamilton score didn't improve statistically, but the MADRS score did. I don't know what to make of that.

It's like some of these companies just throw a bunch of studies out there with the hope that one of them will have positive results. That's been my sense across the years. They'll say, well, this measure improved even though these three other ones didn't, and I don't know what to make of that.

DR. PICKAR: Yes, Dr. Higgins? That was quick.

DR. HIGGINS: That was nice. My question is what happens -- and this is a naive question. I'm the consumer rep here, not the scientist. What happens if this drug is erroneously used with older adults who have cognitive decline that's really

MCI? And what if primary care providers are doing that, as I say, erroneously? Is there any harm to that?

DR. MATHIS: Well, I think you might be asking specific questions about the specific drug product that we're going to talk about this afternoon. But the indication would be for the treatment of -- or the claim would be that there would be depression related cognitive problems, however we define that. And we haven't settled on any of that yet. That's why we're here.

We usually have some older adults as part of our development programs, and it would be considered the same disease with the same cognitive problem in an older adult. It's up to the physician to decide if they've got the right disease or not. You get what you study, and that's what you would study, and that's what would be labeled. Could it be used for other things? Certainly off label it could, but it wouldn't be indicated for other types of cognitive problems.

DR. PICKAR: Dr. Temple and then Dr. Stein.

DR. TEMPLE: Some of the questions before, who would you use it in, have a lot to do with what kind of studies people do. I mean, for what you might call the lowest level, they would simply look at what are the components of the scales that we now use more intensely. They'd look at cognitive -- there's already some element of cognitive function in MD.

But they would look specifically at that component and reach a conclusion about it that wouldn't represent comparative data with anything else. It would just say, when people with depression have this problem, this treats it.

We don't always do that, but because we were worried that these were pseudospecific, it was just part of the syndrome, why are you singling this one out? But as all the people here have been saying, there's enough indication that maybe cognitive function isn't totally going along with everything else, doesn't always respond the same way, that that's not a crazy idea.

The concept that seems most interesting to

me is treating residual cognitive dysfunction after the basic disease is better and showing that when added on to an effective antidepressant now improves the cognitive function. If anybody could show that, we'd be home. That would be an easy thing to put in the label; probably be an indication. The kinds of studies you do have a lot to do with what conclusions you reach, and there's not a lot of track record here.

DR. PICKAR: Dr. Stein?

DR. STEIN: So I'm confused because I'm hearing different things about the guide -- not guidelines but kind of the thinking behind it. If there's a drug out there that treats insomnia, and insomnia's a big problem for a lot of people with major depression, there would be no way, from what I'm hearing, that somebody could get an indication for insomnia in major depression because the thinking is, well, there are drugs that treat insomnia. That's fine.

Is it the case, then, that cognitive dysfunction is different? What if we had a really

good drug to treat cognitive dysfunction, generally? There'd be no way for that drug to get an indication for cognitive dysfunction in MDD?

DR. FARCHIONE: Not exactly. So for instance, in the insomnia example, the assumption is that if you've got a medication that helps you to sleep, it should work across all different causes of sleep problems. So because we have so many things out there that are already approved for sleep, you would have to show that somehow your drug is working differently in patients with depression and that it addresses the sleep issues that they have specifically but doesn't necessarily address the sleep issues associated with other conditions or with just primary insomnia stand-alone.

With this issue for cognitive dysfunction, because the population that you're studying is a population of depressed patients, then we can only really answer the question, at this point, of whether a product would be working for that population. Now, if a company came in and had a

product that they said, okay, first we'll do this study in folks with depression; look at this. It helps cognitive dysfunction in depression.

Then they went on and studied it in patients with schizophrenia who also had cognitive problems, and lo and behold, it worked there, too, I don't know where the threshold would be, if we would need across two conditions or across three conditions. But at some point, you're going to look at that and say, hey, this thing maybe deserves a more general indication, but that's really far down the road, I think.

DR. STEIN: Okay. Then what you are saying is that the reason you couldn't get a specific indication for insomnia in major depression is because there are already drugs out there to treat insomnia across the board. We don't have drugs that do that for cognitive dysfunction, so that's why you're willing to entertain the possibility of major depression. That's the only logic I'm able to come up with.

DR. FARCHIONE: Yes. I think that's the

gist of it.

DR. STEIN: And does it need to also treat depression?

DR. FARCHIONE: It depends. Right? So like Dr. Temple was saying, if you have something that you think is strictly a cognitive enhancer of some kind, but you don't think it's going to be effective for mood symptoms, well, that's a case where now because of what you think your drug does, you're going to want to do an add-on design.

So treat the depression first, and now you've got an enriched population of folks who their mood symptoms have been addressed but they still have cognitive problems, and lo and behold, your drug treats that. But if you also think that your drug is useful for both mood symptoms and cognitive symptoms, now it gets more complicated. It gets a little stickier.

DR. STEIN: Which is sort of the case we're talking about here.

DR. FARCHIONE: That we will be talking about.

DR. STEIN: We will be talking about.

DR. PICKAR: With regard to this question -- let me see if I can summarize the first part, and then we'll get to the second part. The concept of it is cognitive dysfunction in MDD an appropriate drug development target? It would feel to me -- but, please, everybody chime in on this. I think the panel is saying it is. There are questions and issues with it, but it sounds like an appropriate target. Now, exactly defining it and so forth and so on, yet to be done.

Is that reflected in the conversation or am I off on that?

(Affirmative nods.)

DR. PICKAR: Okay. So that part, we've heard a lot about cognition, so back to you guys. It's an appropriate target. We don't quite got it all. We're not quite sure what to do with it all, but it's appropriate.

Now, which domains are mainly affected by cognitive dysfunction in MDD? Should we start peeling the onion a little bit? What is the best

method to assess these affected domains? Do we know that? So we like cognitive dysfunction. It's real. It hurts people. It's a target. Now, what are the domains? Let's start peeling the onion about what in specific we should be looking at. What do people think? Murray? Dr. Stein?

DR. STEIN: I think if we start peeling the onion, we're going to get a lot of tears.

(Laughter.)

DR. PICKAR: Was that your comment, Dr. Stein? Very nice.

(Laughter.)

DR. PICKAR: That was very smart. Dr. Narendran?

DR. NARENDRAN: So I think -- I mean, it's clear that there are some domains, like executive function and attention. I just wanted to kind of -- if FDA could give us some history on -- schizophrenia seems to be much more advanced or there are two batteries. I read somewhere that FDA had input into those batteries, what drug companies.

So maybe there's -- is it more appropriate to have it in a forum where you can have some real cognitive experts from NIMH. It seems like that would be a more appropriate forum to come up with a battery, at least a framework that could be out there, and then industry can pick and choose from that framework. Is that in the works or is it in the plans?

DR. FARCHIONE: That's what we're aiming for at some point. But I think the purpose of today is we've heard some information from our guest speakers in terms of data to support various domains potentially being involved. Do we think that we've got some kind of consensus around at least a few of those?

I think you're right. Like I was saying, we're trying -- we really want to come up with a framework so that we don't end up with just a MATRICS type battery that we're saying everybody should do because we've had the MATRICS for a really long time, and yet we still don't have any products that are indicated for cognitive

impairment associated with schizophrenia.

One of the complaints that we've heard is that perhaps it might be too much; that there might be some things out there that are able to address one or two of those domains but not move the overall score. And I don't want to get stuck in that rut with this. I want to make sure that there's some flexibility, that if you have a product that you think is going to target a particular domain, and if that domain is meaningful, I want to know.

DR. PICKAR: I'm sorry.

DR. NARENDRAN: Can I continue?

DR. PICKAR: Finish it, yes.

DR. NARENDRAN: It seems like having a particular battery is problematic because then you're sort of stuck with it. Also, just to see if there could be some sort of an outline of what potentially -- some consensus agreement about what are the domains. They could be neurochemically dependent, so maybe there's dopamine-dependent symptoms that they could pick and then choose, or

some glutamatergic specific symptoms they could pick and choose and just look for an indication for those symptoms. But I feel like that hasn't really evolved very well in depression. Maybe there's something -- we need to accelerate it.

DR. FARCHIONE: Right. And that's one of the things where, like I was saying, the goal is to come up with this framework. And that's exactly the kind of set of instructions that I hope to be able to offer to companies; that if you have a product that you think targets this particular transmitter or this particular kind of functioning, make your justification based on that, so at least we understand why you're targeting the symptoms that you're targeting.

If you move them, it doesn't mean that you're going to be able to have something in the label that says the mechanism of action is based on yaddi, yadda, yadda, but this idea that you're not just throwing a bunch of tests on there to see what sticks. I want this to be a rational way of approaching drug development.

DR. PICKAR: Let's move it. Dr. Hinkin had a question, I know.

DR. HINKIN: Yes, or more of a comment even in response to what you just brought up. I think there's a reasonable consensus as to the types of cognitive deficits that are most likely to be seen. Actually, I would argue that there's going to be some degree of cognitive abnormality in any patient with major depressive disorder, a matter of degree. But things like speed of cognition, attentional processing, controlled attentional processing, that ability to really focus, concentrate, switch attentional set, clinically effortful measures provide the greatest degree of difficulty for depressed patients. They just don't want to do it.

Often, if you give a little nudge, they'll be able to get over the hump and actually perform adequately on a cognitive test, whereas if they're not nudged and just give you an I don't know, you'd be out the door. So either whether that's coming out of an apathy or anhedonic kind of construct or not, I don't know.

But what I started thinking about, though, is that it's quite possible, just as there's different flavors of depression in terms of emotion and side effects, agitated or vegetative, there may well be different cognitive deficits in different types of depression.

If that's the case, we might see that that very thing, where like someone was saying whether HAMD changes but the MADRS doesn't, or whatever, we may see a study where there will be subgroups where speed of cognitive processing is affected or is improved but not attentional processing and vice versa. So it may end up being like a marker for a different typology of depression.

DR. PICKAR: Dr. Conley?

DR. CONLEY: In thinking of the cognitive domains and what's the best method of doing it, one thing that I wanted to emphasize a little bit again to the FDA's comments is that it's important I think for the panel to hear from the industry side of things, that a battery won't get us a drug, from the MATRICS, to cognition, from negative symptoms

and psychosis. We basically know that.

So I think the important thing here is when you talk about the best method of assessing things, given the objective nature of the way to judge evidence, it's hard for me to imagine -- unless you guys can suggest something that I'm not thinking about, and please do if you can -- something that's going to sort of like other than a neuropsychological type test, something you need to have good statistics on in a sense and the way of doing it.

I think a lot of the measures that we'd ultimately like to see, which is a marked functional change, getting back to work or some of these other things, that's honestly not something that you can assess before you even understand what's going on in many ways. People bury so much. You can set that bar. I can tell you it's just going to be a super high bar that maybe there will be some magic differential thing that will get over.

So I would like to impose -- because we've

got a bunch of experts in the room here, and we've heard other testimony -- not only is, for the drug condition we'll talk about today, the DSST a good measure, but -- I mean it as more of a general discussion item -- is anything a good measure? Will you believe a neuropsychological test? Because that will always be something that's a bit hard for the clinician to translate.

So it's not as if -- at least, again, to my knowledge, there isn't one where there's just so much face validity that people are going to translate it easily. So it would be helpful, I guess maybe for today's discussion, certainly helpful from a drug discovery standpoint, to understand that.

DR. PICKAR: Dr. Compagni Portis?

DR. COMPAGNI PORTIS: Yes. I'm, as the patient rep, always arguing for more time, for patients to have time with clinicians because I think we get better data and we get better responses, as you pointed out, when patients get that nudge, and they have more time to adequate

respond, and for us to really see how well they can perform, and to really tell us about that.

I think what I got out of the discussion this morning is that any one of these tests, the DSST or one of these things, doesn't really adequately tell us what we want to know. And I think if we're talking about cognitive domains, it sounds like we agree that attention, and memory, and executive function are important, but I think there are other issues when you look at the DSM. And what matters to patients is really about their impaired function and social, occupational, and educational settings.

That's where the meaning is. It's like can you do the Trails test faster or better, but how do we really hone in on do patients feel like they're able to function better in their daily lives? And I don't think we have an assessment tool to do that.

DR. PICKAR: Dr. Higgins? That was the question?

DR. HIGGINS: Yes.

DR. PICKAR: That was very handy.

DR. FARCHIONE: If I could actually --

DR. PICKAR: Dr. Grieger? I'm sorry.

DR. FARCHIONE: Could I comment on that?

DR. PICKAR: Please?

DR. FARCHIONE: So that's one of the issues that we're struggling with, as well as not just how do you assess the core, cognitive symptoms, but also how do you then assess whether or not it means anything. So this was what I talked about in terms of do you need a separate functional measure to ground that in the real world in some way and would that have to be a co-primary? Would you have to win on both in order to get a claim or could it be a key secondary?

So you've got this change in some kind of a scale, and then a change in -- or a change in some kind of an objective measure, and then a change in some kind of a scale or performance outcome. I don't know.

For a point of reference, in schizophrenia, when we're talking about cognitive impairment

associated with schizophrenia, we do require a functional co-primary for that, but the kinds of deficits that you see in schizophrenia are so much more severe that the measures that we use to assess functional impairment in that condition might not even matter in depression. I figure somebody with depression, even if they have some cognitive symptoms, they're probably still going to be able to read a bus schedule and navigate how to get to work, you know?

DR. COMPAGNI PORTIS: I think it's very different. We keep talking about these schizophrenia measures, but I think we're talking about very different situations.

DR. PICKAR: We're going to come back to this issue before this discussion is over for the fun. Dr. Temple?

DR. TEMPLE: One of my worries about a functional measure is that it's going to be confounded by all the other improvements that are going on in this person. I mean, the person's not depressed anymore. That must help your function,

and all those things. But if you really wanted to focus on the cognitive thing, you need something specific enough to do that in the middle of broad, global improvement, and that's what seems more difficult.

DR. PICKAR: Dr. Grieger?

DR. GRIEGER: I think some of these questions have been alluding to that as well. The question is what is "this"? Are you going to say it improves your ability to think and concentrate? Are you going to say it improves your ability to perform the DSST? Does it improve your memory? Because you look at it, just from one of the slides, it impacts processing speed, copy speed, visual/motor coordination, motivation, effort, age.

Do you say it improves all those things or how do you phrase it? What are we saying we're really measuring here other than we have one instrument that has a finding?

DR. FARCHIONE: And we're not necessarily wedded to the terminology cognitive dysfunction. I mean, if you've only shown that attention improves,

well, you're not going to get cognitive dysfunction generally because you've only demonstrated one aspect. That's another thing to consider, how many different domains do you need before you can confidently say you've sort of improved cognition globally? And I have no idea what the answer to that is.

DR. GRIEGER: I think that's the fundamental question. If any single instrument measures across multiple domains, then how do you define what it's truly -- it probably isn't improving all those domains, but it's improving some domains in some individuals. How do you phrase it?

I mean, ultimately, this is going to come down to what are the words that are going to say what this drug does that's not comparably different, but what it has the capability of addressing. And I don't know the answer to that based on the fact that this test covers a broad domain of measures.

DR. FARCHIONE: Well, I think that's why Jenni was suggesting that it's a good idea

not -- even if you don't necessarily have a battery per se, if you've got this one measure that you're relying on, if you have a couple of additional measures that also assess similar domains that can be either supportive and say that, yes, if you've got this other measure that looks more specifically at one piece of the puzzle, that is similar to the overall results; or if you have several of them that all support it, you can try to -- you can make some effort to parse out what you're actually dealing with.

That's where we run into the difficulty with having one test that is a little bit broad because, like you're saying, what do you make of it?

DR. PICKAR: Dr. McMahon? And then we're going to summarize on this question and move on because we're already moving into the other questions, which is fine.

DR. McMAHON: What I took away from the presentation this morning is it seems like we're talking about a number of diffusely defined domains that are subtly impaired with depression and where

there isn't really any clear evidence that they can be measured in a valid way when someone's in the throes of a depression. So I think it makes it very hard to say what kind of instrument we would use.

I'd like to see an instrument where someone has demonstrated it can be validly performed when someone is depressed, that is a relatively mood independent measure of cognition. Because right now, what I've heard, it seems like the cognition measures and the overall mood state are awfully intertwined. Think a logical extreme. Somebody comes to the emergency room with acute abdominal pain. They have appendicitis. You don't know that. You can treat that pain very effectively with an opioid and kill the patient.

So I think syndromes do matter when they have an underlying process. So I think we can't completely take them apart without being concerned that we're not really going to be treating the problem.

DR. PICKAR: Syndromes are what clinical

medicine is all about. And in psychiatry, there's no post-mortem to help us. So that's what we have to struggle with.

Let me ask you, Dr. Temple, do you feel the discussion has identified cognitive domains that are in MDD? Do you have a sense that we've been -- I'm trying to piece together the presentations and the discussion.

DR. TEMPLE: Well, one of the big questions here is whether something like the DSST or some other tests provides an adequate assessment of cognitive function. And there has not been too much discussion of that. Obviously, it's not the whole nine yards, but is it enough of it so it represents a plausible effect on this domain?

I think that's something we definitely, eventually are going to need to know about because people are proposing to use it. And I guess I haven't heard too much of that. It's possible I just missed it.

DR. PICKAR: Well, the afternoon session, I think there's going to be more focused

discussion --

DR. TEMPLE: Okay.

DR. PICKAR: -- on the DSST itself. So let's take away from this the first part of the question. We all believe it, but we don't quite have it defined in a simple, concise way. I stand corrected on that.

DR. TEMPLE: Well, remember, the way we used to think about these things in the older days was that this was all part of the depression syndrome. Picking out one of them didn't make any sense because they were all going to get more or less better. If you looked at certain ones, you might believe that. You might think being sad and being suicidal might go together all the time; don't separate them. I'm not sure everybody believes that, but you might think that.

But cognitive function is not self-evidently a consequence of being depressed. Maybe there are explanations for why it is. So one of the questions was, is that different enough from the totality that it deserves individual attention, and

I think most people are saying it is. It doesn't necessarily go completely with the other components, so it might be separate. There might be a drug that does better on that than it does on depression overall.

The other thing is I think we're talking here mostly about antidepressants that might have a particular effect on that, not a sleep aid or something like that. So that should be remembered, too. But I hear -- I'm interested what others heard -- a fair consensus that there's enough chance that it behaves differently from the other parts of the depression syndrome that it's reasonable to look at it separately.

The other thing I just wanted to know, when we use an HAMD, we're kind of throwing all things together. We're doing what people are worried about. We don't try to separate out the components. We give the total score. And the question is, is that the best you can do if some of the components may or may not track.

DR. PICKAR: Let's go to the second

question. What are the acceptable primary efficacy endpoints for a claim of treatment of cognitive dysfunction? Are we along far enough to be able to identify such primary endpoints?

The other comment on your point, Dr. Temple, which is a good one, neuropsych deficits exist outside of depression in Alzheimer's disease, and how much is somebody who you're looking at, who didn't recover, is sitting with much earlier deficits that are their clinical characteristics. Our neuropsychologists do this for a living, and you certainly see deficits outside of depression. So this is a tough question.

So let's go to this one. How about from neuropsychology? Any primary acceptable primary efficacy endpoints? Dr. Dickinson?

DR. DICKINSON: So before I talk about that, I'm going to go back to the last question, briefly, and just say I think we heard some evidence today that was presented by speakers and some discussion from Dr. Hinkin and maybe some comments from Dr. Pacheco that zeroed in on one piece of what I

think of as -- it's a big piece, but it is a distinction. And that's between more effortful cognitive processes and more implicitly automatic cognitive processes.

I'm not sure that the evidence that was presented or that exists in the literature at this point gets us much beyond that. It seems as though the range of different things spans across attentional -- effortful attention, effortful speed tasks, effortful memory tasks, effortful executive tasks. I'm not sure that there's a really good case that's been made so far that it's more specific than that.

In terms of primary efficacy endpoints, I guess I would come back to comments that Dr. Farchione was just making about maybe the thing that we need to do is have -- you need to balance the importance of the cognitive claim in a given case versus the mood treatment claims. You need to decide about how much effort do you want to put into this.

But if this is a main purpose of a given

application to have a cognitive claim in an antidepressant context, well, then I think you'd probably want to have a couple or more effortful cognitive measures and see that they're moving in the same direction. And maybe one will be stronger and one will be weaker, but at least you'd like to know that they're kind of telling you the same story.

I'm not that convinced that the kinds of measures, the kinds of neuropsych measures that we've been using traditionally do a very good job of saying, oh, it's just this or it's just that. I think I would be much more comfortable and feel more confident that three measures vote the same way than that one measure votes one way and the other measures vote a different way. That, as my colleague at the end of the table was saying, I don't really understand.

DR. PICKAR: Let me just go back to you on that. The primary endpoint question, do you have any that would stick out as a primary endpoint? Primary endpoint is what drug development is about.

DR. DICKINSON: And by that, do you mean like specific neuropsych tests?

DR. PICKAR: So I like --

DR. DICKINSON: The symbol test, I mean, that's one of my favorites, to be honest, but I'm not sure that I would take that by itself as a primary endpoint. I would rather have Digit Symbol, List Learning, and Letter-Number Sequencing together, and have them all vote the same way in a given case than to have any one of them by itself.

DR. PICKAR: How about other people's -- yes, please?

DR. HINKIN: Whether it's Digit Symbol or an assortment of tests, I think something I always wrestle with in these kinds of issues is, are we worried about statistical significance or clinical, clinically significant difference, improvement in cognition? Because it's easy to get a big enough and you can get a low enough p-value with just a negligible improvement on a Digit Symbol test, for example, but is that of clinical significance? I think that's much, much harder to --

DR. PICKAR: That's right. The choice of a primary endpoint should have some impact in a clinical sense, and certainly we do live by statistics, as I recall. So both are going to be in play. But you're absolutely right about the clinical significance. Otherwise, it's not right.

DR. HINKIN: Right. And I think the former is going to be very easy.

DR. PICKAR: A statistical significance with those kind of tests you can get there.

DR. HINKIN: Yes, but --

DR. PICKAR: But does it have meaning? Dr. Temple?

DR. TEMPLE: Well, we go through this agony all the time, how big a difference matters. How did we decide that a HAM D-17 difference of 2 is clinically meaningful? Maybe there's some basis for it, but it seems pretty small considering the response of the placebo group is usually 10. So the drug beats it by 2, 12 versus 10. Is that obvious? I mean, I don't know. But we agonize about that all the time.

I just want to throw one thing out. Looking at the mean is not good enough. You really need to look at the distribution of responses, at least sometimes. I just want to throw that out.

DR. PICKAR: Visual differences are a huge piece of this.

Let me go to the functional question. Could you go to number 3? They're all related, Kalyani, I think enough, and we can move through those. Functional assessment. Reference was made earlier to MATRICS. And Dr. Conley I think had mentioned something that we all know, that this has been around for 15 years almost, or whatever, and there's been no effective -- really, it's been silent. Was the bar set too high? I remember at the time the issue of functionality and said, boy, what a drug trial to do that.

Is it important here? We want clinical significance, but do you want a functionality assessment? Dr. Compagni Portis?

DR. COMPAGNI PORTIS: So I guess my question, especially maybe for the

neuropsychologists, goes to both of those things: do you see that someone could do well on those three measures that you threw out there and not have -- I mean, is there a correlation necessarily between that and improvement in daily functioning? Could somebody do better in all those measures and still say, but I'm not working well. I used to be the CEO of a company, and my brain just doesn't work anymore or I can do that DSST test.

DR. HINKIN: I think if you had a regionally big enough improvement in cognitive functioning is assessed by neuropsychologic tests, there would be a improvement in that person's life. Now, whether it would be picked up on the kind of tests we use to assess functional ADLs, IADLs in that executive -- it could improve their cognitive faculties, but they still might not be able to run a board meeting.

Conversely, often the types of tests we use come out of the Alzheimer's literature, PD, or schiz. And those diseases have greater functional compromise than do depression. So we will be

talking about some of that stuff this afternoon.

DR. COMPAGNI PORTIS: Because I think therein lies the challenge when you're trying to compare schizophrenia, or this afternoon we'll talk about a study in the geriatric population. That's different than a lot of -- you know, you've looked at the huge number of people that are struggling with depression, and it's a lot of people in the prime of their life who are significantly impacted for a long period of time in terms of cognitive function.

DR. PICKAR: Do people feel that there's more data needed before they hang their hat on these questions other than in a discussion, more firm? The speakers, each of them sort of said -- everybody said, oh, we don't have data on this, unknown, whether it was imaging -- there's just not a lot of data out there. If all things being equal, would you request that we just get more broad data before we contemplate? I just want to hear different thoughts on that.

Dr. Narendran?

DR. NARENDRAN: That was my question. It seems to me like there just isn't enough data to support a lot of these -- to answer these questions. For example, you say the DSST may be -- is 5 percent improvement good enough, or 10 percent improvement good enough? And how do you get there? And that's what -- if you agree with a set of tasks that potentially are definitely impaired in depression, and then people can go do research on these things, validate them -- because PhRMA is not going to be able to validate their own scale and do all this work.

So if we agree that these are the tests that are most likely to be impaired in depression, and NIMH can fund it or other people can do it -- and it will be interesting to find out whether 5 percent change is meaningful, or 10 percent change is required in the general population of healthy people, in depressed people, in schizophrenics. And then PhRMA can use that data to say, okay, we have a drug X, which works through neurochemical mechanism Y. We think we want to

look at executive function and see if it impairs it. Hey, it changed it by 5 percent, so it should improve functional outcome.

I feel like forcing functional outcome as a co-primary makes it even more difficult I feel within time frame to demonstrate that, especially in the mentally ill population, for example. It's even harder, I think. So my thought is it's good to have secondary measures in a convergent data set to see if it all aligns well, but to force it on a co- -- I mean, we don't do that for HAMD. We don't do that for PANS to say have these schizophrenics improved all of a sudden. We just say, okay, their symptoms are improved. We take it as an assumption that potentially it should make their life better.

So I'm very reluctant to force a co-primary endpoint of a functional outcome measure, I think. That's my thought.

DR. PICKAR: Dr. Temple?

DR. TEMPLE: Well, it's a very thorny question. We face this all the time. It's of interest that in, say, Alzheimer's disease, the way

we resolved it was to ask for 2 endpoints, one the ADAS-Cog, but there was some concern about how much that means, so there was always a clinical global along with it, and the clinical global had to be positive. They were co-primary endpoints. You had to win on both.

So that was one way around it. But it's a very thorny problem, how do you decide whether this is big enough to matter, especially since it isn't really the average that's the only thing. It's changes in individuals and their distribution, which is not an easy thing to analyze.

DR. PICKAR: Generally -- oh, I'm sorry.

DR. McMAHON: I was just going to say, I think maybe I disagree with the previous speaker's comment. I think having a functional assessment at the end is important in order to get exactly at this issue that Dr. Hinkin raised about something clinically significant. Even if it is something as broad as a clinical global impression, at least it gives some information.

I could imagine that there could be a drug

that might improve some aspect of depression and worse in others. Without that overall impression of improvement, then you really don't know if you're helping the patient.

DR. PICKAR: Did you feel functional outcome interfered with getting -- how about this to say -- drug development? Did people back away from going after that? Did it stymie drug development? Because it makes it a little bit tricky doing functional assessments. It's just more to do. I'm referring to the schizophrenia thing, and I wondered whether that was part of the reason we haven't seen much. I'm just curious.

DR. CONLEY: Well, I feel like in some ways that would be to me. Yes and no. I think part of the challenge in psychiatry is honestly finding good targets to go after right now, so it really isn't the outcome scales. But the worry that I have about functional outcome scales -- and, Dr. Temple, you alluded to this correctly -- is what are they before you know what they are? You have to do some exploration of what that is.

So it isn't -- it's easy to say what we'd like our patients to do in the extreme of getting back to being fine, but given that it's unlikely, you're suddenly going to find something like that, what is truly a relevant functional scale that's doable? And I'm not saying they're impossible. We've embraced them in cognition, for example, so we are doing that. The worry that I'd have here would be this general worry.

You've seen our whole panel now talk about how hard it is, even with the neuropsychological measures, to figure out what means something and what doesn't. I'm sure we could have an equally robust discussion about exactly what functional measure means something and what doesn't.

So that would be a problem because that would put things back; just saying it would be nice if we had it. We need it just to put it to your point. And it can't just come from us. As you know, it wouldn't be appropriate just for a sponsor to say here's some. We just invented a functional scale, and it looks really good on our drug. I

understand why people wouldn't believe that. You do need some field validated measures. We're not there yet.

DR. PICKAR: Dr. Narendran?

DR. NARENDRAN: I do want to kind of refute that point. It's much easier to show a functional outcome measure improvement in a continually deteriorating population like Alzheimer's as opposed to in patient population like depression or schizophrenia, which is not continually deteriorating. It's very hard to show, within a period of, I don't know, 8 weeks, or 12 weeks, or 6 months, that they can alter.

DR. CONLEY: I actually -- I would agree with that. That's another reason why.

DR. PICKAR: Dr. Ionescu?

DR. IONESCU: Just thinking from how to measure functionality in these patients, I'm wondering if we can kind of pull from the recent change in depression clinical trials that are using these more external raters to -- that aren't necessarily involved in the trial but they're

either calling people or they don't have anything really to do with the medication.

But they would interact with the patient more frequently, not in a therapy session, not as an MD treater, but more as a external person that can objectively somehow -- and I don't quite know the details of how they would do this, objectively go through their functionality and give some sort of score or something.

This would need to be developed, but maybe this sort of new way of thinking how to measure functionality in depression might be helpful in informing if a medication would be targeting that symptom in particular.

Again, I don't know the details how this would work, but just a thought. Since we know from the data that patients with depression already have a bias that they're maybe not doing as well as they are as part of the disease, and maybe if we have someone externally rating this as well that has nothing to do with their clinical care, it might inform the data to these new medications.

DR. PICKAR: Dr. Hinkin?

DR. HINKIN: I would like to lobby against the use of a self-report measure as a functional outcome because, as we all know, patients with depression tend to be a little hard on themselves. And actually there's other research suggesting perhaps they're more accurate appraisers of their lives. But self-report of how well they're able to do might not actually correlate well with how they can do in life.

I do a lot of work in medication adherence, and patients' self-report of whether they're taking their medication often is a variance from the electronic measuring devices. So using some sort of objective indices, whether it is as crude as are they gainfully employed or not -- that would be probably too high in a threshold and too many multi-determinants. But some sort of objective indices that's not simply the patient saying I'm doing better.

DR. PICKAR: Other comments? Dr. Dickinson?

DR. DICKINSON: So I'm just thinking about

the experience that we've had in schizophrenia trying to develop functional measures. And it seems as though they range from objective external indicators like employment to these assessments that have been developed that have to do with can you balance your checkbook, can you read a bus schedule, things like this.

The problem is that functioning is multiply determined, so if you go with something objective like employment, it might not capture improvement that's actually there because so many other things combine to determine whether you're employed or not.

But at the other end, where we've come up with these more objective measures, the more reliable the measurement is, the clearer the read out of the measure, the more it's like a cognitive test, and the less it may actually reflect real functional improvement. So I think some of the most reliable functional measures on the schizophrenia side also correlate incredibly highly with cognitive measures.

Adjournment

DR. PICKAR: I hope this discussion's been helpful. Those are tough questions you gave us there, but I think you've got some information from speakers that was really up to date, and hopefully, the discussion is helpful in how you think about it. We certainly would like to see it as a target, and we're not quite sure exactly what domain or what endpoint, but that's to be determined.

Thank you very much, our outside speakers. That was terrific. We're going to adjourn for lunch. And I have to read that it's a one hour break, and we will start in the afternoon session here. Take your personal belongings with you at this time. The standard rule which is appropriate is no discussion of the meeting during lunch amongst yourselves talking to the panel members here or with the audience.

Thank you very much for a very interesting morning session. Thank you.

(Whereupon, at 11:58 a.m., the morning session was adjourned.)