ACTTION - BEYOND THE MU OPIOID SYSTEM FOR TREATING OUD (B-MOST-O)

November 21, 2019

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ACTTION

BEYOND THE MU OPIOID SYSTEM FOR TREATING OUD (B-MOST-O)

Thursday, November 21, 2019
9:05 a.m. to 4:37 p.m.

W Hotel
Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:05 a.m.)

Overview, Introduction, and Goals

DR. STRAIN: I realize just now standing up here that there's a big mirror behind me.

Does it show my bald spot?

(Laughter.)

DR. STRAIN: That's my biggest concern right now.

(Laughter.)

DR. STRAIN: I'm Eric Strain, and I will be moderating this session, this meeting, along with my distinguished colleagues, Dennis Turk and Bob Dworkin from ACTTION.

Welcome to this meeting, Beyond the Mu Opioid System for Treating OUD, or as we call it, B-MOST-O, is the acronym that's been used here. I'm going to just do a few housekeeping things, but before I get started, maybe I'll ask Bob Dworkin to come up and say a few words about ACTTION. Many of you are familiar with it, but perhaps not all of you, and Bob can explain to you the organization.

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Bob?
DR. DWORKIN: I'm Bob Dworkin, half of Dennis Turk, who's over there. My colleague Dennis Turk and the ACTTION public-private partnership with the FDA, I want to welcome all of you to this meeting.
ACTTION launched by the FDA in 2010, so we're almost 10 years old at this point. I want to start off, even though they're not here, by acknowledging the steadfast support of Dr. Sharon Hertz and Dr. Allison Lin over the last 10 years in supporting ACTTION and all of its activities.
The mission of ACTTION, it's evolved over the past 10 years, but it's currently to accelerate the development of treatments with better efficacy and/or safety tolerability in four different therapeutic areas, which is where ACTTION started, but then was expanded to include substance-use disorders, peripheral neuropathy, sedation, and anesthesia. Those are the four areas that ACTTION covers.
Substance use disorder, part of ACTTION, has been led from the beginning by Eric, and it is completely accurate to say that we would not be here

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and we would have accomplished absolutely nothing with regard to substance-use disorders without Eric's help, mentorship, and leadership of that part of the ACTTION public-private partnership. So thank you very much.
What ACTTION does is to really focus on how to optimize the design, analysis, execution, and interpretation of randomized clinical trials across those four therapeutic areas. We've done a bunch of things, ranging from systematic reviews and consensus meetings to actually sponsoring various types of studies and developing novel clinical outcome assessments.
So ACTTION is willing to consider anything that could help move forward the development of better treatment in those four diverse therapeutic areas.
There have been multiple stakeholders over the last 10 years for ACTTION; obviously professional societies; government agencies like FDA, NIH, DEA, et cetera; academic clinical researchers; patient advocacy organizations; foundations; and definitely pharmaceutical and device companies. I'm sure I've left some stakeholders out. The general public, of

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course, is a stakeholder when we're talking about the development of improved treatments.
The funding for ACTTION, in case you're wondering, has come from grants and contracts from the FDA -- the FDA started ACTTION -- and also unrestricted support from pharmaceutical and device companies; a little bit philanthropy; and a little bit of royalties. Those funds are supporting this meeting and all of ACTTION's other activities.
Have I left anything out?
DR. TURK: What the end product is going to be; what we're working toward.
DR. DWORKIN: This meeting or in general?
DR.. TURK: This meeting.
DR. DWORKIN: I'm going to defer that question to Dr. Strain. That's out of my wheelhouse.
ACTTION has a website updated on a very regular basis, and it's a simple website address. It's www.acttion, with two T's, .org. Let me say, because it's so important these days to do self-promotional things, I'm going to promote ACTTION by saying we're all very pleased that at some point in the middle of

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last year, ACTTION surpassed 100 publications in peer-reviewed journals. So that's one measure of our success over the last 10 years, though I think not the only measure.
Any questions from any of you about ACTTION, how it works.
MALE VOICE: Our website.
DR. DWORKIN: www.acttion, with two T's, .org.
Alright. Thank you all very much. Take it away.
Presentation – Eric Strain
DR. STRAIN: Thank you, Bob.
This meeting is focused on -- I'm going to just go over some of the big picture aspects of this meeting. We're going to be focusing on examining outcomes measures, risk-benefit assessments, and trial designs for studies of the treatment opiate-use disorder that may need to be modified or developed as the field identifies and studies novel non-mu opioid treatment interventions. As you'll see, we're going to hone in on four particular topics over the course of the day and a half.

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The goals of the meeting, which you should see, and they're at the top of your agenda, are we're going to be reviewing the current outcome measures and trial designs used for treatment of OUD, and then talk about novel non-mu agents that are being considered as treatments for this disorder. We're going to look at whether existing trial designs need to be modified or new ones established in light of these non-mu agents being considered.

That's primarily going to be occurring tomorrow in our discussions; and whether new outcome measures need to be developed in light of these non-mu agents; and how do the risk-benefit assessments need to be conducted in light of these mu agents.

It's an ambitious agenda, and it's especially critically important, as we go through, to be engaged in a discussion with these things. I think one of the characteristics of ACTTION meetings, that I've come to appreciate, is that they tend not to be meetings that have somebody standing up here droning on, hour after hour, and then at the end of the meeting, there's a half hour to discuss things. They tend to be much more

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interactive and thoughtful that way.

Our agenda today, this morning, we're going to basically be looking at current designs and outcomes from mu agents used for the treatment of opioid-use disorder and a set of talks. Then this afternoon, we're going to shift gears, and we're going to hear a set of talks about mu agents and current general approaches for studying each as a therapeutic agent, and we're specifically going to be looking at cannabis, sleep aids, vaccines, and psychedelics as those four topic areas.

Then tomorrow is really much less structured in the sense that we won't be having PowerPoint presentations in the same way we are today, but we're really going to be talking as a group about specific domains that need to be studied, designs, outcomes, risks, and benefits for these mu agents; what can we take from perhaps what we're doing currently with agents, and where do we need to perhaps move in new directions for developing new aspects in this area, new outcome measures or designs.

I will maybe do a little sidebar on ACTTION in

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this respect because Bob didn't mention this. I hope I'm not speaking out of turn, Bob, but ACTTION has also at times provided small seed grants to investigators to help move something along. So if somebody, for example, has an existing data set where they say, gee, I can go back -- if I just had a few thousand dollars for biostatistical support and a research assistant to spend 40 hours or 80 hours on this, I could really get something done that would be helpful.

ACTTION has funded things like that in the past. I don't know if that's possible going forward. Bob's saying yes, so see Bob if you want money.

(Laughter.)

DR. STRAIN: Did you bring your checkbook?

Let's see. A few housekeeping things. Needless to say, silence your phones. I was saying to Valorie, who's helping to staff the meeting, one of the best ACTTION meetings we ever had was in a basement of a hotel where there was horrible WiFI service. Everybody was really engaged in active because nobody could look at their email, but it sort of dank and dungy down there.

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I think you probably know that restrooms are out these doors to the left. If you go right, you're going to walk out of the building. We will be recording this session, so I would ask to use the microphones. The mics are state-of-the-art things, where they come on and off when you talk, so you don't have to be pressing buttons. But we will be recording it. ACTTION often creates transcripts of meetings or at least keeps records of meetings if there are things that we want to go back and do.

This goes to Dennis' question about next steps, a couple of things on this respect. Annie Kleykamp, who I managed to catch just as she was taking her sweater off -- but Annie, wave your hand. Annie is at the University of Rochester and basically is a faculty member there who works for ACTTION, does medical writing for ACTTION. Annie is going to be taking notes on top of the transcript. She'll be taking copious notes throughout these days.

We often will produce a paper out of these. As a matter of fact, I think, virtually, every ACTTION meeting I've been involved with has had some form of a

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peer-reviewed paper come out of it. Sometimes they're commentaries. We just did one on craving in JAMA Psychiatry. We did one on a scoping review that Annie's had; a review on cannabis outcome measures that Dustin Lee published.

So I'm not exactly sure what the product will be from this meeting because we have four different topics; as I mentioned, sleep aids, vaccines, psychedelics, and cannabis. But I think that we will be trying to produce some form of a paper out of this. That's usually our goal for these things. Often, and typically, we'll look at who's attended, and these do turn into papers that have 20 or 25 or 30 co-authors, so there are opportunities in that respect as well.

I think that was my last slide for this. Does anybody have any questions about any of that, ACTTION, the meeting, meeting, what we're trying to do?

DR. KOSTEN: Are there minutes that are going to come out of this or is there going to be some sort of -- everybody's presentation gets put on line, or what's going to happen with that?

DR. STRAIN: Often, we do put the PowerPoint

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presentations on the ACTTION website. I think we've been doing that regularly, right, Dennis?

DR. DWORKIN Yes. So the standard is the presentations will all go online, and the speakers can take out any slides that they want to take out. So the presentations go online; names and affiliations of all the participants; the agenda for the meeting. And typically, we do put the transcript of the recording that's being made online. So you should all watch what you say because it's quite possible it's going to be available on the Web in a couple of months.

That's not a decision we've made. We've been encouraged by FDA to put transcripts online, so we do that almost always.

DR. KOSTEN: The next question to that is it's one thing for the speakers to get all their stuff online and be careful; it's something quite different for me to be careful when I ask a question, and ask it in such a way that the New York Times finds it interesting. So when we say stuff as participants --

DR. DWORKIN: It's a great question. There has not been, to my knowledge, anyone who's dug through

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the transcripts that are available online and written about it in the New York Times or any other publication.

As you can imagine, the transcripts of a day and a half, two-day meeting like this are extremely lengthy, and it would be a challenge, I think, for anyone to read through them. That's, of course, not to say that it couldn't happen, so it's possible, but to my knowledge, it's not ever happened. We actually have wondered, given preparing the transcripts is not inexpensive, is there anyone who's actually looking at them. But yes, it's possible that could happen.

DR. KOSTEN: We are in the city where they seem to read 800-page documents overnight.

DR. STRAIN: And Tom, that comment is now in the transcript.

(Laughter.)

DR. TURK: I don't know if you're aware of this. Since we do the transcripts, and since they are recorded and someone tries to type out, we ask people to say their name before they make a comment, at least the first time until we sort of know your voice.

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Therefore, you could, quote, "be identified" and you should be identifiable if someone really wants to track you down.

DR. STRAIN: Well, my name's Eric Strain.

(Laughter.)

DR. KOSTEN: And I'm Tom Kosten, and I think that Eric Strain guy is just --

DR. STRAIN: Does somebody else have a question or comment?

(No response.)

DR. STRAIN: Let's, obviously, try to keep -- and I think we all will -- a collegial discussion. This is not an opportunity to take political stands in inflammatory ways, despite what might be going on just a few miles from here.

Anything else?

(No response.)

Presentation - Eric Strain

DR. STRAIN: If not, without further ado, I will introduce the first speaker who is me. I'm going to be talking about an overview of the futures of clinical trial designs for traditional mu agents. I'll

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try to move briskly. As the moderator, I'll try to keep things on track.

The goal today, briefly, is to review some of the study designs used today, and we should be thinking about whether some, or all, or none of these should be used when looking at non-mu therapeutic agents. I'm going to be talking about clinical trial designs. Kyle Kampman's going to be talking about outcome measures. We'll have a break, and then Kenzie Preston's going to be talking about risk assessments. So I will try not to bleed into their discussions, although it's hard to sometimes.

My own line is actually agents that have been studied, I'll talk about briefly. Aspects of trial designs, I'll go into a little more detail. Then summary and final thoughts actually turned into sort of a wastebasket for me as I was putting this talk together because I discovered there were more and more things I wanted to draw out. I've never done this before, but I actually have figures in my summary and final thoughts section on this talk. I apologize. When I get to the summary and final thoughts, you may

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think I'm at the home stretch, but I'm not necessarily.

Let's start with agents that have been studied. I think people are probably pretty familiar with this. Basically, we've got mu agonists, mu partial agonists, and mu antagonists, the three categories to consider.

For mu agonists, things that have been studied as I was thinking about this, obviously there's heroin, or what has been rebranded as diacetylmorphine, not in this country so much but in other countries, Canada, Europe, European countries; hydromorphone, which has typically been done as a control condition in some of the heroin trials; LAAM, or l-alpha-acetylmethadol, which is no longer marketed; methadone of course; morphine in extended release form, and there were some studies done in the UK. Tramadol has been studied, and that's a weak mu agonist.

There may be others as well. I put this list together, and then I would think of something and I would add it. So there's been a wide variety of mu agonists I would describe.

Now, on the mu partial agonist side, obviously

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the medicine is buprenorphine. There are a number of other mixed agonist/antagonist opioids. They may have partial agonist effects. I don't think any of those have been really studied as therapeutic agents in any meaningful way, beyond buprenorphine.

Then antagonists, there's of course naltrexone, which comes in both an oral and an extended-release form. Nalmefene and naloxone have been studied in various ways; naloxone, not really, but I felt for completeness sake, I would put it up here, and nalmefene has been studied as an agent.

So for all three of these, I think there's unique features to the design of trials for each of these categories, especially when you -- and I'm going to do this. I'm going to lump together these two and contrast it with a mu antagonist because they're really sort of two different categories, and in the Venn diagram, the circle virtually doesn't overlap on them in many ways.

With that in mind, let's dive into the aspects of the trial designs that have been used when studying these agents traditionally. Studies have been both

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inpatient and residential, as well as outpatient studies. The residential studies, or inpatient ones, are often within subject studies. They can test safety and efficacy, assessing outcomes such as withdrawal, suppression, or blockade efficacy. There have been a number of these, especially with buprenorphine, as it was being developed.

On the outpatient side, these are often group designed studies. They're closer to the real world but still can be quite different, and I'll come back to this certainly. But they're closer to what might be going on in clinical practice, although they still have features that contrasted markedly from the real-world experience with a medication.

Most efficacy and safety studies have generally been these outpatient, randomized and controlled clinical trials, and I'm going to primarily focus on outpatient group design studies. We may want to return to talking about within subject studies as well as some point on our discussions over the course of the next day or so, but for the moment, I'm going to talk about the group design studies, the outpatient

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ones. As I mentioned, Kyle and Kenzie will be talking more about outcomes and risk assessments.

So as I think about this, there are a number of issues you have to consider when you're doing these studies. Obviously, one is what's your control conditions going to be, placebo versus active controls; the dosing, fixed versus flexible dosing; the blinding or masking; the transition on to the medication -- and I'm going to come back and elaborate on these in a moment -- the psychosocial support, the type of support, the intensity of it, the inclusion and exclusion criteria, especially with respect to comorbidities and other drug use; and stratification variables. Some of these can be more specific for opioid-use disorder.

Let me go back, and I'm going to first talk in a little bit more detail about the general aspects of trial designs, and then I'm going to talk about aspects that are specific to agonists, partial agonists and antagonists. So let's start with general aspects of trial designs. In particular, I want to talk about three things: inclusion and exclusion criteria and

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psychosocial support and dose selection. We can talk about more as well as stratification, for example, is one that comes to mind, but I'm going to focus in on these three for the moment.

So when thinking about inclusion and exclusion criteria, the issue is whether you include or exclude other drug use with opioid-use disorder. If anybody tries to do an outpatient clinical trial of pure opiate users, you'll probably need 20 years to find enough people to populate it. Nobody's a pure opioid user the way they might've been 50 years ago. Even 20 years ago, we looked at subjects enrolled in an outpatient clinical trial for opioid use, and at the day of application, two-thirds of the urines were positive for cocaine. So it's just not out there.

Then you get into this issue of balancing feasibility, rigor, and generalizability, and I think this is going to be something -- not to jump too far ahead, but this is going to be something that we've got to think about when we're talking about doing things like psychedelics, for example, and who's going to get enrolled in a psychedelic study; and if it's for

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opioid-use disorder, what else? Is it just opioid use or is it all drug use, or is it nothing else, something besides that?

I think it's also going to impact other studies as well. For example, sleep aids, when we were talking about sleep aids, are you going to exclude people who are abusing benzos from a study?

There's other criteria that can impact generalizability as well. Comorbid, psychiatric, and medical conditions, these are very common in this population. High rates of psychiatric comorbidities, certainly hepatitis C, very common; HIV, not uncommon. There's also this issue of past experience and treatment and in studies, so certainly a lot of people -- and I'm going to come back to this at the end -- cycle in and out of treatment. Do you want to exclude people who have been in treatment before or should they be allowed in?

There's been a lot of concern now in the broader field of clinical trials with people who are professional research participants, who cycle in and out of studies, and certainly do we want to exclude

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people who've been in past studies? The INSIG trials, which are multisite trials of pharmacotherapies for alcohol-use disorder, have been increasingly raising the bar on excluding people who have been in past alcohol pharmacotherapy studies, which makes it more and more difficult to recruit.

The second thing I want to reflect on is psychosocial support. This is generally overlooked in clinical trials of pharmacotherapies for OUD, especially the older studies that were done. Some studies have attempted to standardize the treatment provided, and we certainly tried to do that. We created a manual at one point that our counselors would use.

We've certainly seen standardization in other trials. It's sort of weird or peculiar because, on one hand, we're not necessarily doing a good job in our clinical trials here. On the other hand, when you do a clinical trial that's looking at psychotherapeutic interventions, there's high rigor for what's being provided. So you'll see further psychotherapies for substance-use disorders such as alcohol-use disorder.

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This is something that I think we probably will need to be considering as well going forward.

There's this risk of the loose cannon effect, I call it. It's a therapist or counselor who provides highly effective treatment that is superior to others in a clinic, but that's not assessed; or the reverse, a very ineffective therapist or counselor.

I got worried about this 25 years ago, where we had a counselor in our clinic, and it was a research clinic, and he was horrible with documentation. He was horrible at doing what he was supposed to do. But he would be out in the hallway all the time talking to all the patients, not just his, encouraging them, slapping them on the back, asking how they were doing, all these things. And I just thought, "Oh, my gosh; this guy's a loose cannon. You can't track what he's doing, and he's going to be helping people in a way that I can't quantify." So I'm aware of this effect.

Some non-OUD studies have simply dropped in-person therapy. Again, the INSIG trials for alcohol-use disorder are basically using a computer-based treatment module. So rather than having

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any counseling services by a person, the participant is put in front of a computer and has to complete certain modules regarding their alcohol use.

Then dose selection, I want to talk about this for a moment. OUD clinical trials often use fixed doses. Everyone gets the same dose of the medication, which may confound a medication effect with a dose effect. Some studies have tested different doses, and it's more rare, but some clinical trials have used flexible dosing as an approach, double-blind flexible dosing.

This, for example, is a study that Walter Ling did about over 20 years ago now. He randomized patients, opioid-use disorder patients, to 148 or 16 milligrams a day of buprenorphine. He's not just saying, well, does buprenorphine compared to placebo work, which was the study. The primary study was 8 milligrams primary outcome versus 1, with one being an active placebo, but he also had these other conditions as a way to try to look at dose effects.

This is a study that we did, again, 20 some years ago, 25 years ago now, that used a double-blind,

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flexible dosing, and compared buprenorphine and methadone. We flex people between 8 and 16 milligrams a day of bup and 1590 milligrams a day of methadone, because we were looking to test the medication effect rather than a dose effect. So unbeknownst to people, they could get dose increases if they were still having positive urine samples in this study. There are strategies to do that, and there have been other studies that have done that as well.

Let me then turn to talking about aspects that are specific to agonists, partial agonists, and antagonists in these designs. I'll start with agonists and partial agonists, and lump them together, because they often overlap.

Most agonist and partial agonist studies, they're using an agent that essentially replicates the receptor effects of the abused drug such as heroin or oxycodone or fentanyl. That's what buprenorphine and methadone do. Generally, these agents have lower abuse potential. They have something like a slower onset of effect, a longer duration of action. There are easier modes of administration than the abused drug. They're

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producing the same receptor effects, but in a way that doesn't have quite the same profile of abuse liability.

When considering clinical trial designs with mu agonists, placebo conditions become a challenge in persons with physical dependence on opioids, which is who's typically enrolled in these studies. As you start to think about it, if you do a double-blind, placebo-controlled study of methadone, anybody who's assigned to placebo with the first dose, within a few hours is going to say, "Hey, wait a second. I'm in the placebo condition," because they're going to be going into withdrawal, so that becomes obviously an issue.

There are strategies to address this. For example, we did a study many years ago that looked at periods of an agonist to achieve withdrawal before transitioning to placebo dosing. This was this study design. This was done back in the early 1990s. Everybody who came in was put on 25 milligrams of methadone, double blind. One group over 6 weeks was titrated up to 50 milligrams, which in the early '90s was considered a robust dose of methadone in the Baltimore area, where we did it.

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Another group stayed on 25 for a few weeks, and then dropped down to 20 milligrams and stayed on it. But another group, unbeknownst to them, went through a 6-week detox off of methadone withdrawal and then were maintained on placebo dosing. So at least for these first few weeks, everybody is experiencing an active drug effect, so the placebo group doesn't drop out immediately, was the idea.

You can also use an active control that is placebo like as another strategy. This goes back to that Walter Ling paper again, where, as I mentioned, they used a 1-milligram dose of sublingual buprenorphine as an active control condition. The thought was, well, people experience something with 1 milligram. So it isn't that they're just getting placebo, but it's a low, and they expected it to be a poorly effective dose.

Then you can use a true active control condition in these kinds of studies. These have been mostly comparisons of buprenorphine to methadone, and there are a bunch of studies. We did this one, which I already mentioned. Walter did one as well, a

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multisite. I think this was a CTN study. Tom Kosten did one when he was at Yale, and there are a bunch of other ones as well that we could look at; but basically testing the efficacy of buprenorphine using methadone as an active control.

What about trial designs with respect to buprenorphine specifically? There are just a couple of points I want to draw out here. The primary issue is getting patients stabilized on buprenorphine and not precipitating withdrawal with the first dose. That was a concern early on. The trials generally can manage this through protocol-based dosing; although, I would make note that that's more of an issue in recent years, given the higher levels of physical dependence in clinical populations we're seeing with fentanyl use.

The studies that were done with buprenorphine 25 years ago, the pivotal trials, may be harder to do today, given the higher levels of physical dependence I think we're seeing in populations now with the widespread use of fentanyl.

Another issue with buprenorphine is it's hard to get matching placebo doses of buprenorphine now,

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depending upon what you're using. Back 20 years ago, it was much easier to get placebo doses from companies that were interested in getting it out there and getting it tested, but a lot of those dose formulations are no longer available, and because it's a sublingual administration, you can't simply put it in a capsule and have the person swallow an inactive capsule.

What about trial designs with respect to antagonists, then? I want to talk about transition on to the antagonists and adherence of blinding. Just for the transition on to the antagonist, probably everybody's familiar, but you need to go through some form of supervised withdrawal, AK detox. That's assuming participants are opioid physically dependent.

This raises issues of selected populations because if you can get somebody successfully through withdrawal, are they highly motivated, are they a special population for getting on to naltrexone? Again, this could come up with some of these trials as we think about some designs going forward.

Even when you get through a withdrawal, it can be a challenge to start people on naltrexone. This is

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from a recent CTN study done by Lee, et al., published in 2018, comparing naltrexone ER, the injectable monthly formulation, to sublingual buprenorphine.

What you see is this is the folks who got inducted to study men 72 percent of the naltrexone group versus 94 percent of the buprenorphine group. So even after going through withdrawal, supervised withdrawal, and getting successfully through it, there's this striking difference in the success rate, which was significant in who actually gets on to the medicine.

What about adherence? Unlike agonists or partial agonists, where adherence are generally fairly good, there's markedly high dropout rates in many antagonist studies. That's the lack of the mildly reinforcing effect produced by an agonist medication. If people don't feel anything, they don't want to take the medicine again.

This was from NIDA monograph number 9, which was on naltrexone. This is a study done at Penn. This is just a descriptive report of people treated with naltrexone. There were 142 that they reported on; 86

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took naltrexone in the first month of treatment. By month 4, it's down to -- not 86 percent; 86 people; 6 people were on it by a month into it, so you see these dramatically high dropout rates.

This is another report from the same author on oral naltrexone, which is just really striking to me; 386 patients expressed an interest in naltrexone; 242 were withdrawn off opioids and got a dose; 153 got 6 days of doses; 60 got 2 months; 3 took it for one year. So less than 1 percent of the people expressed an interest in oral naltrexone.

What about blinding? Well, there's a chance a person on an antagonist will try using an opioid while on a study. If they're on a placebo, they're going to get high effect, and they're going to know what they're on. So again, you get into these issues with blinding.

Where does this all leave us? So my winding summary. Many of the design features of clinical trials for mu agents are unique to these medications, I think. Typically these are chronic dosing studies. These are maintenance treatments. The physical dependence on an opioid adds complexity to the design

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of the studies in terms of control conditions, blinding, stratification; there are all sorts of features.

The studies tend to target drug use, but other features of opioid use can be significant issues for patients and families and are not typically addressed in the clinical trials. For example, this is from an FDA session that was held back in April of '18, where they asked patients and family members, in general, what are the most bothersome health effects related to you or your loved one's opioid use disorder? The most common thing reported was craving, which we're not even typically looking at as an outcome measure in these studies.

Now, you can say this is not good -- this is very soft data, but still, it's something we're thinking about here as we consider what we think is important, urine positive rates versus what do people out there think is important.

A significant and often underacknowledged issue is that patients drop out of treatment, even with an agonist and often in clinical trials, and we tend to

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overlook this. This is that study of 0, 20, and 50 milligrams of methadone. At 20 weeks, 50 percent who were on 50 milligrams stayed for 20 weeks. People drop out, and that's not just in clinical trials, it's also true in treatment.

We did a follow-up of an outpatient randomized-controlled trial of methadone dosing and found that there was 60 percent retained who were treated with 80 to 100 milligrams a day of methadone through 30 weeks. So even when you get the dose up to like 100 milligrams, you're still seeing over a third of people dropping out of treatment.

Does this work help us when we start thinking about non-mu trials? Well, I think there are some issues of commonality: controlled conditions; the potential need to transition from a state of physical dependence; the need to pay attention to ensure not missing a medication effect by testing the wrong dose; and careful attention to inclusion/exclusion factors and stratification variables as well.

Finally, there's been refinement of clinical trial designs for these agents, after all, these

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studies go back 50 or more years, it's likely the designing trials for some non-mu agents will require considerable new thinking about trial designs. I think at the end of the day, this is not a plug and play. I don't think we can simply say, well, that's how we did it when we were developing buprenorphine, so that's how we're going to do it for this. So thanks.

(Applause.)

DR. STRAIN: I'm going to next ask Kyle Kampman -- where did Kyle go; there's Kyle -- to come up. Kyle's going to give an overview to primary and secondary outcome measures used in studies of traditional mu agents?

Presentation - Kyle Kampman

DR. KAMPMAN: Good morning. Thank you all for coming, and thank Eric for inviting me. We're going to talk about overview to primary and secondary outcome measures used in studies of traditional mu agents. These are my disclosures.

Here's how this is going to go for the next 30 minutes. First, I'm going to do a brief discussion of the methods of this review that I did, and then I'm

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going to subdivide my topic into three subtopics because the trial outcome measures for these trials are very different when they have different goals and strategies. So we're going to talk a little bit about withdrawal management trials, talk a little bit about outcome measures for antagonist trials, and then agonist trials, and then sort of wrap it up with a summary.

This is a non-systematic review with me doing Medline searches and going through. As I started to do this, I realized that there are many more trials here than I could ever talk about, so I'm going to give you examples of each one of these and the outcome measures from some typical larger trials.

I'm going to limit myself to naltrexone, buprenorphine, methadone, and I added lofexidine only because there are some big trials, fairly new, for withdrawal management that I thought the outcome measures would be interesting to talk about there; again, limited to randomized-controlled trials, maybe phase 3, some phase 2, and a couple of human lab trials made it in here as well.

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So let's talk about alpha-2 agonists, specifically lofexidine, which is a selective alpha-2 agonist. The first trial -- and I've got to do notes because there are way too many trials to keep the details all straight. The first trial, 68 patients admitted, 35 randomized to lofexidine; 33 to placebo; stabilized on morphine for 3 days, and then started on lofexidine or placebo for detoxification.

Primary outcome was the Modified Himmelsbach Opiate Withdrawal Scale, picked specifically because it was an objective measure of opiate withdrawal symptoms. Secondary outcome measures in that trial included the Subjective Opiate Withdrawal Scale; the SOWS-Gossop, which is the short opiate withdrawal scale, which is sort of like the Subjective Opiate Withdrawal Scale but shorter; visual analog scales for opiate withdrawal symptoms; and concomitant medications for opiate withdrawal.

The second trial here is much larger. It is a 600-plus patient trial. Patients were admitted and were randomized to either 1 of 2 doses of lofexidine or placebo, and again received the 7-day detoxification.

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The primary outcome in that trial was, again, the SOWS-Gossup with secondary outcomes being proportion of completers for the clinical withdrawal scale.

Other withdrawal management trials, buprenorphine or methadone for the treatment for withdrawal management; 45 subjects admitted to either 2 milligrams of buprenorphine, 30 milligrams of methadone for 3 weeks, followed by 4-week dose titration and 6 weeks of placebo medication. That was in this trial. It's an old trial back from 1988. Again, the primary outcome measure was the Subjective Opiate Withdrawal Scale with secondary outcomes of treatment retention and use of ancillary medicines for withdrawal symptoms.

Walter Ling did a buprenorphine versus clonidine detoxification involving 113 opiate-dependent subjects admitted for a 13-day detoxification. His primary outcome was fairly simple. You completed treatment, and your urine drug screen was negative at the end. For secondary outcomes, he measured ancillary medication use, the SOWS, and something called the Adjective Rating Scale for Withdrawal, craving visual

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analog scale.

Finally, George Woody -- and this is the last of our methadone detox -- looked at adolescents, and compared groups giving 12 weeks of buprenorphine maintenance um, adolescents given a 14-day buprenorphine taper, then followed up for up to 12 weeks. The primary outcome was opioid positive urine drug screens at 4, 8, and 12 weeks, and secondary outcomes of retention, self-reported opiate use, and injection drug use.

Now, I'm moving up a little bit in here, closer to the present day. We have studies of very low-dose naltrexone. The first one, a Manneli trial, and again, that was 127 subjects. They were put on a 6-day methadone detox and supplemented either with low doses of naltrexone versus placebo. The primary outcome, again, were the SOWS and the OOWS; with secondary outcomes of treatment retention and use of ancillary medicines.

Very low-dose naltrexone studied plus buprenorphine. This is was a Sullivan trial. This was 150 subjects either randomized to a single dose of

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buprenorphine and then a gradually increasing dose of very low-dose naltrexone over a week versus a standard buprenorphine 7-day taper, followed by a 7-day period, and then followed by an injection of extended-release injectable naltrexone.

Again, the primary outcome was simply transitioned to extended-release naltrexone, who got the naltrexone shot, and also looked at who got the second shot of extended-release injectable naltrexone after a month. They looked at the proportion of patients completing detoxification measured in an ad hoc way, and then the typical withdrawal measure, SOWS, COWS, and they also looked at depression scores using the Hamilton Depression Inventory.

Then finally, a much larger trial with very low-dose naltrexone. This was a multicenter trial and involved about 380 subjects, and patients received either 3 days of reducing dose of buprenorphine plus extended-release naltrexone -- I'm sorry, plus oral naltrexone; so oral naltrexone plus a few days of buprenorphine, or placebo, buprenorphine, and oral naltrexone, or placebo, both of the naltrexone and the

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buprenorphine. They were tapered and transitioned on to extended-release injectable naltrexone.

The primary outcome was a well-tolerated transition to extended-release injectable naltrexone. So not only did they have to get the Vivitrol shot, but they had to demonstrate that they weren't in severe withdrawal; so a COWS less than 12 and a SOWS less than 10 was a successful transition. I also looked at some visual analog scales, desire for opiates, looked at the Clinical Opiate Withdrawal Scale, and then abstinence during the trial. This was an outpatient trial.

Those are your withdrawal management trials, mainly standard measures of withdrawal and treatment retention being the main outcomes there.

Let's move on and look at antagonist trials. Again, you have oral naltrexone, which I won't talk about at all. I'm going to mention some of the implantables, the Go Medical implant; there are several trials of that; Prodetoxone, the Russian implant, we'll talk a little bit about that; and I'm going to ignore the New Jersey implant and the Chinese implant since I couldn't find papers on those, but they are out there.

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Then we'll talk a little bit about injectable naltrexone, mainly talking about extended-release injectable naltrexone, Vivitrol. I also mention the Depotrex trial; that was done as well.

For antagonist trials, first implants, Prodetoxone. This was a trial done in Russia, 306 subjects randomly assigned to either an active implant plus active oral naltrexone, a placebo implant plus active oral naltrexone, or placebo implant and placebo naltrexone.

So there were 3 groups followed for 6 months, and the primary outcome measure was retention and treatment without relapse, and relapse being defined as a return to physiological dependence. So anybody with positive urine drug screens received a naloxone challenge.

Secondary outcomes included just percent urine negative drug screens, which they received twice a week and then relapse at 9 and 12 months follow-ups, and they looked at liver function test as well as a secondary.

The Go Medical implants, there were two

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trials. The first one done in Australia involved 72 subjects followed for 6 months on that, double-blind placebo controlled, active implant versus placebo implant. There's an interesting primary outcome. It was actually maintenance of therapeutic naltrexone levels; 2 nanograms per milliliter tested monthly was the primary outcome level and measure of that trial.

The second primary outcome level and measure was also kind of interesting, the number of overdoses that required hospitalization at secondary [inaudible - mic fades]. The secondary outcomes in that trial was returned to regular heroin use more than 4 days a week by self-report. Other heroin use was also a secondary outcome of that.

The Go Medical implants were also studied in a Norwegian trial, and this was 56 patients randomized either to the naltrexone implant or treatment as usual, and again followed for 6 months. The primary outcome was self-reported opiate use, although they did verify that with hair testing, interestingly. Also, another primary outcome measure was the number of overdoses at the end of the 6-month period.

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Secondary outcomes, there are a lot of instruments, the ASI, close to my heart, rarely used, but they used it. The MINI was used as an outcome measure, the criteria for opiate-use disorder at the end of the trial; depression by the Beck Depression Inventory, craving visual analog scales, which are used in virtually all of these trials. Depression Subscale of the 25-item Hopkins Symptom Checklist and the Temporal Satisfaction with Life Scale.

Depotrex, another injectable naltrexone product studied in a human lab trial as well as a clinical trial. In the human lab, 12 subjects were admitted, detoxed, given Depotrex, and then challenged with various doses of IV heroin. The primary outcome was the ability to block the opiate high and physiological effects of opiates; 26-item subjective effect of heroin visual analog scale; the SOWS; and a 13-item opioid symptom checklist, and the Drug Effect Questionnaire. Secondary outcome: performance tasks and some neuropsych testing.

In the clinical trial, 60 opioid-dependent patients done at two centers. We were one of them,

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actually. Patients were assigned to receive 2 doses of injectable naltrexone versus placebo and followed for 8 weeks. It was a short trial. The primary outcome was number of weeks in treatment and percent opioid negative urine samples. The secondary outcomes, time to drop out; percent of urines negative for other drugs besides opiates; severity of opiate and cocaine use; CGI, both subject and clinician; and a visual analog scale rating opiate craving; and depression measured about by the Hamilton Depression Rating Scales.

That brings us to the last group of naltrexone trials, which are the injectable naltrexone trials. The first one was the Krupitsky trial done in Russia, 250 subjects, 6 months, double-blind placebo control. The primary outcome was abstinent from opiates during week 5 to 24 of this 24-week trial, with secondary outcomes of number of opiate-free days; an opiate craving visual analog scale; number of days retained and relapsed to physiologic dependence, but again identified by a naloxone challenge.

The Lee trial, this one was written up in 2016. This was a probationer trial, opiate-dependent

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patients involved in the criminal justice system; 308 of them were assigned randomly to either receive extended-release injectable naltrexone or treatment as usual in the community. The primary outcome was time to relapse, which was defined as 10 or more days of opiate use in a 28-day period; secondary outcomes, percent opioid negative urine drug screens; rates of alcohol and other drug use; HIV risk behavior; and rearrest or reincarcerations.

This then takes us from naltrexone trials to naltrexone compared to buprenorphine trials, two of the largest ones out there. The first one was the X:BOT trial, a pretty big trial, 570 subjects with opiate-use disorder; started on an inpatient unit, detoxified and randomly assigned to either receive injectable naltrexone or a sublingual buprenorphine, and followed for 24 weeks.

The primary outcome in this trial was time to relapse, which was defined as any use in 4 consecutive weeks or 7 consecutive days of use; self-report, and that was judged by self-report using a timeline follow-back and weekly urine drug screens. The

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secondary outcomes, percent inducted; frequency of illicit opiate use by self-report and weekly urine drug screens, and an opiate creating visual analog scale.

The other trial, the Tanum trial, was a 12-week multicenter trial done in Norway, 159 subjects randomized to either sublingual buprenorphine or extended-release injectable naltrexone. The primary outcome was retention in the study and also the proportion of total number of urine drug screens without illicit opiates, and the number of days of heroin use and other illicit opiates.

The secondary outcomes, days of other drug use; days on injection; a craving visual analog scale; the satisfaction with the study visual analog scale; Temporal Satisfaction With Life Scale; Hopkins symptom checklist 25; anxiety and depression.

So moving on, methadone trials; two examples, a trial that Eric did in 1999, where he compared a moderate dose of methadone, 40 to 50 milligrams a day versus a high-dose methadone, 80 to 100 milligrams a day; ran these people for 30 weeks, 192 of them, with the primary outcome of self-reported opioid use, in

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this case using the Drug Use Questionnaire, urine drug screen results, and treatment retention, and measured adverse events, secondarily.

The methadone trial that I'm looking at here was an interesting trial, 179 subjects randomly assigned either 12 months of methadone maintenance or 6 months of an extended methadone taper, followed by 6 months a psychosocial treatment. The primary outcome was treatment retention, opiate use by self-report and urine drug screen, and a bunch of secondary scales, ASI again, risk of AIDS behavior, and treatment services review.

Trials comparing buprenorphine and methadone, the first one, the Johnson trial, randomized, double-blind, controlled trial, looking at 8 milligrams a day of buprenorphine, high dose of methadone, 60 milligrams or a low dose of methadone, 20 milligrams a day. Patients followed for 17 weeks in this particular trial, with the primary outcome being treatment retention, percent opiate negative urine drug screens and relapse, with a secondary outcome looking at other drug use.

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Another trial looking at methadone, and in this case comparing low-dose methadone, versus high-dose methadone, versus LAAM, versus buprenorphine; another 17-week trial with the primary outcome being, again, treatment retention, percent opiate positive urine drug screens, and then 12 weeks of continuous absence by both self-report and urine drug screen data; secondary outcomes looking at other drug use and severity of a drug problem, visual analog scale.

Then finally, the last of these, the Hser trial done in 2014, which was fairly huge, about 1200 patients randomly assigned to receive methadone maintenance flexible dose versus buprenorphine, with the primary outcome being simply treatment retention; secondary outcomes being urine drug results obtained weekly.

We're almost to the end of this, and then we'll sum it all up and try to make some sense out of it. I apologize for some of the repetition, but you see the outcome measures are very similar across the trials. The two injectable buprenorphine products have very similar studies. CAM 2038 had a blockade trial

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and a clinical trial, and sub-blockade, the same.

First we'll talk about the CAM 2038, the blockade trial, 47 subjects admitted, started on CAM 2038 the weekly 1 of 2 doses, and then challenged with hydromorphone. The primary outcome would be the maximum rating on the drug liking visual analog scale. The goal was to see if CAM would block the subjective effects of the hydromorphone; the secondary outcomes was drug high and desire to use, visual analog scales, COWS, OOWS, and physiologic measures of withdrawal.

The clinical trial of CAM 2038 was 428 subjects randomly assigned, double-blind, double-dummy to either CAM 2038, weekly for the first 12 weeks, monthly for the second 12 weeks, versus sublingual buprenorphine over the same period of time. The primary outcome was the mean proportion of opiate negative urine drug screens over 24 weeks, and there was a responder rate, and the responder rate was required by the FDA. No illicit drug use at prespecified times while participants received either weekly or monthly injections.

Secondary outcomes, urine drug screen results

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starting at week 4 and going on to week 24, visual analog scales for craving opiate withdrawal symptoms, supplemental buprenorphine, and supplemental counseling, whether or not they were required during the trials.

For extended-release buprenorphine sub-blockade, the blockade trial was similar to the one done from CAM 2038, but had a little change in that they added a drug versus money choice task. Patients were stabilized on the extended-release buprenorphine and then received hydromorphone challenges during this time. The primary outcome is the same as for CAM 2038, which was maximum rating, and a drug liking visual analog scale with a secondary outcome, which was a drug money choice task, a progressive ratio task looking at how hard they would work for a drug or money.

The clinical trial, which was published in 2019, 504 opiate-dependent subjects randomly assigned to 2 extended-release buprenorphine conditions, 300 milligrams monthly for the first 2 months, followed by 100 milligrams monthly, or patients continued on 300 milligrams a month for the entire 6 months of the

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trial.
The primary outcome was percentage of abstinence from opioid use defined as the percentage of negative urine samples and self-reports of illicit opiate use from week 5 to week 24 with a secondary outcome of treatment success, in this case defined as at least 80 percent opioid abstinence during weeks 5 to 24; also looked at treatment retention, withdrawal scores on the COWS, and opiate craving visual analog scale.
The last of the review slides, this is for buprenorphine implants, three trials. I'm going to talk about the first trial, the Ling trial published in 2010, which is 163 subjects randomized either to placebo or to active buprenorphine implants and run for 6 months. The primary outcome was the percent of urine drug screens negative for illicit opiates during the first 16 weeks of the trial.
The secondary outcomes was the percent of urine drug screens negative during the second half of the trial and treatment failure; patients were allowed to have rescue doses of sublingual buprenorphine during

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the trial under a schedule, and if you exceeded that schedule, then you were considered to be a treatment failure. So the number of treatment failures was a secondary outcome, looked at opiate withdrawal symptoms, craving on a visual analog scale, and CGI severity and improvement.
The second trial of buprenorphine implant, similar to the first, except they added a group that received open-label, sublingual buprenorphine, and they tightened the criteria for who was allowed to getting rescue doses of the sublingual buprenorphine; ran it for 6 months again.
The primary outcome was the same as the first trial, was the percent of urine drug screens negative for illicit opiates during weeks 1 to 16, with secondary outcomes including urine drug screens during the second half of the trial for completers, opiate withdrawal symptoms, a craving visual analog scale, and the CGI.
The third trial was markedly different from the first two trials because the target was different. It was sent to identify patients who would benefit from

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being placed on the implants who are already stable on a lower dose of buprenorphine.
So you had to be stable on 8 milligrams of sublingual buprenorphine for about 6 months. You had to have 90 days of no drug use prior to being randomized into that trial. And when you were randomized into the trial, it was double-blind, double-dummy, sublingual buprenorphine versus buprenorphine implants, followed for 6 months.
The primary outcome was the proportion of responders, and that was defined as participants with at least 4 out of 6 months without evidence of illicit opioid use, based on your urine tests and self-report; urine test once a month with 4 random ones during the 6-month trial for a total of just 10 urine drug screens over that 6-month trial. The secondary outcomes would be retention, time to first use, opiate withdrawal symptoms, and as almost always a craving visual analog scale.
So what does this all mean? Efficacy outcomes used depends on the goal. You have withdrawal management trials, you've got blockade trials, and

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you've got maintenance trials. Again, I'm not going to talk at all about the safety and adverse events that were universally measured in all of these trials and will be discussed later today, is my understanding.
For opiate withdrawal, or withdrawal management trials, detox trials, the main outcomes, almost always, obviously, opiate withdrawal signs and symptoms with the Subjective Opiate Withdrawal Scale being a favored withdrawal Scale, with a close second being the Objective Opiate Withdrawal Scale, the COWS somewhat third down the line in preference.
The Modified Himmelsbach Opiate Withdrawal Scale was used in the one trial but not in the others. Completion of detoxification is a clear primary outcome measure, and in the more recent trials, it's initiation of extended-release injectable naltrexone as the primary outcome measure of choice.
Blockade trials, subjective effects of opiates using drug liking visual analog scales was the two that I looked at, the primary outcome in both of those; also tend to measure withdrawal symptoms; visual analog scales measuring high desire to use. People usually

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identify that differently in their particular trials. And of course, there was a drug versus money task in this one.

In the clinical trials, the most common primary outcome by far was opiate use measured by urine drug screens. That was number one. Several trials used the combination of measuring opiate use by both self-report, supported by urine drug screens, and then retention was a distant second as to being a favorite outcome in the clinical trials.

Relapse was a common trial, especially if you're looking at antagonist trials. Overdose was an interesting outcome in the Australian trials. Visual analog scales are used almost universally and mainly for craving, but other phenomenon show up on visual analog scales as well.

The CGI is commonly used, but there was actually not a whole lot of instruments, like the Hopkins Symptom Checklist, the Temporal Satisfaction with Life. Those were used in some of the trials, but generally tended not to be primary outcome trials and not favored as outcomes, in general, in the clinical

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trials. And that I think is all I've got for you.

(Applause.)

DR. STRAIN: We have a couple of minutes before we go into a break. Are there questions?

DR. DUNN: Eric, I have general thoughts about outcome measures and how they relate to retention withdrawal. Should we save those for the discussion after Kenzie's talk.

DR. STRAIN: I think so, although I likewise have similar thoughts, but, yes, maybe focusing on this. We're going to have, before lunch, a chunk of time for general questions.

DR. KOSTEN: I've got a question --

DR. STRAIN: Tom Kosten, and that was Kelly Dunn that just asked.

DR. KOSTEN: Yes, Eric Strain, that's right.

When you look at these outcomes, the ones that we're doing, like 4 randoms during the month and then just one other, was there any way of looking at the validity of that, or reliability of that, or anything?

DR. KAMPMAN: All you had were self-reports, and 1 urine a month and 2 urines a month, and 4 out of

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6 times. So you got 1 or 2 urines a month and self-report, so I don't think there's any way to look at validity.

DR. KOSTEN: One of the things that happens when people come in for treatment for opiate dependence is that they only come into treatment when they're using pretty much every day, all the time, and they meet every criteria, 8 out of 8, in terms of having a diagnosis, and how much of that was true in these kinds of studies?

The question we always have is experimenting when you have a blocker is very common. Rats learn in two trials, don't self-administer, but people, it takes 20 before they get the point.

DR. KAMPMAN: We'll see in a couple of those trials, they specifically eliminated looking at people during the first month, so they picked weeks 5 to 24. Krupitsky did it in his Russian trials, and the implant trials did the same thing.

DR. KOSTEN: Is there any way to see if that's a good idea or a bad idea?

DR. KAMPMAN: Not that I know of. Eric?

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DR. STRAIN: I don't know. I got stuck in my head, actually, thinking about something, which is -- maybe this relates to what you're asking, Tom -- we've got data sets where we collected urine samples like 3 times a week around a clinical trial, and it seems like -- maybe somebody's done this -- you could go back and look at, well, what's your sensitivity to detecting drug use if you drop that to just one randomly a week, picking at random one from each week out of the clinical trial?

DR. KAMPMAN: You know, in the cocaine trials, Tom, there's a lot of controversy between how real is self-report, and a lot of people believe that it's very valid. In Philadelphia, it doesn't seem to be quite so valid.

(Laughter.)

DR. KOSTEN: We have a lot of liars in Texas, too.

At any rate --

DR. STRAIN: Philadelphia football fans, there's no Santa Claus training, only Eagles' games.

DR. KAMPMAN: So true.

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DR. STRAIN: Other questions?
(No response.)
DR. STRAIN: I'm not about the question, but I was making a long list of all the outcome measures that got mentioned in the primary or secondary pile. I found myself starting to think about relapse prevention as a primary outcome measure.
Was there a study that looked at relapse?
DR. KAMPMAN: relapse was a primary outcome in a number of the naltrexone trials.
DR. STRAIN: It's interesting --
DR. KAMPMAN: I'm sorry.
DR. STRAIN: Go ahead.
DR. KAMPMAN: Even in the implant trials, the third implant trial, time to first use, which essentially would be relapse. It comes up.
DR. STRAIN: That may be a useful measure to be considering for some of the study designs.
In the back of my mind, as well, is the thought that we've got these 4 drugs -- or 4 categories: psychedelics, cannabis, sleep aids, and vaccines, but it seems to me that -- maybe leave this

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as a thought as we go into the break -- some of those could be primary interventions: psychedelics and vaccines, and maybe cannabis, and some of them would be add-ons to an existing pharmacotherapy like sleep aids and maybe cannabis; and does that change the outcome measures that we're thinking about, depending upon whether it's a primary intervention or an add-on? I'm not sure. It's something for us to think about.
Yes, Frances?
DR. LEVIN: The other question is that with the withdrawal studies -- and I don't remember as well; maybe you do because you just read the whole literature -- is whether they all were inpatient versus outpatient.
If you remember, like with cocaine withdrawal, supposedly, there was this idea of a cyclic effect, and you're in the environment, and you're more likely to have symptoms, and in the inpatient units, everybody just dropped. I know that's not the same with opiates, but you may have very different symptomatology based on where it's being done in. I think most of them were inpatient, but I wasn't quite sure.

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DR. KAMPMAN: The lofexidine trials were both inpatient. The very low-dose naltrexone trials were all outpatient.
DR. LEVIN: But the ones for induction on to induction --
DR. KAMPMAN: We take people actively using, and we did an outpatient detox with them, and got them on extended-release injectable naltrexone. We did that outpatient.
DR. LEVIN: Right.
DR. STRAIN: Roger Weiss?
DR. WEISS: A couple of thoughts about these, and it's a more general issue, I think, and it has to do with the distinction between so-called subjective versus objective symptoms.
Subjective is often called now patient reported, which makes it sound better than, quote, "objective." I was just thinking of when you looked at the different withdrawal scales, there's the SOWS versus the COWS. But then you have that other one --
DR. KAMPMAN: The OOWS the Objective Opioid Withdrawal.

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DR. WEISS: You have the, quote, "objective." So there's a question of which should be considered primary, because patients act based on their own subjective feelings. So if they say, "I'm in withdrawal; I'm going to use," you can say, "No, you're really not in withdrawal," and that's not going to affect what they do.
So that's just one thought, and I think that covers a lot of different outcome measures. The second thing has to do with different definitions of relapse. Most studies have different definitions, and to some extent, they are different not for no reason, but because of the details of the way the study -- the context of the study and the study objectives.
For example, if you look at the X:BOT definition of relapse, that was very different from the definition that we used in the POTES study. We had a much lower threshold to call something relapse because we would put people back on buprenorphine if they started to relapse, whereas they weren't going to do something different in the X:BOT study early on.
So I think it's, again, sort of the internal

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versus external validity of these things. We would like to have the same outcome measures for every study so that we can compare studies, but it doesn't always work, and I think that's a real challenge for the field. Now, particularly when you get into different kinds of treatments, it may even be more variable how people measure the same thing.

DR. STRAIN: Next question?

DR. COMER: One thing that I think has not been paid attention to enough, really, especially in the withdrawal studies, is the use of ancillary medications. There's always a background of other medications that are allowed, or not allowed, or whatever, and that can potentially have pretty big impacts on the outcome measures, and there's no consensus, I don't think, on that.

DR. KAMPMAN: I agree, because I'm a big believer now on non-narcotic detox, based on my experience in one of the very low-dose naltrexone trials, where the placebo group just did great in Philadelphia, and they got clonidine, trazodone, and Imodium --

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DR. COMER: Exactly.

DR. KAMPMAN: -- and clonazepam, which made a big difference.

(Laughter.)

DR. STRAIN: That was Sandy Comer for the transcript.

We've gone over a few minutes, but we've got a generous break time. So let's take a break now, and we'll reconvene at 10:45. Thanks.

(Whereupon, at 10:22 a.m., a recess was taken.)

DR. STRAIN: We are now going to go into a talk by Kenzie Preston for our program. Kenzie's going to be talking about an overview to risk assessments used when studying traditional mu agents. So without further ado, Kenzie?

Presentation - Kenzie Preston

DR. PRESTON: Good morning. I actually have a cold, so hopefully, my voice will hold out. I'm going to cover risk assessment in four areas: adverse events, dependence potential, opioid antagonist activity, and physical dependence potential.

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Adverse events, do undesired, harmful, unintended effects result from taking the medication? We know that there are mu receptors all over the body, in both the central nervous system and the peripheral nervous system.

If we give a medication, for example, for analgesia, it's likely going to have effects on all these other mu receptors. So indeed, if we look up the list of adverse events associated with morphine, you can see that the list is quite extensive.

It's also important to note that not all mu agonists have the same set of adverse effects. Some drugs have off targets of non-mu agonist activity such as methadone, which causes QTc prolongation by blocking the flow of potassium ions through the hERG channels, and this can lead to even more serious adverse events.

Then there are also a set of molecule-specific adverse events that relate to metabolism and allergy. Codeine, for example, interacts with drugs that affect the cytochrome P450 isoenzymes and has a higher than expected rate of allergies. Meperidine is another example of an opioid agonist, but it has a metabolite

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that has serotonin effects, which can lead to serotonin syndrome.

This is a list of typical safety assessments that are done in clinical trials with opioid drugs. The only one I'm going to talk about a little bit are the treatment-emergent adverse events. One approach to collecting these is through spontaneous reports. The research staff would ask the participant how have you been feeling since your last visit? And if the participant reports something, then they record it appropriately.

They also would report anything that the participant just spontaneously brings up outside of being asked that question, or if the clinic staff notices a participant, say, has an arm in a sling, then they might ask about it. There are very specific ways of what to report, the reporting procedures, and following regulatory requirements.

Another approach is to actually have a questionnaire. I took this from the NIAAA studies. They use a modified safety questionnaire, which includes three general inquiry questions, which they

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record then the responses and various variables. Then they go through a list of specific events at every single study visit, so they have a complete set of information about the presence of those specific events in addition to anything the participant brings up themselves.

The nice thing about this kind of approach is that you can get standardized severity indicators on the common ones so that you get consistency across staff members, as well as if you're doing a multisite study, you can get greater consistency in reporting of the adverse events.

The next three areas I'm going to talk about in relation to a drug, tramadol, as an example. It's a marketed analgesic. As Eric mentioned, it has been examined for potential treatment utility in treatment of opioid-use disorder. It's kind of on a borderline of traditional and non-traditional mu agent because its analgesia is partly through mu receptor activity but also through noradrenergic reuptake blockade, so it has some stimuli-like properties. And it has been studied in all those assessments that I'm going to talk about,

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so I thought it would be nice to show the data for that drug.

Dependence potential, how likely is it that this medication would be abused, diverted, or lead to addiction? There are a number of different approaches that are taken to look at this. The most common one used are the single-dose studies, and this was really pioneered way back when at the Addiction Research Center, when they were studying opioids very seriously but also testing a series of medications that have been developed by the pharmaceutical industry to have analgesic activity, but with less abuse potential. So they were interested in identifying the best ones of that.

In these kind of acute drug administration studies, the idea is to determine the profile of effects of the test drug, focusing mostly on subjective effects but also looking at physiological pharmacokinetic activity. In those studies, we compared the test drug to placebo and to a prototypic drug, and that's typically a drug that has significant known abuse potential.

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It's important to do a dose-response curve, so you do 2 or more doses of drug that's tested, and they also test higher than therapeutic doses because, historically at least, drugs when they are abused are taken at higher than therapeutic doses. Drug administration is double-blind. There's random assignment, and if it's a crossover study, that's done appropriately. The study population is typically individuals with experience using drugs within that same class.

This is a list of the kinds of subjective effect measures that are collected and includes measures of global effects like drug effect, liking, good and bad effects; the Addiction Research Center inventory, which was a questionnaire developed at the addiction research center, testing many people with different types of drugs and looking for the items that were consistently elevated after administration of different kinds of drugs.

So the ones that are usually using these kinds of studies are the MBG, or euphoria scale, pentazocine, chlorpromazine-alcohol group scale, or sedation scale,

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and then LSD, which probably measures dysphoria. Participants are often given a list of symptoms to either endorse presence or absence, or actually to rate, and they're asked about what kind of drug that they think they received.

So it's important that we're looking for the positive mood facts, so how much do they like it? Does it have good effects? Does it increase ratings on the NBG or euphoria scale? Does it have some negative effects that might mitigate the likelihood of using those, such as having ratings of bad effects or increasing the LSD or dysphoria scale?

Then there are the ones that are more qualitative in nature; how strong is the drug effect? What exactly kind of effects does it produced, based on the symptom questionnaire; and what kind of drug does a person think they got? It turns out that people who are experienced opioid users can identify a drug as an opiate under double-blind conditions.

The most important measures include liking, which is rating how much do you like the drug. It's typically done on either a Likert scale or a visual

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analog scale, and then the MBG scale, which is a 16-item true/false subscale. I put some of the items on here because none of them actually say I feel euphoric. They're all a little more subtle than that.

This is a slide that shows the effects of prototypic opioids with high abuse potential. That includes drugs like morphine and heroin. They increase ratings of drug effect, feeling high. They reliably increase ratings of liking on the MBG scale. They also increase ratings on the sedation scales, PCAG, and they have a very specific constellation of affects that they produce, including things like nodding. As I mentioned, participants can identify them as being an opiate under double-blind conditions.

The other kinds of drugs that they typically studied at the Addiction Research Center were these non-morphine like opioids, which we now know probably have some kappa agonist activity, things like nalorphine and cyclazocine. They also increase drug effect and high, but they don't reliably increase liking. They increase ratings on this dysphoria scale, as well as the sedation scale, and the subjective

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affects that people reported included things that aren't typically seen, like heroin, including feeling drunk or nervous. When participants were tested with them, they identified them as being like a barbiturate.

This results from a typical addiction research center study that compared heroin, morphine, and methadone. The top panel shows the objective measures and the bottom panel shows the subjective measures. You can see that the effects of these three drugs are virtually identical on these measures. The only differences is that heroin is about twice as potent as morphine and methadone.

These are a result of a study that looked compared morphine and pentazocine, and now morphine being agonist/ antagonist opioids. You can see that pentazocine didn't produce the level of liking that morphine did. It also didn't increase the MBG scale to the extent that morphine did, but it did increase the LSD scale.

Back when tramadol was being considered for marketing in the United States, Don Jasinski and I did a study comparing tramadol to morphine by the

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intramural administration route, and tramadol did not increase liking and it did not increase the MBG scale. But it turned out we were looking at the wrong route of administration, and the subsequent studies, such as this one that compared tramadol to oxycodone, we did find that tramadol increased liking to the same degree that oxycodone did.

There were still, nevertheless, some differences. For example, when they looked at the maximum time, how long did it take for that high effect or that liking effect to come on, for oxycodone, that was about an hour, whereas for tramadol, it was about 2 hours.

In yet another study that compared tramadol to oxycodone and codeine, what was noted is that tramadol also increased ratings as having some bad effects as did codeine, but you can see that oxycodone, that's on the left, did not produce increases in ratings of bad effects.

That's going to switch to drug self-administration. This is a procedure in which participants are given the opportunity to take drug in

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the laboratory. It's a behavioral response. It's often required for them to earn a dose of drug, so that work requirement can then increase with each successive dose that they earn. It's called a progressive ratio system. The point at which people say I'm not going to work anymore for that dose of drug is called the breakpoint.

These studies often include the opportunity to choose between the drug and an alternative reinforcer, and that could be a different drug, it could be money, and it could be food. The outcome measures that are used for these can be the proportion of test drug that the participant chose to take or the breakpoint, or sometimes both.

They're often done in two phases. So the person gets the opportunity to sample the drug that they're going to then have the opportunity to work for, and then they have that opportunity; so there's the sampling and then the self-administration. In these kinds of studies, other kinds of measures can also be collected within the context of the study.

This is a paper from Sandy Comer's lab. They

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did a very extensive study where they did dose-response curves for IV heroin against three different monetary alternatives, 10, 20 or 40 milligrams. You can see that the IV heroin at increasing doses was more increasingly likely to be chosen over money, and also that that breakpoint increased with dose.

So it's kind of interesting. The circles there are the dose-response curve when the alternative was $10, and the triangles are the ones when it was $20. You can see that it was more potent as a reinforcer against the $10 versus $20; although the data for $40 didn't further shift that to the right. So I'm not quite sure why; maybe Sandy can tell us. They also did a collected self-report, and they got lawful increases, the kind of effects that you would expect from heroin.

This is another study from her lab in which they looked at self-administration of intravenous heroin against intranasal heroin. You can see that the dose-response curve for IV is shifted to the left. It's more potent in producing self-administration compared to intranasal, and they collected blood

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samples. So they were able to look at the pharmacokinetics of these two routes against the self-administration, and it was consistent across what you would expect, based on the pharmacokinetics.

So tramadol has been tested in a self-administration study. They looked at placebo, oxycodone, tramadol, and codeine. The top panel there shows the proportion of times that the participant chose the drug over money, so placebo wasn't ever chosen over money. Oxycodone and tramadol both showed dose-related increases in the proportion of times that the participants chose the drug codeine. It was just flat.

If you look on the bottom panel, that's the data looked at as breakpoint, and you can see that there's consistency between these two kinds of outcome measures with dose-related increases. It almost looks like tramadol was more likely to be self-administered compared to oxycodone.

Lastly, I want to talk about drug discrimination. This is a procedure in which participants learn to identify the presence of one or

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more training or prototypic drugs. They get a minor small reinforcer each time they correctly identify the drugs, which are identified by letter code, or color, or some other way. If they meet a criteria for being able to discriminate among the drugs, then they can be tested, then the novel test drugs are just substituted in for one of the training drugs, and we look for how the participant identifies it. In these studies, other kinds of measures can also be collected concurrently.

So I thought I would show one drug discrimination study that we did, where we trained participants to discriminate saline, hydromorphone, or butorphanol and hydromorphone did produce those related to increases hydromorphone inappropriate responses. Butorphanol produced dose-related increases in butorphanol appropriate responses; then we did dose-response curves for three other agonists/antagonists.

Nalbuphine also increased dose-related butorphanol appropriate responses. Pentazocine was a mixed bag. It didn't come out either clearly hydromorphone like or butorphanol like, whereas

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buprenorphine did produce dose-related increases in hydromorphone appropriate responses. I would say that, just based on the likelihood or frequency of abuse of these three different drugs, that's really pretty consistent with how much they were abused when they were on the market.

Tramadol has been studied in drug discrimination studies. In this one, the training drugs were hydromorphone, methylphenidate, and placebo. The drugs were identified by letter codes. I'm sure methylphenidate was chosen because it has the noradrenergic reuptake blockade. And indeed, the participants learned the discrimination between those three drugs.

Now, when tramadol was tested, it produced dose-related increases as hydromorphone appropriate in the squares, peaking about 200, 400 milligrams, a little bit less, but you can see it was virtually never identified as methylphenidate.

Another study was done where they actually used tramadol as the training drug, teaching participants to discriminate between tramadol

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100 milligrams and placebo. They tried it in five different people, and only three of them were actually able to learn that discrimination and meet that acquisition criteria that I mentioned.

When they tested the three patients who got the discrimination, 2 out of 3 of them discriminated hydromorphone as tramadol, and then they did a naltrexone pretreatment intervention, and they found that that shifted the response curve to the right. The investigator suggested that the results showed that the discrimination was based on mu opioid effects, and that's actually consistent with that previous study that I just showed you.

I thought I'd go through advantages and disadvantages of each of these. For the single-dose studies, the advantages are that the methods are very well established, and it really takes a minimum of number of sessions to do the study. You just need enough to do a good dose-response curve.

Disadvantages is it relies entirely on self-report. And if you have a mix of good effects and bad effects, you kind of have to interpret what's going

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to predominate when the drug's out and available.

For self-administration, the advantages are that it has faced validity. After all, drug taking is what we're generally concerned about, and it's a behavioral or objective measure. You can get other kinds of self-report measures at the same time that you're collecting the self-administration data.

Disadvantages are that it can take more sessions than the single-dose studies. For example, the tramadol self-administration study I told you about, it took 7 sessions to get subjective reports, that was the sampling, but it took 14 sessions to get the drug self-administration data. So that's time, money, and exposure of the drug to research participants.

While it sounds kind of simple, in fact, it's harder to get right than it seems, and there are a lot of factors that can affect a participant's decision to take drug. So they might come in, and they're there to earn money, and it doesn't matter what you offer them, they'll choose money. Or they might come in, and they're there to get drugs. And it doesn't matter what

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the alternatives are; they're going to choose to take drug. I think a lot maybe more parametric work needs to be done to get a very reliable procedure.

For drug discrimination, advantages are that it's a behavioral measure, again, and it gives one answer to similarity, so it assimilates across those divergent kinds of measures. So you don't have to decide; the participant tells you what is it most like, and you can get those other kinds of measures at the same time.

The disadvantage for drug discrimination, it takes many more sessions than it would for a single-dose study. Also, I didn't have time to go through it, but in fact it does matter what you choose for your training drugs and the doses of those drugs.

I next want to jump to opioid antagonist activity, and will administration of the drug precipitate withdrawal symptoms in the patients taking opioid agonists? It actually is really important, and I found many papers where they talk about having to deal with buprenorphine precipitated withdrawal. So you'd want to know in advance whether your drug

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produces precipitated withdrawal.

Among the many things that were done at the Addiction Research Center, it was actually characterizing physical dependence. What were the effects of these opioids when they were given over long periods of time? At the top there are the physiological and at the bottom are subjective measures. Then they looked at what happened when they abruptly stopped them.

Believe it or not, there was a time when people didn't believe that opiate withdrawal was real, so they did a lot of work in this area characterizing it and developing scales. In fact, that Himmelsbach scale that Kyle mentioned was developed. I think he was one of the early scientific directors of the ARC.

One of the things they also found when they would say test one of the novel drugs while people were on repeated administration of morphine, that it would produce withdrawal-like effects. So they developed a method for looking at precipitated withdrawal. This is the dose-response curve for four different drugs: cyclazocine, naloxone, nalorphine, and pentazocine.

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Tramadol has been tested in this same sort procedure. These were patients who were receiving methadone 60 milligrams per day, and then they were challenged with placebo, naloxone, hydromorphone, and tramadol. What was found is the tramadol did not produce withdrawal effects in any participants, and indeed it produced some agonist effects even in these people who were being maintained on 60 milligrams of methadone per day.

Lastly, we talk about physical dependence potential, and will repeated administration lead to a discontinuation syndrome that could make stopping treatment difficult or unpleasant for patients. Of course, the Addiction Research Center did all these studies, direct addiction studies where they gave the drug repeatedly. We're probably not going to see those kind of studies any more, however, there are alternatives, and one of them are the substitution or withdrawal suppression studies.

For these, you work with participants who are being maintained on an opioid agonist, and then you substitute in your test drug for their regular opioid

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agonists. The ARC did all their studies in people on morphine, and I think some more current studies have been done with that. But also you could use other opioid agonists, including methadone or hydromorphone. The outcome measure is severity of opioid withdrawal, the idea being that drugs that suppress withdrawal can be inferred to have mu agonist activity and may produce physical dependence.

These are substitution studies. I just picked pentazocine because I showed it earlier. You can see morphine decreased the abstinence in the substitution setting, whereas pentazocine, the one on the right of the left panel, did not suppress withdrawal; whereas this GPA 1657, which as far as I know never was marketed probably because it looked just like morphine, did suppress opioid abstinence in the same way that morphine did.

Tramadol, again, has been tested, for this effect. The participants in this study were receiving hydromorphone 10 milligrams 4 times a day, and then after 23 hours of receiving their last hydromorphone dose, they were challenged with naltrexone,

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hydromorphone, or tramadol. In this study, tramadol did reduce some opioid withdrawal effects at some doses, but what wasn't seen was a clear dose response, so it didn't seem like it was the same kind of a withdrawal suppression that would be seen with hydromorphone or morphine.

Those are my our areas. I just wanted to end by saying that Kelly Dunn and colleagues just published a systematic review of the abuse potential studies of tramadol, and they concluded that tramadol appears to have a different and perhaps lower abuse potential than other opioid agonists. Thank you.

(Applause.)

DR. STRAIN: Before we go into a general discussion, are there questions for Kenzie?

Kenzie, I'd be curious if you have any thoughts about specific instruments that have been mentioned for safety, but specific instruments that have been used to assess for risks, side effects, and things of that sort in the trials that you were looking at?

DR. PRESTON: I looked at several

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buprenorphine trials. They tended to look for -- like the treatment-emergent events like I mentioned, they often included other measures like the pulse ox, and they looked at suicidality as one of the measures. Actually, because I ran out of time, I cut that part of the talk. But it actually looked pretty consistent across these different buprenorphine trials at least, in the things you typically would expect.

DR. DUNN: Eric? This is Kelly. I have a question related to that.

In the trials that you reviewed, did you see -- so one struggle I think with assessing adverse events in the context of these trials is that symptoms of opioid withdrawal typically come up as adverse events, and then it's hard to differentiate the degree to which they're an adverse event versus the expected withdrawal --

DR. PRESTON: Right.

DR. DUNN: -- whether or not to lump them together or to separate them, and I'm just curious, your thoughts on that.

DR. PRESTON: Right. The trial that was done

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at Hopkins specifically noted that. If you're treating opiate withdrawal, there's not like a switch where you say, yes, that's definitely opioid withdrawal or not; it's a series of symptoms and signs. I know in that trial, they decided to just collect all of those as possible adverse events, and then they looked at the proportion of them that were likely related to opiate withdrawal. And I think in that trial, half of the adverse events that were reported were actually symptoms of opiate withdrawal.

So that is something that you need to consider, is the effects of the indication that you're trying to treat.

DR. STRAIN: Sandy Comer?

DR. COMER: I know that assessments of dependence potential is one of the standard things that we do for evaluating the abuse potential of a drug, but this is a little bit off target from what you're talking about. But what about for non-opioid medications? We don't really focus on the issue of tolerance development to medication effects. I'm just wondering if that's something that we should be

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thinking, especially in the context of a non-opioid medication for treating opioid-use disorder.

DR. PRESTON: I personally think that's an underreported problem. There are some medications like clonidine, which do have a discontinuation syndrome. The SSRIs, I think there are lots of people who are put on SSRIs who are not aware that when they try to stop them, they're going to have withdrawal symptoms, and that actually more attention needs to be paid to that.

DR. COMER: That's an excellent point. That's not kind of the one I was thinking of. For something like clonidine, I absolutely agree with you, that if you use it too much, then there might be this rebound hypertension that should be evaluated clinically.

What I was sort of thinking about was -- and the reason I'm thinking about it at all is that I reviewed some grants recently and this was a topic that came up in the data, where these medications were being evaluated as potential maintenance medications for treating opioid-use disorder, but when you look at the preclinical data, the effect of suppressing opioid mediated responses was pretty good in the beginning,

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but then it sort of dissipates pretty rapidly.

DR. PRESTON: Yes.

DR. COMER: So I'm thinking that maybe we should think more about tolerance development to therapeutic effects for non-opioid medications that we don't really think about with opioid-mediated medications. You know what I mean? Naltrexone doesn't seem to produce tolerance to its therapeutic effects; methadone and buprenorphine don't either.

DR. PRESTON: Yes. Well, certainly among the opioid mu effects, there are different rates of tolerance that develop. So I think it's a pupillary response; supposedly the tolerance doesn't develop to the same degree that it does for other, like feeling good effects.

So, yes, I agree with you that that would be something that should be tested. A lot of the preclinical studies, they kind of ignore that effect of repeated administration, and they can say, Oh yeah, that drug blocked self-administration of cocaine, but does it do it the next day, and the next day, and the next day?

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DR. COMER: Right.

DR. STRAIN: Right. Or sleeping.

DR. PRESTON: Yes.

DR. STRAIN: Patrick Finan.

DR. FINAN: Kenzie, I'm wondering in the work reviewed, how often at all are you running into abuse liability being assessed based not so much on the positive agonist effects, but more on the relief of states like pain, particularly non-withdrawal pain and non-withdrawal related aversive states, like negative affect?

DR. PRESTON: I can't think of any. I mean, I know that people talk about that. People take opioids to reduce the withdrawal that they're getting from something else, but I don't know.

DR. STRAIN: Kit, do you have --

DR. BONSON: Kit Bonson. I'm with the FDA. So use different patient populations. That's the main way you don't confound that issue. In assessing abuse potential, you would use recreational opioid abusers who are not physically dependent and are not pain patients, so there is no question about that.

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DR. FINAN: How does abuse liability pertain to pain patients in particular, then? If the canon of abuse liability measures exclude -- they affect the relief of pain, I'm wondering what we should be thinking about in terms of adding measures, in particular, to distinguish abuse liability as a function of pain relief versus liking and measures like that.

DR. BONSON: I would say that, generally, we suggest that the abuse potential of a drug is a constant in some way and that there are always going to be differences between a patient population and a non-patient population because of the biological differences between them. So whether we assess that specifically is not regulatorily required in that way. It's an interesting clinical question, intellectual question.

DR. COMER: We actually had an ACTTION meeting on this several years ago and discussed -- I mean, that's a really good point that you're raising, liking a drug for its euphoric effects versus liking a drug because it's taking the pain away. Those are very

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different kinds of situations, and we had a paper that came out. There were pain experts in the audience and abuse liability experts. I can send you the paper if you'd like.

DR. STRAIN: Thanks. Did we clap for Kenzie? Let's clap for Kenzie.

(Applause.)

Group Discussion

DR. STRAIN: We now have some time to open it up for more general discussion about these three domains: clinical trial designs, outcome measures, risk assessments associated with pharmacotherapies. I think we should let this go in the direction that we want it to go, and Kelly Dunn has been chomping at the bit to ask something.

Go ahead, Kelly. Say something.

DR. DUNN: Thank you. I've thought a lot about the outcome measures in the field of opiate-use disorder treatment relative to alcohol and tobacco. Alcohol and tobacco have very clearly defined outcome measures that most trials rely on, so it facilitates meta-analyses and clear, I guess, indication driving

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outcomes that would support medication development.

But opiate-use disorder, we have such a plethora of outcomes, as illustrated by Kyle's talk. But even if we narrowed it down to something like withdrawal, we have so many measures of withdrawal, and they capture the same general concepts and symptoms, but they do it in slightly different ways.

Even if we look at just self-report versus observer-rated reports, we get very different outcomes. We're starting to dig into this a little bit in the context of a trial that Eric ran that compared clonidine, tramadol, and buprenorphine for detox outcomes, and we're looking at the time at which people self-reported.

So what's the difference between self-report and observer ratings of withdrawal, and we're finding that the self-report emerges several maybe hours before the observer ratings, and maybe even longer, so that people are detecting and reporting a problem; quite a while before someone would observe that they are experiencing the problem, and that could be a critical period.

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So I just think that it would be useful if we had some consensus about what outcome measure we would prefer. Even if we wanted to collect multiple different outcomes of withdrawal, if we could reliably all report the same one, then we could work towards a meta-analyses and indication driving.

I think it's notable that the lofexidine trials, they used a scale that most of us -- it's not frequently reported, the SOWS-Gossup scale, I believe. They did the work beforehand that showed that a certain change on that scale was associated with clinical improvement, and then their next trial, their phase 3 trial showed that level of improvement, and that was what contributed to them getting FDA approval for that medication. We just don't have those data for the scales, and I think that there would be significant value.

Just to follow up on that, the measure that I see the most frequently reported is retention, which has a lot of strengths, because if you have withdrawal as your primary outcome and people drop out, then you've lost your primary outcome data. But retention

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can be modified by numerous other things, and the FDA has actually recommended against it in their guidance to industry on this topic, because you can incentivize retention. So to use that as a formal indication driving outcomes seems problematic, but it's the one thing that we all have for all of our trials, reliably.

I think we're in this kind of unique state with opiate-use disorder, where it's very challenging to know what the right outcomes should be, so we're all using multiple different things, and some consensus I think would be helpful.

DR. STRAIN: Els?

DR. HOUTSMULLER: I'm Els Houtsmuller from the Patient Centered Outcomes Research Institute, and I just want to say that I really agree with your point, and I was struck by how much this is the case, that the outcome measures, they're all sort of measuring the same thing, but there's really a wide variety. And there is an interdisciplinary group that is actually trying to establish core outcomes across all these studies.

I think they go by the name of COMET, and

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they're doing this in a number of different fields. I think it would really help the field because it would allow for meta-analyses much more easily, et cetera, and that might be something to connect with.

DR. STRAIN: El, it was called COMET?

DR. HOUTSMULLER: COMET, C-O-M-E-T. They started in England. They are also connected to a number of American groups, CMTP in Baltimore, and others.

DR. STRAIN: They flew across the ocean?

DR. HOUTSMULLER: They did.

DR. STRAIN: Okay, like a comet. Sorry.

DR. BROWN: Randy Brown from the University of Wisconsin. Great points, and I think one of the challenges becomes that in some of these cases, I don't think we have complete clarity around the construct. We really want to measure. I'm referring specifically to lapse, relapse, retention, and craving, and whether the instruments used or the measures put forward in a lot of these studies are really validating what we understand as those things [inaudible - mic fades].

I think if we were to ask a number of people

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in this room to write a definition of any one of those things, we'd get a lot of different answers. So I think at some level, the step needs to be taken back around validation with some of these things, too. But Roger had also brought up the point earlier about what that looks like may also depend on the context and design of the study and the goal of the intervention when we're talking about something like relapse or lapse. But that's an additional challenge when we're talking about consistency between studies and what measurement should look like.

DR. STRAIN: That certainly resonates -- thanks, Dr. Brown -- with our last ACTTION meeting on craving, where we concluded that we don't know what it is. So despite Kyle's point that there are all these visual analog scales asking about craving, it's not really clear that the craving I experience is the craving that Bob experiences; that's the craving that Dennis experiences.

Els?

DR. HOUTSMULLER: I want to add a point to that, and that is that it would be, I think, very

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helpful to really represent a patient voice in the discussion about which outcomes to include because there's a risk of this being in its own world, and when you look at -- I mean, the FDA meeting was really interesting in that respect because it really had an enormous group of people who are talking about what matters to them.

There are ways to do that that actually can work very well. I used to be very skeptical about this, but now having been involved in some of this, it can work very well. And it would make for a good connection to effectiveness studies because currently there's such a disconnect between what happens in efficacy trials that are very rigorous, and they have to be, and they have to be done. But I think there could be more of a connection by including some of these more patient-centered outcomes earlier on.

DR. STRAIN: Thanks. Brian, and then Kit. Your name, by the way, even though say your names.

DR. KILUK: I'm Brian Kiluk from Yale. A related question along this, which is actually a more basic question for a meeting like this and thinking

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about clinical trial designs is are we looking to treat opioid use or opioid-use disorder, which we kind of treat them the same way or oftentimes think of them the same. It kind of brings up patient-reported outcomes in opioid-use disorder is actually characterized by a lot more criteria and things that may or may not be directly related to the amount of opioid use a person has.

I was thinking with Kenzie's talk, if the goal of the medication, or the aim or the target, is just stopping opioid use, then a self-administration like trial, where you can show that the medication does stop progression of opioid use or stops opioid use, that would seemingly demonstrate the efficacy. But if they're thinking about trying to treat the disorder, it becomes a lot more complicated. I think that's one of the more basic questions, given the title of this meeting, is thinking about treating OUD. A lot of our outcomes are based on just opioid use.

DR. STRAIN: Kit?

DR. BONSON: I was going to say that I think that the patient outcome is really important to like

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know what they would like to see, but everyone's advocated for some little box at the end that says, "Is there anything else that you'd like to tell us?" because they already know what the whole point of the study is at some level. So if you could solicit that in a open-ended way, I think that we'd get a lot of information.

I know that when I was conducting clinical studies, asking people, "What else would you'd like to tell us about what's been going on?" we had like a lot of interesting stuff that led to new hypotheses, based on what people were able to tell us.

DR. STRAIN: That actually -- it's Eric Strain -- reminds me, we used to do debriefs of clinical trials with the staff after we did these large trials with the 150-250 people. We had an LPN, Robin, I don't know if you remember, and she would sit in the back of the room and after a while she'd say, "Did you ever think of doing X?" And I would sit there and scribble it down because it was inevitably a great idea, yes, that I hadn't thought about.

So staff as well that are working with the

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patient population can often share a great idea.

Sandy?

DR. COMER: This is Sandy Comer. I think that's a really interesting point that was raised about focusing on opioid use per se versus opioid-use disorder, and I have a lot of thoughts around that. One is, I think, unlike for other drug classes, opioid use is sort of inextricably tied to opioid-use disorder, which kind of differs from cocaine.

In our group, from the opposite side of looking at things, we were doing lots of studies with patients with cocaine-use disorder, and we had to change our IRB protocols because a lot of the patients were using tons and tons of cocaine, but they didn't meet the criteria for the disorder. With opioids, it's the other way around, so it's kind of interesting to think about that concept.

But I think as another thought, if it's opioid use that we're trying to reduce -- I know this was raised by Nora Volkow recently in a publication, and the FDA was on the author list as well. What about reducing use rather than eliminating use? I think

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that's an another interesting idea. And we don't have a clear handle on if you reduce the use by half, is that clinically significant? So that's another thing I think we need to get a handle on.

DR. STRAIN: Let me follow up. I felt myself thinking -- I just wrote it down -- are we ready for treatment of opioid use and opioid-use disorder 3.0?

In other words, if you think of methadone as the first wave of pharmacotherapy for opioid-use disorder, kind of a revolution, and then the next revolution in some respects was buprenorphine, that really impacted the treatment of opioid use and opioid-use disorder, are what we say is we're ready for 3.0? Which is something different and something beyond simply getting people to reduce or stop their opiate use, which maybe kind of a variant of what you're saying.

It resonates with the FDA listening session, where people are saying, well, sleep's an issue; craving's an issue; anxiety's an issue. The things that we, frankly, haven't really focused on because we're just curious to know whether we can get their

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urine positive rates down, but maybe that's where this is at. Obviously, that also fits with the afternoon session, so I may be self-serving in proposing that.

Tom had something, and then Els.

DR. KOSTEN: Along with what Sandy Comer and you are both saying, I think that the opiate field offers us an opportunity to actually open up the other areas of substance abuse improvements that have been quite valuable for alcohol, where heavy drinking has now become a reasonable FDA outcome to have, based on other aspects of wellbeing that have gone on with the patient. Whether that's psychological status, medical problems, getting arrested, paying your taxes, getting employed, all of those things, we have excellent data with opiates, and methadone maintenance in particular, but also with buprenorphine, that those things improve.

The fact that this is an illicit drug, you could say, the way alcohol is, but the standard in the community for alcohol is that everybody drinks some, and the standard in the community is not that everybody's taken opiates all the time, it seems to me that we could learn something from opiates that builds

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and is applicable to those drugs that are traditionally viewed as not so good for you, like stimulants, amphetamines, cocaine.

If we can carry that system of looking at that type of outcome, that's psychosocial, not just total abstinence, that will move us a long way with [inaudible - mic fades] the pharmaceutical companies, at least, willing to go into the stimulant area and other areas, where right now criteria just seems totally unrealistic, which is completely stopping. And it's almost like smoking, where you're supposed to completely stop for a year, for example. And even after you stop your treatment, which is ridiculous, most things are not approved on that basis.

But there's a standard that I think we can make sense out of. It's just like opiates and urines, where we can look at this question of how good are the self-reports. We can look at this question of is it good enough if you only get once a week, and carry that over to the other area, where we have nothing right now, and where, in fact, we're not likely to get anything with big pharma support because they don't see

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a road forward.

So long speech, but that's how I see this as useful; not so much for opiates. We've got treatments, but we've got some other areas. We need better agreement from the FDA that these are reasonable outcomes, as happened with alcohol, and that happened from data within alcohol. We're not going to get that same level of data from cocaine, or methamphetamine, or anything. We have it with opiates.

Can we analogize it and move it over to make some of the other drugs of abuse more amenable to participation of investors that it's going to take to jump this 100 million dollar barrier that you have to putting something in the market?

DR. STRAIN: Els?

DR. COMER: I just think there are two ways of approaching this, one looking forward and one looking back.

DR. STRAIN: Sandy Comer speaking.

DR. COMER: Looking forward, we need to develop instruments that can capture quality-of-life type issues, or sort of clinical indicators of

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improvement, of functioning, of life; that kind of thing. I know that Walter Ling has developed this T questionnaire. There are others that are also being used.

Looking backward, I was thinking there's a little pot of money for somebody who has time to do this, but we could analyze some of the existing data that we have of buprenorphine maintenance, methadone maintenance, and try to tease apart individual patients' outcomes. Because there are a variety of people who have complete abstinence to total relapse, and if we have CGI data, for example, that are included in the trial, then we can go back and see whether or not people who have reductions in use show improvements in functioning.

DR. STRAIN: Els?

DR. HOUTSMULLER: So a related point is that I think it's important to think about different populations for different outcomes, or different outcomes for different populations, because the opiate using, and abusing, and addicted population is very different from twenty years ago, as we all know.

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Things that work or matter for people who have been on pain medication are now being moved off in this effort to reduce that kind of prescribing and may be interested in very different outcomes than people who have been using heroin and a lot of other drugs for the last 30 years.

DR. STRAIN: Tanya?

DR. RAMEY: Tanya Ramey. Since we started to talk about alcohol and what's happening in the alcohol field, we haven't touched upon that. Sandy maybe tried to move in the direction. It's the direction of endophenotypes. That is a field that is not so much addressed right now. As we are here, at the present day, we are not discussing that yet.

The patient's that is [indiscernible] drug developed is pointed into the direction of what to focus on as an endophenotype. The previous speaker was just talking about that in a certain way. That would open up a whole new approach. I the alcohol field is now doing several endophenotypes testing. So maybe that's the future or one direction of the future.

DR. STRAIN: Thank you. Roger?

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DR. WEISS: This was the subject of a previous ACTTION meeting, or a couple of previous ACTTION meetings, and led to a paper that Brian was the first author on. To quickly summarize that, the way that the alcohol field got no heavy drinking days as an acceptable outcome for medication approval was by showing that having no heavy drinking -- [inaudible - mic fades] -- to an absence of negative consequences.

The drug field has traditionally not measured negative consequences. The ASI asks about problems, but they don't say have you had family problems as the result of drug use in the last month? They just say have you had family problems in the last month? Which may or may not be related to your drug use. The more chronic those problems are, the more likely they are to continue, even if you stop using drugs; whereas the alcohol field, their use of the sip and the drink asks have you had family problems related to your drinking.

I think that it's a big leap to expect functioning necessarily to increase quickly, but you can potentially make negative consequences go away by

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reducing substance use. I think that's something that, when we design clinical trials, could help lead the way to figuring out whether there are a certain amount of reductions that can reduce negative consequences enough to be meaningful.

DR. STRAIN: Thanks. Bob Dworkin?

DR. DWORKIN: I'm sure this is a naive question. For a clinical trial, you need a primary endpoint, a single primary endpoint. There are co-primary endpoints, multiple primary endpoints, but that's going to increase your sample size significantly.

So at the end of the day, why isn't the primary endpoint the incidence of OUD at some follow-up time point as diagnosed by DSM-5 in your active arm versus your control arm? And if you show a statistically significant reduction -- that's really point prevalence -- in that follow-up prevalence that's also clinically meaningful, that's your primary endpoint. But it sounds like we're all disagreeing. Everyone else in the room disagrees that that's a meaningful primary endpoint.

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DR. STRAIN: Let me take a crack at that. One of the dilemmas has been -- and I should know this -- has been the window of time, typically, that DSM-4 and 4-TDR [ph] uses for the criteria that can qualify for the diagnosis. Now, you could change that, of course.

Does anybody know offhand what is in DSM-5?

DR. DWORKIN: Twelve months.

DR. KILUK: There is an early remission qualifier, which is the absence of the criteria for a 3-month period. It's considered early remission, which could potentially be useful as an outcome, if everybody entering the trial has the disorder.

DR. DWORKIN: And you could also do 6 months.

DR. STRAIN: Or 1 month, or whatever, 6 weeks. Yes, you could tailor to it. But we've had this discussion as well in some other ACTTION meeting, and they all blur together sometimes. We also thought about looking at the number of DSM criteria that a person fulfills. Brian, maybe you had that in your paper. You're saying yeah.

DR. KILUK: Yeah. I've actually been doing

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some more work with that. We had a paper come out looking at a trial we did for alcohol-use disorder and the count of DSM symptoms, which actually could potentially be a meaningful indicator. Now, in our trials, we adapted the assessment to evaluate just the past 30 days of symptoms, which changing the time frame raises concerns about are we kind of setting it up for more likely to see reductions within a short period of time.

But there certainly can be value in that. I think, just historically, it hasn't really been done. There aren't as many trials that have lots -- people enter the trial with a disorder, but there's no assessment during a follow-up period or at the end of treatment, really. So the data to dig back into this to figure out are there changes in the count of criteria have been kind of hard to find.

DR. STRAIN: We are out of time. The dilemma, historically is that -- not dilemma, but historically the field has looked at abstinence through biologic testing. In some ways it was, well, gee; we've got a field where so much of it is self-reports.

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Here's a treatment intervention, methadone, and then buprenorphine, and a biologic measure of outcome, urine testing, and that's pretty useful to have; especially when all that was out there, really, was heroin use, and your test was for morphine. You showed that that decreased or it stopped, and it was a great story.

Not push my idea of 3.0, but this goes back -- I think we know how to get people, in some respects, a lot of people to stop use, but what about those people who are struggling because they're craving, they're anxious, they're having sleep difficulties, or the subpopulation that's dropping in and out of treatment or is continuing to use despite the fact they're on 160 milligrams of methadone a day?

So those are the ones that are the tough cases, and that's where I think we start to ask, well, do we add cannabis? Do we add Sonata? Do we add Ambien? Do we try a psilocybin session? Do we just go to something different?

Well, stay tuned, because we will answer all those questions this afternoon.

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(Laughter.)

DR. STRAIN: But in the meantime, it's time for a lunch break. Time flies when you're having fun. The morning's gone quickly. We have a little less than an hour. The luncheon is down the hall, and we'll see you back here in 55 minutes. Thanks.

(Whereupon, at 11:50 a.m., a lunch recess was taken.)

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

(12:48 p.m.)

DR. STRAIN: We're going to go ahead and get started with the afternoon session. I think there are a few people still trickling in, but for the sake of trying to stay on time.

We're now moving into mu agents that can be potentially used for the treatment of opioid-use disorder. We're going to start with the cannabinoids, and it's my pleasure to introduce Ryan Vandrey, who will be giving this talk.

Presentation - Ryan Vandrey

DR. VANDREY: Thanks, Eric.

This is a really interesting thought exercise because this isn't something that I would necessarily think about or even endorse prior to this week, but it's been fun to think about this. Here are my disclosures. This isn't something new. There's a lot of talk in the media about cannabis opioid interactions and the concept of using cannabis to treat opioid

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disorders. In Maryland here, it's actually been pushed for as being approved as a therapeutic use of cannabis.

Just a quick background here, cannabis was legal initially, then it was made illegal. Now we're in this process of slowly moving back towards legalization. It started at state levels with California, and now we're rolling in, I think, 34 U.S. states of legalized medicinal use of cannabis. Several of them actually have opioid treatment or pain relief as an indication for medical use of cannabis.

Recently, we've got the legalization of hemp at the federal level. Hemp is a subcategory of cannabis defined by the THC concentration of being 0.3 percent or less. This map shows you the areas in which you have legal cannabis. In the dark green states is where any use of cannabis is legal for adults; the slightly less green states are medical cannabis law states; and then the really light green states don't have medical cannabis.

As we go through this, I think part of the exercise here is to understand what we mean by cannabis versus cannabinoids because what used to be a very

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simple term that described the dried flowers from the cannabis plant that would be smoked by individuals is now very, very different, so it requires some distinction and level of understanding. So I'll go through this a little bit and kind of come back to this several times throughout the talk.

Cannabis as a botanical is a very complex entity. It's composed of over a hundred different phytocannabinoids, which are chemical contents that are specific and unique to the cannabis plant, in addition to hundreds of other chemical entities that are not necessarily unique to the cannabis plant but could have behavioral or physiological effects.

This should be distinct from cannabinoids globally because there are synthetic cannabinoids that interact with the endogenous cannabinoid receptor system that are not part of the cannabis plant. So there's a lot of diverse pharmacology that can happen with all of these compounds. When we're talking about botanically derived versus synthetic, there can be very different effects based on those pharmacological differences.

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As I mentioned, there's this distinction between cannabis and hemp. Hemp is cannabis, but not all cannabis is hemp. In addition, when we think about these phytocannabinoids and some of these differences in pharmacology, the two main players here are THC and CBD. THC, up until recently, was universally the most predominant phytocannabinoid, or the most abundant phytocannabinoid in the cannabis plant.

THC is what drives most of the hallmark effects of cannabis. When you think about acute cannabis affects, you feel high, you get giddy, you laugh a little bit more, you appreciate music a little bit more, you get the munchies, and things like that. Those are THC-driven effects.

CBD is kind of the new guy on the scene and has really been promoted as driving a lot of the health promoting and therapeutic effects of cannabis. It's important to note and to remember, though, that both THC and CBD are part of FDA-approved products. THC is available as an FDA-approved medication for the treatment of wasting syndromes or nausea due to chemotherapy or advanced AIDS wasting syndrome.

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CBD is part of a formulation that was just recently approved to treat rare childhood seizure disorders. THC and CBD in their therapeutic use is not a totally novel and new idea, but in both of those cases, these molecules have been kind of isolated and provided in a vehicle of some description, whether it be sesame oil or some other kind of oil. They're also limited to oral consumption.

Whereas THC tends to drive a lot of these hallmark, intoxicating, euphoric experiences of using cannabis, CBD tends to not have the same properties, and it's because of a differential pharmacology. CBD works as an allosteric modulator of the endocannabinoid system, whereas THC is a partial agonist. It has a number of other off-target pharmacological targets as well, and we're still figuring out and determining which ones those are.

Contrary to popular belief, CBD does not mitigate the acute effects of THC in most circumstances for most types of effects. We see a little bit of a signal there for it mitigating some anxiogenic effects of THC, but not much else.

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In addition to these two, there are several other minor cannabinoids that we don't know a lot about, and there have been no human controlled studies of cannabigerol, cannabinol, cannabichromene, chromium and some of these other things. The reason I bring that up is that with the advent of legal retail cannabis sales in the U.S., we're starting to see these products pop up.

This is an example over here of a CBG oil that's on sale right now. So we don't know a lot about what that kind of a product is going to do, what it's going to have, but given the retail environment and the kind of loose regulations about cannabis products right now, and given the wide stake from the business sense, we're seeing companies come up with a lot of diverse products trying to kind of corner a market or create a unique niche market, and they make a lot of claims about what these things can do.

I've kind of gone into this -- and I'm going to skip over and not drill too far down into the pharmacology of all of these different cannabinoids, partially because it's not terribly important to this

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discussion, but it's important to know that there is this diversity. You get partial agonism. You get full agonists with the synthetics. Then, with CBD, there's some preclinical research indicating that there might be some direct interaction with opioid receptors or modulation as an allosteric modulator. But again, we can have dose-specific agonism/antagonism, and just a lot of differences in terms of effects here.

So where does that bring us and where do the opioids come into the picture? Why do we think that cannabinoids might be a useful target to look at treatment of opioid-use disorders? Opioid receptors have multiple subtypes and, basically, what we can look at, when we look at cannabinoid opioid receptor similarities, they're G-coupled protein receptors, and they inhibit neurotransmitter release. They have comparable distribution in the central nervous system.

There's a lot of indication of crosstalk between these two receptor systems. The acute administration of agonists for cannabinoids or opioid receptors have some comparable types of pharmacodynamic effects, including analgesia, catalepsy, hypothermia,

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motor depression, hypertension, immunosuppression, and sedation. They also are common among drugs of abuse in that they increase dopamine release in the reward pathways of our brain; so they are both drugs of abuse in terms of agonism.

A number of preclinical studies have been conducted that look specifically at how these two systems interact with each other and how administration of exogenous cannabinoids and opioids intersect with each other. Some studies have demonstrated cross-tolerance. If you train an animal up on administration of an opioid, and then give a high dose of a cannabinoid, you see evidence of tolerance to the cannabinoid and vice versa. You see some evidence in some studies of antagonist precipitated withdrawal.

So if you get an animal dependent on an opioid and then give a cannabinoid antagonist, you can elicit some withdrawal symptoms, and again, vice versa. There is some substitution for self-administration in preclinical studies, but these studies tend to be a little bit mixed and depends a little bit on the species, the medication, and the dose that you're

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using.

With respect to receptor knockout models or what might be the interplay here, how required is the interaction of these two receptor systems? If you look at models of opioid self-administration and dependence in cannabinoid knockout mice, you can still get self-administration and condition place preference, but it seems to be modulated to some degree. Similarly, cannabinoid models of dependence, they seem to be attenuated in mu opioid knockout mice. So there's some interaction there in terms of modulation of one receptor system and drug abuse on the other.

With regards to analgesia, one of the main pushes for the therapeutic use of cannabinoids within the context of the current opioid crisis is the argument that cannabinoids can replace opioids for treating pain. In preclinical data, we do see evidence of synergistic interactions between cannabinoids and opioids, where you can use smaller subtherapeutic doses of the two medications and get super therapeutic effects.

What's interesting there is that we focus in

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and we really drill down on that analgesic effect, and we're not really looking at the other effects. So one thing that we have to keep in mind going forward is, is there synergy in potential adverse effects and other types of pharmacodynamic effects like impairment?

We do see neurobiological adaptation. If you give chronic high doses of cannabinoids, you see altered expression of the endogenous opioid system; and the same thing if you give chronic doses of opioids, you see altered expression of the endocannabinoid system.

From a mechanistic standpoint, acute administration of cannabinoid agonists have shown to increase the synthesis and release of endogenous opioids, so that might be another way in which dosing of a cannabinoid can modulate the opioid system and maybe help in the treatment of opioid-use disorder.

To summarize this preclinical data, what I think we see are very clear indications from preclinical studies of an interaction between the cannabinoid and opioid systems in our bodies. Both drug types can induce analgesia, and there's evidence

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of substitution effects in preclinical models of drug taking. The mechanism of the analgesia appears to be different. We do see some signals of exogenous cannabinoids modulating opioid effects and endogenous opioid release. But again, there's variability across studies, and we need to see how much that translates from the preclinical to the human work.

I'll take a little bit of time now and talk about some of the human data that we have. There's a study by Donald Abrams that looked at the impact of vaporized cannabis in combination with morphine or oxycodone. This was a lab study with patients maintained on these opioids. What they did is they ran a laboratory session with them before dosing, and then they gave them vaporized cannabis for 5 days, and they ran additional tests.

I don't know if you'll be able to see this, but on the top, up here, these are pain reports by opioid medication. What we see is the difference in pain ratings from day 1 -- this is before cannabis, and day 5 is after 5 days of cannabis -- go down, overall, across the study, and pain is reduced, so the addition

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of cannabinoids to the opioid maintenance doses were comparable across morphine and oxycodone. So cannabis added analgesic efficacy in this patient population.

What's interesting is that here you see morphine plasma levels on day 1 and then on day 5. You can see the addition of the cannabinoid for 5 days reduce plasma levels of morphine, and they're maintained on their stable level of morphine. We didn't see any impact on the pharmacokinetics of oxycodone. This translated to a little bit of a difference in peak subjective ratings of feeling high when they were exposed to cannabis in the laboratory on day 5.

What's important to note here is that when people are taking their opioids, they don't really feel high, but when they smoke cannabis, by and large, yes they do. So something to keep is we're reducing pain, but we're producing a very discriminative drug effect.

Yasmin Hurd has got a lot of press recently for her research looking at cannabidiol all as an impact on opioid-use related outcomes. What she did is a pilot study, then followed by a larger study, looking

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at heroin cue reactivity in the laboratory. In her pilot study, she showed that when showing people heroin-associated cues and given a placebo, you see the appropriate expected increase in craving and cue reactivity to heroin-associated cues versus neutral cues, and that this was attenuated by cannabidiol.

She followed that up and replicated it in a larger study, with longer term exposure to CBD that was just published recently. Here she showing that, again, this is kind of a replication of that pilot study here, where neutral cues do not increase reactivity, but heroin-associated cues do, and you see dose-related suppression of cue reactivity with 400 milligrams of oral CBD and 800 milligrams of oral CBD.

Interestingly enough, this pattern was maintained 24 hours after exposure but seemed to wash out a week later. The other important thing here, in contrast to the Abrams study, you don't see acute self-reported drug effects in this study, and you don't see much in the way of adverse events.

Stacy Gruber has run a longitudinal observational study with patients initiating the

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medicinal use of cannabis up at her lab in Harvard. This is an interesting cohort study, where she's getting people with no history of cannabis use. They're looking to initiate cannabis use for therapeutic purposes for a variety of reasons.

One of the key outcomes from her early work here is that she's seeing a 42 percent reduction in self-reported opioid use, not elimination, but a reduction in dose. In addition to reduction of opioid use, she's seeing reductions in self-reported use of benzodiazepines and a number of other prescription medications and increases in sleep, depression, quality of life, and cognitive functioning.

Now the increase in cognitive functioning can mistakenly be interpreted, in some cases, as being that the cannabis is improving cognitive functioning, but I think if you're reducing opioid and benzodiazepine use, that's probably more likely mechanism.

There have been a couple, really high profile, epidemiological studies, evaluating the rate of opioid overdoses in states that have adopted medical cannabis laws. The first study conducted by some of our

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colleagues at the Hopkins school of public health made a big splash a couple of years ago by showing that medical marijuana states had drastically reduced opioid overdoses after the passage of their medical cannabis laws, but a reanalysis of the same data set by other folks this year, and looking at more recent data, have shown that that trend is actually reversed.

So it's important that when we look and we see data like this, that we think about, carefully, that this is correlational, and that there are a lot of other things happening. And that while early on, we did see a reduction in opioid overdoses and that data is real, there might be other things that were happening at the prevention level, at the treatment level, that might be driving this other than the new availability of medicinal use of cannabis.

Thinking about other kind of big, broad public health impacts of this stuff, there's a study by Shi and colleagues, showing that the rate of hospital admissions related to cannabis and prescription opioids increased dramatically from the period of 1997 to 2014, and that the medicinal cannabis law implementation at

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certain states was associated with a reduction in the number of opioid dependence admissions in those states by 23 percent and prescription opioid overdoses by 13 percent.

So again, this is kind of pointing towards medical cannabis laws having these really positive effects on opioid-related harms, but again, correlational.

Some folks in Australia did an interesting study, where they looked at a community sample of individuals who were prescribed opioids for chronic pain. They found that 16 percent had used cannabis for their pain and an additional 25 percent of this population said that they would use cannabis if it was available to them. So at the time, Australia did not have an active medical cannabis program. They do now, and it's just kind of getting going.

What they found and what they report is that the cannabis users in this population were younger, had greater pain, more pain-related problems, and also had more out-of-control opioid use. Now again, interpretation is tricky here and needs to be evaluated

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carefully. This was a cross-sectional study, and I've seen people look at these data and think, well, the cannabis use is driving up more reckless opioid use, but they're not accounting for the fact that the people who are using cannabis may have been more problematic and had greater pain to begin with.

This was not a longitudinal study, so you can't really look at the individual patient level, whether the addition of cannabis use to the prescription opioids was improving, making things worse, or keeping it the same for these people.

There's another big kind of convenient sample study done in New England, as is Massachusetts, Maine, and a couple of other states up there legalize cannabis for therapeutic purposes, where they interviewed a bunch of people who are using cannabis for their pain, and they said, by and large, most of them said it was really helpful. It was helpful for a variety of pain conditions, and that they had significantly reduced their use of opioids.

This kind of goes in contrast, a little bit, to the National Academy's report that kind of

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identified cannabis as a therapeutic as really being good for neuropathic pain and not necessarily a lot of other pain conditions. The data there is just really a struggle to try to figure out because most of those studies have been done with dronabinol versus cannabis used in any other form, so we're trying to tease all of that stuff apart.

The reduction in opioids is a consistent thing, but I think reduction in opioid dose is different from the elimination of the use of opioids. When this study and Stacey Gruber's study, and in an unpublished study by Mark Ware in Quebec, pretty much the consensus is that you see a reduction in opioid dose but not an elimination of opioid use in chronic pain patients when they introduce cannabis.

To kind of summarize where we're at in terms of clinical and epidemiologic studies on cannabis opioid interactions, there seems to be evidence of substitution of cannabis for opioids in the reduction of opioid use. Cannabidiol has potential for the reduction of craving and anxiety during opioid withdrawal. THC has potential for the reduction of

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withdrawal, but we don't know much about any of the other cannabinoids.

There are these terpenes that are not specific to the cannabis plant that people are all excited about in the cannabis world. While we have a lot of uncontrolled studies, we don't have anything not focused on pain and focused on the treatment of opioid-use disorders, so this is an area that we have really no data to draw on.

With that background, I want to drill in and talk about what I'm supposed to be talking about, so clinical trials, designs and measurements. As I tried to start to think through this, I came up with way more questions than I had answers. So my job here is to create a lot of confusion and make everybody just really think carefully, and I think the discussion tomorrow morning could go on for hours.

Based on what we have and what I've presented there, there are a number of key considerations, and I'm going to go through each of these on separate slides. We'll start with, at what stage of opioid-use disorder do we intervene with cannabinoids? How are we

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thinking about this working in an actual practical place?

Are we thinking about replacing opioids with cannabis for pain to prevent the onset of prescription opioid-use disorders and transition to heroin?

Are we thinking about cannabinoids as a way of suppressing opioid withdrawal in early treatment seeking?

Are we thinking about it as a mechanism of reducing craving and then a relapse prevention measure for people who are already detoxified and out in the world?

Do we promote cannabis as a substitute for illicit opioids? Do we just take a harm reduction approach here and say, you know what? Cannabis isn't great but it's better than heroin. People aren't going to OD. Maybe we should just encourage everybody to just smoke as much weed as they can.

Each one of these approaches requires a completely different approach and has completely different endpoints. We don't have enough time to go through what all the possible outcomes for each of

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these approaches would be, but it's something that we could discuss when we have more time.

The other thing to think about is what do we mean when we say cannabis or cannabinoids for the treatment of opioid-use disorder? As I mentioned before, there are pharmaceutical cannabinoid products. We have up here dronabinol, nabilone, which are a synthetic THC or THC analog products that are FDA approved; oral-dose formulation.

Shown up here is also Epidiolex, which is an oral dose of cannabidiol, and we have Sativex, which is not approved by the FDA in the U.S. but is approved in a number of other markets, which is kind of a balanced, 1-to-1, THC-CBD solution.

So are we thinking about this or are we thinking about this? This is the non-FDA approved cannabis market, which literally is thousands of products and covers all different routes of administration, and has every combination of different cannabinoids -- phytocannabinoids, synthetic cannabinoids -- and terpenes under the sun.

Literally, insanity, but when you think about

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the people who are using cannabis right now, this is what they're using,, not the previous slide. So we have to think about smoked cannabis, vaporized cannabis, oral cannabis, suppositories, transdermals, high THC, high CBD, balanced THC-CBD, CBG, CBN. I could go on.

The issue there is that slide of the current medical retail cannabis, here in D.C. and just north of us in Maryland, the reality is that most of the products are very high-THC, high-potency products. There's not very good quality control or regulation. The consistency from one batch to the next, to the next is not standardized.

There are challenges with dosing. So how do we track this stuff? How much do people use? What's the best route of administration for this? Is it something where they need to inhale it when they feel an acute high craving to use heroin?

If you've got an acute craving, and you've got to swallow an oil, and it takes an hour and a half to take effect, that's not going to be very effective; or are we talking about and thinking about a long-term

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maintenance or reduction of anxiety, or stress, or other antecedents that might trigger opioid use? It might be some combination of these things? We don't know, and we need to figure that out.

Within the retail space, there are issues with contamination and accuracy of labeling. What's actually in the product? Then trying to come up with what an appropriate placebo would be for a lot of those products and who makes it. The companies selling retail cannabis are not making and selling placebos.

With that, how is the product going to be used? Are we thinking about this conceptually as a short-term nicotine patch type thing, where we get you through your withdrawal, and then you stop, or are we thinking of methadone, buprenorphine, a long-term maintenance kind of thing? So again, is this a deal with the difficulties of initial cessation or are we looking at it as a substitute and a long-term maintenance type approach?

Will the cannabinoid products or therapies be used in conjunction with other treatments; and if so, which ones? Do we think that cannabis by itself as a

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standalone can replace heroin as a reinforcer for a lot of people who are struggling with opioid abuse? My guess is probably not. So what else needs to come along with it?

Again, there's this idea of do you use a combination of things? Do you use one cannabis product type in the morning, one at night, one during the day, one for different things? Are we looking to, again, develop a pharmaceutical product that can be prescribed, or are we looking at more of a harm reduction approach just to replace opioids? I think these are really important things.

Then in any of this, it's going to be critical that we evaluate any cannabis product or therapy that's proposed to what the current existing treatments are, but what's the benchmark for evaluating the safety and efficacy of cannabinoids? Is it just cannabis versus placebo? Is it cannabis versus methadone or buprenorphine?

If we just take those first two and use the same product that's got a little bit of efficacy, you're going to come to very different conclusions. If

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you've got a difference in improvement from placebo, but far substandard compared to methadone or buprenorphine, what's going to be your recommendation?

Do we compare it to naltrexone? Naltrexone's got a different safety profile, but nobody likes to take it. THC is reinforcing and rewarding; CBD is not. If CBD ends up attenuating some anxiety and helping craving a little bit, can you get people to take it if it doesn't get you high?

Cannabis to benzodiazepines are other alternative products that are being used that are non-opioids, or opioid related, but not methadone and buprenorphine; so lofexidine, tramadol, kratom, and things like that. Cannabis versus psychosocial treatments; do we look at cannabis alone versus cannabis plus the psychosocial treatment?

So these are all really, really critical questions to figuring out the efficacy of this, but I don't know what's the right approach. So this is going to be complicated, and it's going to ultimately impact, significantly, what the conclusion in doing a clinical trial here.

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Key safety and feasibility concerns. I think, by and large, we can say that for most individuals, cannabis is safer than heroin, but it's not safe, necessarily, and it's not equally safe for all people. My biggest concern, and I've been asked about this a lot of times, is that methadone and buprenorphine have demonstrated capabilities of reducing the likelihood of an opioid overdose because of its pharmacology. Cannabis doesn't. So are we putting people at greater risk of opioid overdose by not giving them an opioid maintenance medication?

There's a high rate of psychiatric comorbidities in people with opioid-use disorders, and we know from really well-conducted studies in cannabis that cannabis can exacerbate psychosis, and long-term use of cannabinoids -- again, THC in this particular case -- can be harmful to the disease progression for people with anxiety or depressive mood disorders.

There's tolerance to the effects of cannabis over time. How likely is this going to be sustained? How high do they have to increase the dose? What's the long-term health ramifications of that? Cannabis-use

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disorder is real. We've studied it for a long time. A lot of people in the room are better experts on that than I am and have been doing it for longer than I have.

So how do we reconcile the likelihood of development of cannabis-use disorder with a high THC product? Is that acceptable with a trade-off of opioid-use disorder?

We've got the cannabis quality control issues, and there are adverse events associated with cannabis use. The other thing at the very bottom here -- I don't know if you can see it -- is there's an increasing concern about drug-drug interactions. I showed you the slide earlier about how cannabis can affect the pharmacokinetics of one opioid and not another.

We don't know enough about this. One of the studies we're trying to do in my lab is a really careful analysis of drug-drug interactions at CYP450 enzymes, and we hope to get that started in January or February of the coming year.

I've mentioned quality control issues. They

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are abundant. We see contaminants. We see improper labeling of all of these products. We need standardization if we want to look at this from a pharmaceutical standpoint. Impacts on cognition. You guys have probably all heard this. Early onset cannabis use can lead to a number of cognitive impairment issues, acutely. Acute doses, high doses of THC impairs working memory, attention, psychomotor functioning; a lot of things that are key for day-to-day functioning.

There's some indication that it's sustained for some period of time for some individuals and earlier onset is worse outcomes. But a number of studies have showed that you can reverse with abstinence, but if you are looking to switch people on to a maintenance medication, what's the impact here? So I think it's something to think about.

Then we have the current regulatory environment, which is super complex. Right now, to summarize as of today, and it will probably be different next week, and different again the next month, and different again next year, cannabis,

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synthetic CBD, and multiple synthetic cannabinoids are all Schedule I in the Controlled Substances Act.

Hemp derived from CBD is now legal. THC exists in both Schedules I, II, and II, depending on the formulation. Terpenes are all legal and mostly are generally recognized as safe by the FDA, but that's all for oral consumption. We're talking in a number of these situations about inhaling the drug, and we don't know the safety or toxicology of those things there. Epidiolex is Schedule V.

So if we're thinking about doing something that's Schedule I, which is a lot of this stuff still, trying to do a phase 2 or higher study in a Schedule I drug is near impossible; so that has to be factored in as well.

What are our key trial types or approaches to this? You've got preclinical, kind of mechanism-oriented studies that still need to be done. A lot have been done, but there's a lot more that can be done specific to treatment of opioid-use disorder. I think longitudinal observational studies of people doing this in the states where it's approved as a

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treatment for opioid-use disorder is something where we can get a signal and maybe get some initial sloppy evidence of efficacy, safety, and type of product used, and route of administration and things like that, that we could then translate into a clinical trial.

We've got human lab studies that were talked about this morning, where we can apply a purchase there to look at reductions in craving, reductions in self administration, in models of safety and efficacy, and then the outpatient RCTs, and, again, phase 4 type modeling kind of goes along with those longitudinal observational studies.

Key trial design features; if we're going to go down this road, my recommendation is you get a standardized product, and you have it manufactured like a pharmaceutical, and we evaluate that product at a specific dose, but allow some flexibility in the dosing, again, as was discussed this morning; because based on the cannabis use history of an individual, you can respond very, very differently to a dose of THC. We've shown in my laboratory that 25 milligrams will take somebody who's not tolerant and send them on a

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crazy, crazy adventure and a daily user barely feels 25 milligrams.

The design should be randomized, placebo controlled. Again, I think a positive control with an evidence-based treatment is important; I just don't know which one it is. We want to have a foundational psychosocial treatment layered on top of a medication so that everybody gets it, and it helps with the placebo control.

We've been one of the folks that have adopted the computerized therapy to avoid Eric's loose cannons. I think any trial needs to be powered for sex differences. In the cannabis world, every time we look for sex differences, we see them. I think the other thing that's important is that any trial needs to be of sufficient duration to carefully evaluate long-term health impacts, relapse, and risks of opioid overdose.

Inclusion/exclusion criteria are key here. Again, the psychiatric disorder comorbidities is a concern. Again, I don't know enough about what kind of impact opioid use has on those, but we do see negative impacts of long-term chronic cannabis use on a number

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of psychiatric disorders.

As I mentioned before, cannabis use history is going to be important for tolerance and dose selection. How do you differentiate use of the therapeutic cannabinoid products from other cannabis use? Cardiovascular health is an impact for high THC products. Drug-drug interactions might impact other medications and then pregnancy. So in the opioid world you do have Andre Jones' work, looking at the safety of buprenorphine and methadone for pregnant women. We don't have that data for cannabis.

In terms of outcome measures, we've got, again, differentiating; being able to differentiate use of the therapeutic cannabis product versus other cannabis use. If you give somebody a high CBD product, and they go off and they smoke a bunch of high THC cannabis throughout the trial, how do you draw any conclusions about that, and can you differentiate your product from other products that they can get on the market or on the illicit market?

We need to evaluate the acceptability of the study drug and study retention. Obviously, you need to

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look at opioid use, but in addition to opioid use, you're looking at craving and withdrawal. And, again, I think the most important thing, aside from opioid use, is the overdose risk; use of other medications, other substance use and substance-use disorder severity, including opioid-use disorder severity, and the development or onset of cannabis-use disorder.

Looking at adverse events, looking at broad health. Again, if we're going to take this substitution approach, we need to be looking at broad health outcomes, both mental and physical health; again, given the risk for anxiety, depression, psychosis, but also looking at quality-of-life functioning, pain, sleep, and things like that if we're looking at more of a harm reduction approach here.

Healthcare utilization; in the opioid-use disorder world, these guys that are chronic heroin users show up to the ER every chance they get. If they switch to cannabis, does that go down or does it stay the same? It'd be interesting as an outcome.

To wrap up and summarize here, can cannabis help with the opioid epidemic? As this guy says,

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"There's nothing wrong with cannabis; it's just all good, right?" So what do know? We know that cannabis is really complex, so it's going to be a challenge to figure out a single product type, a dose, things like that.

It's neither benign nor an ideal from a medicinal standpoint. It's tricky moving from what's currently available in the retail world to a pharmaceutical clinical trials approach. Observational studies suggested it's relatively safe and associated with reduced opioid use. But we need clinical trials. Currently, there's none where opioid-use disorder or opioid use is a primary outcome.

So what do we need to know? Pretty much everything else, which is a lot. My recommendation, as far as where we go from here, is that we try to funnel money into more preclinical work, evaluating these mechanisms and interactions; do more observational studies to look at how things are playing out in the world right now because things are happening in the natural laboratory; that anything moving forward should have appropriate product standards.

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We want to minimize unwanted adverse effects; so again, thinking about daily functioning and people. You don't want to give them a whole bunch of really high doses of THC, and that we have to evaluate comparative efficacy with other effective treatments. And that's it.

(Applause.)

DR. VANDREY: I think I'm down to two seconds.

DR. STRAIN: That was great. Thank you, Ryan.

Staying on time, we're going to move on, but we do have some time for discussion later. I think our heads are going to explode with all the questions that Ryan has put out.

Our next speaker is Dr. Andrew Huhn, who's going to be talking about sleep aids. Andrew, take it away.

Presentation - Andrew Huhn

DR. HUHN: Thank you, Dr. Strain.

About an hour after we've had lunch, it's a good time to either go to sleep or talk about sleep.

(Laughter.)

DR. HUHN: So some of you might be interested

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in listening about it, and some of you might do the former; I'm not really sure.

My research is focused treatment outcomes for opioid-use disorder, generally predictive models of relapse risk. Through that research, I've become interested more broadly in what treatment outcomes are, not just opioid relapse or continued drug use, but also mental health, general health, and quality of life. Sleep affects all of those things, and I think in its own right could be a treatment outcome.

This is an outline of the next 45 minutes of your life. First, we're going to talk about OUD treatment options. We'll talk about outcomes for sleep medications and clinical trial designs for sleep medications. As I'm imagining, most of us in the room are experts in addiction and might not double over as experts in sleep medicine, as well; how can we incorporate sleep measures into OUD clinical trials; the role of sleep and stress and treatment outcomes for opioid-use disorder; and then some non opioid receptor targets that could also treat sleep disturbance.

This is treatment in America right now for

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opioid-use disorder. It's like one of those choose your own adventure books. Remember those? If I'm a person who is suspected to have diabetes, I know what to do. I go to my primary care physician. He or she can probably manage my diabetes, and if it's kind of out of control, I might go to an endocrinologist; but the point of entry into treatment and what happens next is all clearly laid out. That's really not the case for people with opioid-use disorder, and it varies wildly based on where you are geographically and state level policy.

There's the big three medications for opioid-use disorder: buprenorphine, methadone, and extended-release naltrexone. People might also opt not to use any medication for opioid-use disorder. In fact, a lot of people opt not to use that, and they go straight into 12-step meetings or other kinds of counseling. There's residential or hospital-based treatment facilities, 1-on-1 counseling or psychiatry.

Most of these options have different treatment philosophies. It makes it challenging to think about -- especially for something like sleep

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medication, even like a treatment for depression, et cetera, and how does that work into this, into what's currently going on?

This is perhaps a more orderly way to look at it. For somebody with opioid-use disorder, they're either going to go on opioid maintenance therapy or they're going to go through opioid withdrawal. We know that the majority of people going into treatment are not getting opioid maintenance therapy at this time. I think that's changing for the better, but it's maybe not changing quickly enough.

On top of the different medications that act directly on the mu opioid receptor, there's also different levels of care, intensity of treatment. Some of those are around-the-clock supervision like you might find in an inpatient or residential setting; outpatient group counseling. Some people will go through opioid withdrawal and just do meetings -- [inaudible - mic fades] -- what the community's recommending right now because it's not been too successful, but that is a reality out there.

The different treatment options, especially

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the medications for opioid-use disorder, we don't know a lot about how these impact biological systems that might in turn impact treatment outcomes or the propensity to continue drug use or relapse, and of course, sleep falls into this.

We know a lot about opioid-use disorder and stress, that there's increased stress reactivity, especially early in recovery, that stress is an issue. There's not as much research about sleep and opioid-use disorder, but there is a clear connection between stress and sleep, and especially via the hypothalamic pituitary axis, which follows a [indiscernible] rhythm throughout the day.

Your cortisol levels, which is the downstream product of the HPA-axis, are highest when you wake up in the morning. They fall throughout the day, and they get lowest right after you go to sleep at night, and then they build up in your system, and that helps you wake up again in the morning.

There's plenty of research on stress reactivity in OUD and practically no research on circadian rhythms in OUD. Here's what we do know. An

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acute dose of an opioid reduces subjective feelings of stress, produces HPA-axis signaling, and interestingly disrupts sleep architecture. Even though, generally, if you were taking an opioid, like in an acute situation, that might be to relieve pain, so thus you might actually sleep better in that one instance. Your sleep architecture is disrupted.

But chronic opioid use increases stress reactivity, and I'll say alters HPA-axis function. So it could increase HPA-axis signaling. It could also flatten out the curve so that your cortisol levels are lower in the morning and higher in the evening. There's persistent sleep disturbance in this population. There are very few studies about sleep quantity and quality in OUD.

This is data from a study done by Kelly Dunn out at Ashley Addiction Treatment, which is a residential facility. We just ask people coming in to fill out the brief addiction monitor and looked at sleep disturbance in the past 30 days as it related to opioid use for the past 30 day, and, in fact, there was a correlation between those two. So more opioid use is

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more sleep disturbance.

There's also a very strong correlation between sleep disturbance, feelings of depression, and anxiety and anger in the past 30 days. These things likely have a cumulative effect. Anxiety and depression disrupts sleep, makes it harder to sleep, and then that in turn makes you feel worse the next day.

This was kind of a retrospective analysis of a first pass attempt. Medications for sleep studies, in general, have much better defined outcomes probably than we have in studies of opioid-use disorder. It's probably worthwhile to go over what some of those outcomes are.

If you just take a minute and think about your actual experience of sleep, usually you get ready to go to bed at night. You turn out the lights. You actually get into bed. You don't fall asleep instantly, at least probably not. There's some kind of period of time that you get into, and then you actually fall asleep. You might wake up in the middle of the night once or twice, get up, and get out of bed in the morning.

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Total sleep time refers to the total amount of time that you slept in that time that you attempted to go to sleep and the time that you actually got out of bed. Sleep onset latency is defined as the period of time from when you get into bed with the intent to sleep until you actually fall asleep. This is a target of many trials for people who have a hard time falling asleep at night.

Wake after sleep onset could be the number of awakenings after sleep onset. Some people get up repeatedly throughout the night. There's, of course, age-related effects with this as well, so this happens as we get older; also, the total amount of time you spent awake after you initiated sleep.

Sleep efficiency is the percent of time you were asleep versus the total time you were in bed. There are more biological outcomes like sleep architecture, time in each phase of sleep, time in REM sleep, and time in deep sleep. Sleep apnea, of course, is a major outcome. It could be obstructive versus central apnea, obstructive apnea, happening usually due to difficulty breathing and oftentimes due to obesity.

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Central sleep apnea actually can be caused by chronic opioid use, and it's generally associated with some other disease state. Then of, course, is your sleep actually restful? Do you feel good the next day when you wake up? Are you able to stay awake throughout the day or do you have chronic daytime sleepiness?

There are also several ways to measure sleep. Many of these could be easily incorporated into trials for opioid-use disorder that aren't even focused on sleep as secondary analysis, and of course many of these can be used for trials of sleep medications for folks with OUD.

I want to go through these one by one. Polysomnography is really the gold standard in assessing sleep. Polysomnography studies are generally done in one night, maybe two. It's inpatient. There are a bunch of wires hooked up. It's fully EEG, monitor breathing, monitor respiration with this belt, pulse, blood oxygenation all through the night.

The level of data you get from this is really deep, but the actual, I don't know, ecological validity is a little bit questionable because you don't usually sleep with a whole bunch of wires hooked to you; at least I don't sleep like that, but very good for mechanistic studies; probably not something you're going to do repeatedly night after night.

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Perhaps an easier way is to use a sleep profiler, which is a headband that can be worn. It has three EEG leads. It can be accompanied by the same kind of breathing monitoring, respiration monitoring, and pulse ox. It doesn't have to be. We're using these in our lab. We don't use any of this stuff; we just use the headband. I've actually tried it before. It's fairly comfortable. I was a little bit worried about that, but once you get it on, after about 10 or 15 minutes, you kind of forget that it's on. That's, again, kind of a gold standard to monitor sleep. Again, you get sleep architecture with that as well.

A secondary measure of sleep that's also good because it's objective is to use wrist-worn actigraphy. There are of course companies that make -- like Fitbit, Apple watch, these have applications that automatically monitor your sleep. The downside of using these in a research study, to my knowledge, most of these applications, they just autoscore your sleep, so there's no ability for you as a researcher to go in and set your own parameters for what you define as time asleep and time awake. We've typically use these actigraphs that give us more options with the data, and we set our criteria before the study of what counts as sleep and what doesn't.

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These are super easy to wear. It's just like wearing a watch. You could wear it all day, and then you would also have an idea of how much activity the participant had during the day, which can be another useful outcome. They can also track room lighting so you know if the lights are on or off.

Pretty much every sleep study is accompanied with a sleep diary, so not only the objective measures of sleep, but also subjective measures of sleep are important. They oftentimes don't match up. Sometimes people think they sleep more than they do. Sometimes people think they sleep less than they do; but still good to use as an anchoring point. Here, I just have a really -- this is like a super basic sleep diary and

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what that might look like; what time did you go to bed; what time did you get up in the morning; did you wake up at all; and how restful did you feel?

Some of our sleep studies, we're using a much more detailed sleep diary, and you can find several examples of these in different trials.

We've also used ecological momentary assessments to measure sleep. EMA has briefly delivered surveys that are given throughout the day, generally on a smartphone. You can ask all sorts of questions with these. You can actually incorporate a sleep diary into EMA assessments. You can incorporate measures of daytime sleepiness into ecological momentary assessments and nighttime sleep diaries. This can further be used not only to look at sleep but also this complex relationship between sleep, mood, stress, craving, et cetera.

The EMA is becoming, I think, more common in trials of opioid-use disorder because you can get a lot of data and I think have a much more granular understanding of what's going on with your participants compared to a traditional trial design; where maybe

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they're coming back once a week to give a urine sample and fill out a couple of questionnaires, here you're sampling them throughout the day, and it eliminates recall bias, which is a problem with folks with opioid-use disorder as well.

There are other wearable technologies that are making it onto the market for sleep as well. One is Oura Ring. This is literally like a ring that you wear. It has an accelerometer like an actograph. It also measures pulse, which could be an important secondary outcome and could be a secondary measure of stress throughout the day.

There's a new one called the Watchpat. This one's actually pretty interesting. The base of it has actigraphy just like the actographs that I showed earlier, but it also has this finger cover that measures oxygen saturation and peripheral arterial tone. You can't get full sleep architecture from the Watchpat, but you can get time in deep sleep, and you can also get apnea events throughout the night. So it adds a few more outcome variables to your study and gives you actually a pretty robust number of outcomes

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for how low maintenance it is.

I will say that I've actually tried this before, too, and I found it a little bit disturbing because to get the peripheral arterial tone, it tightens around your finger periodically through the night, and that was a little bit disruptive to me, but it's another option.

Of course there are retrospective questionnaires. Most commonly used is the Pittsburgh Sleep Quality index, and that's like a measure of past 30 days sleep. This has been used in thousands of studies, literally. If you look up the PSQI, you'll see thousands of citations for that one paper. Beyond that, there's the Stanford Sleepiness Scale, Epworth Sleepiness Scale. These measure daytime sleepiness. These are pretty low maintenance to work in. Your study doesn't have to actually be on sleep for you to give these and be able to compare that to other research.

Clinical trial designs for sleep medications follow the same general designs as we use for medications for opioid-use disorder. After you get

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past phase 1, there's typically a dose-finding study versus placebo to see which dose is most effective, and then there's usually a larger trial that's active sleep medication versus placebo. Then you might see a series of studies that puts one active sleep medication versus another, either within the same class, so like a benzodiazepine versus a benzodiazepine, or maybe a melatonin receptor agonist versus a benzodiazepine to look at the relative effectiveness and also side effect profile.

Other things to consider in studies on sleep and clinical trials for sleep medication is the time duration of the study, so how long do you actually want to put somebody on this sleep medication. This actually varies quite a bit in the sleep literature.

You see some trials that are very short, only a few weeks. You see other trials that are up to a year on multiple doses of a sleep medication to see if there's any long-term effects of that medication. It reminds you somewhat of trials on opioid-use disorder as well, but I feel like we don't have as many studies that go out to a year. Most of our outcomes are like

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3-month outcomes, and that's the most typical.
It's also important to consider the environment. Did these folks live at home? Are they homeless? Are they inpatient? How does that affect their sleep and other secondary outcomes? Do you allow self-titration in the study; so can people up their dose? Can they reduce their dose if they don't like the side effects? What's the relationship to stress? Also, I think importantly for studies in opioid-use disorder, what's the relationship to relapse? Relapse is still our primary outcome for most trials.
I'm going to talk about a couple of studies that I've been involved in, where we did measure sleep; one we did in an inpatient facility in Pennsylvania called Caron Treatment Center. It's important to put this in context because Caron is a residential facility. They have a primary care unit where patients can stay for 28 days, and then after that, some patients will go on to stay for an additional 90 days inpatient; not the typical experience for somebody with opioid-use disorder, which is usually outpatient therapy but still can get some interesting data like

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the biological outcomes.
Before we did a larger trial, there was a pilot sleep study, where we had 7 control participants, 7 participants in the primary care, and 7 participants in extended care; a cross-sectional. What we found was that people in primary care had reduced sleep time in bed in total sleep time compared to controls, and then out at about the 4-month mark, they looked more like controls. So there appeared to be some natural reregulation of sleep.
This went into a larger trial, where we had 77 patients who went through the primary care, and then their numbers dropped off quite a bit. So only 22 made it into the second month of treatment and 11 made it into the third month of treatment. We had 40 age- and gender-matched controls.
This had a longitudinal design. We termed the time that we were collecting data to be a data burst. This happened over a 12-day period after they had already gone through withdrawal. For 12 days, folks did ecological momentary assessments 4 times a day. They had wrist-worn actigraphy. They filled out sleep

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diaries every morning.
Within that 12-day period for 3 days, we took samples of salivary cortisol at 4 points throughout the day so we could look at diurnal rhythms of cortisol. Then within that, we did a neurophysiology session, which I'm not going to talk about; but I'm happy to talk about if anybody asks me later.
The first data burst happened about 15 to 27 days after they had entered treatments, so they're all the way through withdrawal. The second data burst was in month 2; third data burst month 4, and then we followed up with some of these patients for 90 days after they left treatment to determine if they relapsed or not.
This data is under review right now. This is data from 96 patients and controls. It's cortisol throughout the day. In the first month of treatment, you can see that at every time point, cortisol is higher in the OUD patients than it is in controls. I think one of the things we're really interested in was does this HPA-axis reregulate, or is there at least some evidence of that? And that is what we found.

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The end of this drops off, so I just pulled out the subset that actually gave three time points of data with and N of 7. This matches up, too, if I include all the patients in each time point. By the fourth month of treatment, they look a lot like the healthy controls. So what I can tell you is that for folks with opioid-use disorder who are in a structured environment and they have a set bedtime every night, that there does appear to be a reregulation of the HPA-axis over time.
How does this relate to opioid relapse? That's always the big question. For some of these folks that we were able to actually get relapsed outcome data on, there are interesting findings. For people who relapse, the predictive models for like their sleep in month 1 of treatment didn't really predict relapse at all. But for those people who had persistent sleep disturbance into month 2, those were the folks who went back out in the community and used.
Folks who abstained from opioids where the folks who their sleep improved over time, so it could be a protective effect of sleep in this population.

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Cortisol followed the same general pattern. Folks who abstained, their cortisol levels went down over time. Folks who relapsed, their cortisol levels went up over time. It's a small sample size and, of course, with the caveat that these folks are in residential treatment when we're actually taking the measures, but at least good initial evidence that both sleep and stress are important treatment outcomes for folks with OUD.

We also did an ecological momentary assessment study in these folks, where we were asking questions about sleep and also questions about craving and positive affect throughout the day. Of course, sleep quality was directly associated with increased drug craving on a daily basis, and this was partially mediated by low positive affect or feelings of anhedonia.

Essentially, there's this relationship that sleep quality directly is associated with drug craving but also is associated with mood and affect, which is in turn associated with craving. Then the next question, which we weren't able to answer in this

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study, is does all that translate into relapse; and is this kind of an endophenotype, if you will, for folks who are going to go out and relapse?

Also, some of my colleagues have collected data on sleep disturbance during opioid withdrawal. In several of the withdrawal studies that we've done at Johns Hopkins, we've note that folks who are going through the worst withdrawal are also the ones who can't sleep. As soon as they go a night or maybe two nights without sleep, or with very little sleep, those are the folks who leave the treatment study. Anecdotally, we can tell you that sleep disturbance is a driving factor for treatment attrition during opioid withdrawal.

In this, we plotted self-reported withdrawal on the SOWS versus mean minutes night slept per night as measured by the sleep profiler, the headband. At the point where they actually start the taper, withdrawal shoots up and sleep goes down, and then there's some rebound sleep. Then as they get towards the end of the taper again, the sleep is disturbed, relapse, and sleep is disturbed. In association, at

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least within a withdrawal study, again, the low end, but that sleep is associated with the level of withdrawal.

This is data from another study done by Stacey Sigmon and Kelly Dunn, where they were looking at the length of buprenorphine taper. Folks with the 4-week taper had the best sleep, and those folks were also less likely to relapse than folks with a 1 or 2-week taper.

Excuse my voice. It's clearly giving out on me at this point, but we're going to power through.

Kind of circling back into this treatment trajectory, given the limited information we have, if you were looking at doing a clinical trial on a sleep medication in folks with OUD, there might be big differences in their sleep disturbance during opioid withdrawal versus during opioid agonist maintenance therapy; also, depending on the amount of time that they've been in treatment and are they stable yet.

So making decisions about where, if you were to introduce a sleep medication, where in the treatment trajectory would you introduce it? At what dose would

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you introduce it? How would you expect that to affect treatment retention and also relapse?

In general, thinking about what kind of sleep aids might be useful for these folks, benzodiazepines aren't usually used in clinical practice, at least not with the people that we work with. Benzos have a high abuse liability. There's also an increased risk that if people co-use benzos and opioids that they're going to overdose because of respiratory depression. Because of that, sleep aids for people with opioid-use disorder include melatonin, hydroxizine, trazodone, and sometimes off-label, heavier drugs like Remeron.

Thinking, too, about which neurotransmitter systems to target in these clinical trials, NIDA published this paper earlier this year about the 10 most wanted; non-opioid neurotransmitter systems that are of interest for medications development for people with OUD. Some of these, there are sleep medications that act directly on these and could be a good way to directly address the issues in OUD, and also indirectly address it by improving sleep, which might in turn improve treatment outcomes.

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One of the neurotransmitter systems that we've been really interested in is orexin system. The orexin system is actually really interesting. There's only 10[000] or 20,000 orexin-producing neurons in your brain, and they're pretty much all in the lateral hypothalamus.

It's a very discrete system. They project to several different areas of the brain stem, the reward system, but not a neurotransmitter system that's talked about very often in clinical practice because up until recently, there's been no FDA-approved drug that actually acts on the orexin system, and there are no PET ligands that are available to look at this system in humans.

So most of the literature comes from preclinical, but it's a very important neurotransmitter system. It's involved in regulating wakefulness, food and drink, and consequently drug consumption, and also mood.

It follows a circadian rhythm, a lot like the HPA-axis. Actually, within the sleep cycle, orexin signaling is almost nonexistent during REM sleep. So

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not only does it regulate your wakefulness during the day, but it also regulates your movement through stages of sleep throughout the night.

There are two orexin receptors and two orexin neurotransmitters. Orexin A acts on both, but mostly acts on OX1R. That has more influence over consumption behaviors and natural reward, so might have implications for opioid craving and the motivation to use drugs.

OX2R has more influence on wakefulness, so perhaps drug-seeking behaviors but also sleep disturbance. There's a complex and reciprocal relationship between the orexin system and the HPA-axis, which I'm not going to get into the details. But over time, increased stress signaling will increase orexin signaling, and these probably exacerbate each other.

There's this whole host of preclinical literature that looks at the orexin system in opioid-use disorder. In preclinical models, orexin is involved in opioid tolerance, and drug cue reinstatement, and there's a dozen or more studies on

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orexin and opioid withdrawal. So if you give a rat going through withdrawal an orexin antagonist, it will greatly reduce their withdrawal.

The only real published research on this system in humans is a postmortem study that was published last year, and it showed that people who were long-term heroin users, compared to age and gender-match controls, had 50 percent more orexinergic neurons in their hypothalamus, and then they back translated that to a mouse model and showed that it was indeed true in a preclinical model as well. So orexin is a clear target, I think, for sleep trials for opioid-use disorder.

You could also consider serotonin. Serotonin is directly involved in the sleep-wake cycle. Depletion of serotonin is associated with fragmented sleep and, of course, also depressive symptoms, which are highly prevalent in folks with opioid-use disorder. I only know of one clinical trial that's looked at a serotonin agent for sleep and that's trazodone. It was done by the Stein group, mostly negative results.

It was in methadone patients. It could be

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that chronic methadone disrupts sleep and trazodone wasn't enough to overcome that. It could be that you need higher doses of trazodone or that trazodone might work better in folks who are using naltrexone versus methadone.

There are also other agents that are tricyclics and antipsychotics. Some of these have heavy side effects but potential targets because they also work on the serotonin system in addition to several other neurotransmitter systems. But they do cause sedation. Some like doxepin and quetiapine are often prescribed for sleep.

Melatonin is another potential target. Melatonin is a hormone that regulates the sleep-wake cycle. Melatonin, of course, is available over the counter. The question is whether melatonin would be strong enough to help sleep disturbance in these folks. There's also ramelteon, which is a newly approved melatonin receptor agonist that could be of interest.

You don't have to use medication to treat sleep. There's also cognitive behavioral therapy. For insomnia, this has been shown effective in several

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studies, and it might be relevant to folks with OUD, especially people who are already in recovery, as a tool for relapse prevention, improving sleep and generally improving health and mental health outcomes.

We do have a couple of ongoing studies with people with opioid-use disorder. These are clinical trials on suvorexant. Suvorexant is a dual orexin receptor antagonist. The first study we have uses suvorexant during opioid withdrawal. We're examining the effect on sleep, of course, but also whether it reduces withdrawal and addresses some of the issues with craving and mood. I'm not blinding us to the actual drug, but I'm binding us to the doses. You can probably guess that one dose is higher than the other, but you'll have to wait to see which doses we use until the end.

This is a dose-finding study. It's three arms, so people would get either suvorexant low dose, high dose, or placebo. First, they come in and they get stabilized -- this is all inpatient -- for 3 days on buprenorphine, and then they have a 4-day taper, and then a 4-day post-taper period. We start the

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suvorexant right before the taper.

In this one, we're using the sleep profiler to monitor sleep architecture, actigraphy as a secondary measure of sleep, and, of course, sleep diaries as measures of daytime sleepiness. It's a way to follow what's a traditional clinical trial for an opioid withdrawal medication, but with the twist that it's a sleep medication, and that this is a really significant problem for folks with OUD.

The second study we have is looking at sleep during opioid recovery. Again, we're using suvorexant in this trial as a probe of the orexin system. This trial is for people who are either on methadone or extended-release naltrexone. It was kind of conceptualized as a mechanistic study, not just to look at suvorexant but also to look at a full agonist versus antagonist medication-assisted treatment and how that might impact sleep and stress.

For folks coming into the study, they have to be abstinent from opioids for 3 to 6 weeks. So we're getting people who have some initial success in treatment and looking at this in terms of relapse

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prevention. I don't personally think a sleep medication on its own is going to affect drug use behaviors enough to get people off of opioids, but as a way to tip the scales in their favor. For relapse prevention, I think it could be very useful.

The aims we're looking at here are the relationship between orexin signaling and sleep disturbance in OUD and also orexin signaling and diurnal measures of stress. People are going to be out in the community. This is an outpatient study. They'll be wearing actigraphy every day, doing ecological momentary assessments, and giving salivary cortisol samples throughout the trial, then also, to look at the relationship between sleep and stress on treatment outcomes in people who are in recovery and actually in the community.

This is the kind of rough design of the study. Folks will come in and do a screening visit. We'll do what we term, again, a data burst, where they're doing ecological momentary assessments for 7 days and also giving salivary cortisol for 3 days within that 7 days before they start taking the study medication, then

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they'll be randomized to either suvorexant or placebo for an 8-week trial. Once weekly, they'll come in and do an outcomes assessment with us and also monitoring through the smartphone.

So we covered a lot. My voice didn't hold up through the whole thing, but we did make it through. Sleep disturbance is a big issue in people with opioid-use disorder. We see this firsthand. Patients are reporting this to us anecdotally. The FDA has had a patient listening session, where it was brought to light that sleep disturbance is a major issue, in addition to craving and anxiety. These were things that people wanted treatments for.

It's a big issue in withdrawal, especially for folks who are in very severe withdrawal and can't sleep for one or two nights at a time. Sleep assessments on their own, especially the self-reported stuff could easily be incorporated into clinical trials for OUD medications and doesn't have to be a sleep trial to incorporate some of these measures and start recording this stuff across several different studies. But then I also think -- and I think this because I'm doing

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it -- that sleep is really important, and it should be actually be the focus of clinical trials in this population.

With that, I'm done. I think I have a couple minutes if there are any questions.

(Applause.)

DR. STRAIN: Thanks, Andrew.

There's a question in the back. I can't see who it is. Can you identify?

DR. HENDRICKS: It's Peter Hendricks, UAB. I think I have a question that dovetails with what Patrick asked a bit earlier. And that is, I'm curious what we know about pain and how that might relate to sleep disturbance. I think, Patrick, you're an expert in his, so I probably shouldn't say much more, but it's just interesting that we don't know much about that, from what I can tell.

DR. HUHN: Patrick's the pain guy.

DR. STRAIN: What is your question?

DR. HENDRICKS: I think there's an emerging literature on not just opioids and pain, but a range of addictive substances and pain and how there could be a

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reciprocal relationship there. I'm curious if pain could be a mediator of this relationship; in other words, if people are having trouble sleeping because they're in pain. This is regardless of whether chronic pain is there. It seems likely or possible that pain would be an issue even for those who don't have a chronic pain condition.

DR. FINAN: These are great observations. I can tell you what we know, pretty well, at this point in the sleep and pain field, is that, yes, sleep and pain are definitely reciprocally related. In the past decade, we've started to learn that there appears to be more of a predominant focus in the data that's being presented on sleep disturbances driving pain problems to a greater extent than the reverse.

It's definitely not a unidirectional relationship, and we'll see both patterns, but as longitudinal designs, EMA designs, cross-panel analyses have become more prominent in the literature. We're seeing this kind of more consistent effect of sleep problems begetting pain problems.

So if we're thinking about how to

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conceptualize mediators versus moderators, I think you're on the right track there to think that pain may be an important mediator in the relationship between sleep disturbance and opioid-use outcomes.

DR. STRAIN: Interesting. Thanks.

Kelly?

DR. DUNN: It's Kelly Dunn. I'll just add that I think it's notable that sleep disturbance is one of the few symptoms that is evident across all forms of drug withdrawal. It seems that there's this kind of underlying mechanism. I don't know that the opioid field knows enough about the relationship in terms of whether or not sleep contributes to withdrawal severity or if withdrawal severity contributes to sleep problems, but it certainly seems that there's value, and that there would be cross-translation across drug classes.

DR. STRAIN: Tom, did you have a question?

DR. KOSTEN: It's a practical question. I don't know if those are allowed here.

DR. STRAIN: Absolutely.

DR. KOSTEN: Okay. The sleep profiler itself,

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how good an outcome did the FDA say it was? And then, how much does it cost?

DR. HUHN: Definitely, it's an acceptable outcome measure for a clinical trial and a sleep medication. Actually, wrist-worn actigraphy is an acceptable outcome for a clinical trial and a sleep medication.

DR. KOSTEN: I was thinking about it mostly in terms of the withdrawal phase; that risk outcomes on the withdrawal phase are a little problematic --

DR. HUHN: Right, tough, yes.

DR. KOSTEN: -- and bounce around. But the sleep profile is a whole lot easier than the usual EEG.

DR. HUHN: Yes. We couldn't do that for somebody in withdrawal, like a whole polysomnography. It wouldn't happen.

DR. KOSTEN: I saw where you're using it in withdrawal, and it was showing a pretty big effect.

DR. HUHN: Yes. They're not that -- I don't know, 8 grand, maybe, for one. I'm not sure.

DR. KOSTEN: That's knowledge --

DR. HUHN: Yes, I think so; something like

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that.
DR. KOSTEN: That's my practical question.
DR. STRAIN: Kurt?
DR. RASMUSSEN: Just to follow up on Kelly's point, it's well known that chronic morphine will increase the orexin system in animals and in man, but also chronic administration of cocaine will also increase the orexin system, the number of orexin-producing neurons. There's a chance that suvorexant and other orexin antagonists could have useful utility and stimulate use disorder as well.
DR. STRAIN: Thanks. Patrick?
DR. FINAN: I'm wondering if we could talk a little bit about suvorexant dosing and get some -- we don't have to talk about the dosing that is blinded here, but if you talk with sleep clinicians who are prescribing sleep aids, a common refrain is that suvorexant thus far has not been very effective in practice, and that many clinicians will not prescribe it.
The culprit that you'll hear is that the FDA has only approved a lower dose, the 20-milligram dose

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that is not as effective in treating sleep as the 40-milligram dose, which was seen as more effective in earlier trials but also had more adverse events that prevented it from getting approved.
So I wanted to see if anybody had thoughts on that, practically speaking.
DR. HUHN: Just to add to that, one issue is suvorexant has a relatively long half-life, so the higher dosing -- and it has, actually, a pretty safe and mild side effect profile. But one issue is that with that long half-life, there's next-day drowsiness, and that was the issue with the larger dose. Although, it's common across sleep medications, anyways. The safety profile is much greater than that, like benzodiazepines. That would be the competition for a suvorexant level medication.
DR. STRAIN: I've prescribed it clinically. When it came out, I was all excited because it was a non-benzo, and it's supposed to have a different mechanism of action and stuff. I think I'd say probably about a quarter to a third of the patients that I've tried it with have responded. It's not been

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as robust as -- you know, everybody likes Ambien; at least in my prescribing of it.
DR. LEVIN: That's what Roger and I were just saying to each other, quietly.
DR. STRAIN: About a quarter to a third.
DR. LEVIN: Maybe.
MALE VOICE: At best.
DR. LEVIN: At best. I use a lot more. I use a lot more trazodone than I do that, in higher does. I don't know what doses you were saying you needed to go on that slide, but --
DR. HUHN: Trazodone?
DR. LEVIN: Yes.
DR. HUHN: He started at 75 and went up to 150, but I know in different scenarios, we've used up to 300.
DR. LEVIN: Yes.
DR. STRAIN: Do you have a sense that the limited efficacy is due to perhaps the dosing or do --
DR. FINAN: People start at 20 milligrams. I never asked the question, except talk to --
DR. STRAIN: Initially when it came out, it

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was really hard to get prior auths on it, which was a pain, so that probably discouraged some. And I'll stop on this story, and it's just an anecdote. I've got a guy -- I didn't do this -- he was on 3 milligrams of Klonopin to sleep at night. I started him on it, and he's down to 1 and a half of Klonopin, and intends to keep titrating down; otherwise, a well-functioning guy.
DR. KOSTEN: Can I ask one practical question? You said there were 50 percent greater orexin responsive cells --
DR. HUHN: Um-hmm.
DR. KOSTEN: -- in opioid addicts. Does that have a practical impact that orexin might work a whole lot better in opioid addicts?
DR. HUHN: That's the thought. If increased orexin signaling is ubiquitous in folks with opioid-use disorder, then an antagonist might kind of kill two birds with one stone. It might help you sleep, and it might improve other outcomes as well.
DR. KOSTEN: Right now, whenever we do detoxes -- I hate to admit this, but clonidine doesn't work that perfectly, and we typically add a

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benzodiazepine to it. I'd be happier adding orexin to it than a benzodiazepine.
DR. STRAIN: Kurt?
DR. RASMUSSEN: So that addresses the dose question as well. Suvorexant, my understanding is 40 is a much more efficacious dose for sleep, but there's some daytime sleepiness, and that that's problematic. However, in this OUD population, where it's clear that the number of orexin-producing cells is increased by 50 percent, no wonder they can't sleep.
The orexin is a lower drive, first of all, but to me, it would indicate that a higher dose may be needed in the OUD patient population. So that dose of 40, with any luck, will be more effective and less problematic in this patient population.
I'll also point out there are two other non-selective orexin antagonists in development. They're in phase 3. These companies are eager to get these on the market and looking to differentiate them. We're in discussions with both of them. So there could be more choices soon for orexin antagonists.
DR. STRAIN: Okay. We've gone over thanks.

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Thanks, Andrew. We're going to take a break. Let's reconvene, though, in 10 minutes, and really nice looking snacks out there.
(Whereupon, at 2:20 p.m., a recess was taken.)
DR. STRAIN: We're going to get started. We have two more talks. These last two talks, actually, is a tag teaming. The first one on psychedelics will be Roland Griffiths for about 15 minutes, then Matt Johnson will finish out with the last 30 minutes, and then we'll do vaccines, which will be Sandy Comer for about a half hour or so, and the last 10 minutes will be Marco.
So without further ado, Roland Griffiths will start on psychedelic.
Presentation - Roland Griffiths
DR. GRIFFITHS: Thanks, Eric.
As Eric said, Matt and I have been working with psychedelics together for the last 15 years. This is a tag team effort. I'm going to give a background, and Matt's going to go into psychedelics and drug-use disorder treatment and opiates.
Just by way of background, we're talking about

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the classic psychedelics. These are serotonergic mediated compounds that produce this unique profile in changes of thoughts, moods, and emotions. Among the classic psychedelics are psilocybin, DMT, mescaline, and LSD. Historically, there was a lot of research done with these compounds back in the '50s and '60s, then this research went largely dormant and has been reinitiated in recent years.
Just where we sit with the classic psychedelics -- and I'm going to refer to psilocybin here because that's what we've worked with mostly, but this is true of all of the classics -- these drugs are classified as Schedule I compounds. They're not considered to be drugs of addiction by NIDA. They don't produce compulsive drug-seeking behavior.
Medical emergencies are incredibly low in the DAWN epidemiological network databases. However, concern about adverse effects is nonetheless there because of engaging in panic reactions, dangerous behavior, and possible precipitation of enduring psychiatric conditions.
At Hopkins, the last 20 years, we've completed

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a variety of studies in healthy volunteers, in novice and long-term meditators, and religious professionals. I'm going to talk a little about depressed and anxious cancer patients and major depression to illustrate this work. I'm also going to illustrate what we do and show you some data with healthy volunteers, and then Matt will talk about cigarette smoking and the addictions. To date, we now have treated over 370 participants. We've had over 700 sessions, so we've had quite a good bit of uh, experience with these compounds.
With respect to healthy volunteers, these are rigorous, double-blind studies. Participants were medically psychiatrically healthy. Most were without any histories of prior psychedelic use. They meet with our monitors or session monitors for about 8 contact hours prior to the first session to build rapport and trust.
Sessions are conducted in a living room like environment. Participants come in. We encourage them to lay on the couch throughout the session in the presence of two session monitors, who are there just to provide reassurance should people feel anxious. So

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this isn't a guided session per se. It's not psychotherapy as such. We're asking people to go in and have their own inner experience.

Under these conditions, this just shows the dose and time effects with psilocybin over the course of a 6- session. You can see onset occurs in about 30 minutes. Effects peak at 2 or 3 hours, and taper off over the afternoon. By the end of the session day, the volunteers are released into the care of a friend or family member that accompany them home.

The qualities of these experiences are varied and substantial. Two of the elements that we think are most interesting and may be related to the therapeutic effects of these drugs are these drugs produce -- and this is post-session ratings of mystical type experiences and psychological insightful experiences.

These are dose effects in healthy volunteers. Their quality is particularly of the so-called mystical experience. There's a sense of the interconnectedness of everything. That is felt to be precious. Some people would use sacred. It's also felt to be authentically true. It's more real and more true than

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everyday waking consciousness.

I think it's the amalgam of those features, this interconnectedness of all things, the preciousness of the experience, and the authority with which that experience comes through that may account for why these experiences turn out to be so memorable, and the memories of these effects endure.

This is just post-session, but here's where it becomes interesting. When you follow these people up at 1 month, or 14 months, or anecdotally 10 years later, people are attributing very substantial positive changes in their attitudes, moods, and behavior to that experience.

This is 1 month after high-dose sessions. About 80 percent are saying that that experience a month ago was among the five most personally meaningful experiences of their life, comparing that, for instance, to the birth of a first-born child. But 90 percent are endorsing increased life satisfaction, positive behavior change, perhaps relevant to substance use.

These positive attributions are sustained way

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out. We've gone out to 14 months, as I said, anecdotally many years later. Importantly, they're confirmed by the ratings of community observers; that's friends, family members, and colleagues at work. So this is something other than just a narrative that the participant is volunteering. Their closest people among their friends and family endorse changes of the types that they're claiming to have made.

Turning to the therapeutic indication, this is a study we did in 2016 similar to the one that was conducted at NYU. In this case, 51 cancer patients, a randomized, double-blind, crossover design, 2 sessions, 5 weeks apart, comparing a high dose of psilocybin to a very low dose of psilocybin.

This jumps to the primary outcome measure. Along with this, there were mystical type experiences and these attributions of the important piece of these experiences. However, when you look at HAM-D, a gold standard measure of depression -- it's a clinician rated depression measure -- we're looking now at percent of the participants, and this is 5 weeks after the high dose, 92 percent of the participants are

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showing clinically significant improvement, as 50 percent drop on the HAM-D, and that's sustained out to 6 months at almost 80 percent.

Here's remission to normal range. For HAM-D scores below 7 are within the normal range, and here we have 60 percent have remitted. At 5 weeks, it's 70 percent out of 6 months.

This is a unpublished data and won't show up in the public slides yet. It's a randomized delayed treatment. It's a wait-list control treatment, examining the efficacy of 2 psilocybin sessions under these same psychologically supported conditions. This is, again, HAM-D for delayed treatment group. This is prior to receiving psilocybin in the immediate treatment group, and these time points coincide between these two groups, and this is HAM-D again.

We're getting these enormous effect sizes, delayed treatment control, so that weakens the design. But these are effects sizes over 2 and a half. At 3 months, if you take a look at all participants that were treated, we have about 70 percent clinically significant response and 54 percent remission to normal

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range; so enormous effects.
The conclusion from this piece of it is that psilocybin occasioned discrete experiences, having marked similarities to classic mystical and insightful type experiences. These experiences are associated with enduring positive changes in moods, attitudes, and importantly, behavior.
Data suggests efficacy in depression, both MDD and depression associated with life-threatening cancer diagnosis. Two companies, COMPASS Pathways and Usona, are now pursuing FDA compliant registration trials, and FDA has given breakthrough therapy designation to one of the trials focusing on treatment resistant depression. It's plausible the therapeutic efficacy of psychedelics will have transdiagnostic generality, and that's the hope and the promise for these compounds. We don't understand their mechanism of action. We can tell stories about that.
Matt now will present the data suggesting such efficacy and treatment of various drug-use disorders. Thank you.
(Applause.)

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Presentation - Matthew Johnson
DR. JOHNSON: Thank you, Roland.
I'm going to say a little more about risk and safety because that actually relates to some of the outcome and design considerations I'm going to get to at the end, and then give you a backdrop of why we would expect these psychedelic compounds might be effective for opioid-use disorder and other forms of addiction. Then I'm going to dig more explicitly into recommendations and thoughts around design and outcomes for opioid-use disorder.
Going over the risks, if you want to learn more about this, for you, a recent review paper that Roland, Jack Henningfield, and Peter Hendricks, who's here, published within the last year, going over specifically the abuse liability of psilocybin. Largely what I'm going to say here is relevant to the other classic psychedelics, the other compounds that are serotonin 2-way agonists, so LSD, DMT, or dimethyltryptamine, and mescaline.
It seems pretty convincing that they can cause harm in people with either active psychotic disorder or

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recognizable predisposition for those disorders. It appears that for anybody that passed the screen, they can have, particularly at a high dose, an experience of fear, panic, confusion, and this is what people out there called the bad trip.
The important thing is that can lead to dangerous, and sometimes injurious, and even fatal behavior out there in the wild. Even if not the typical response, it certainly happens. That's one of the reasons why in the clinical research and potential medical use, all of these sessions come only after preparation and continuous monitoring of the participant.
Another area is that these compounds cause moderate elevations in pulse and blood pressure. That's going to exclude folks at the higher levels of severity for cardiovascular illness. Then we've published some data showing that for psilocybin specifically, that it causes dose-related systematic increases in headache the day after the use of the compound; typically not severe, nothing we would anticipate that would interfere with potential medical

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use, but something to be aware of that might be a clue into some ongoing research, exploring the use of these compounds, to treat potentially migraine and cluster headaches, some work going on at Yale currently on those disorders.
Finally, there is a pretty rare phenomenon of hallucinogen persistent perceptual disorder. It's a DSM diagnosis, pretty mysterious. A lot of things are called flashback. This is only a subset of that. This is not just seeing some perceptual things like the next day. This is a chronic disturbance to the individual in the perceptual realm.
The important thing to learn, to note here, pretty rare even amongst recreational users, but has never been identified in either the older era from the '40s through the '70s of classic psychedelic clinical research or in the modern era. It seems to be an exclusive product of recreational use. It could be a result of some type of vulnerability that we're screening out even though we're not targeting for any known factor to screen it out, and it could be a result of polysubstance use, including alcohol, but something

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important to keep screening for.

For everything that I've gone over, we know that there are good methods for squarely mitigating these risks in clinical research and in potential medical use through screening, monitoring, and follow up of the participant. As Roland mentioned, one last thing is that it does not appear that the classic psychedelics, the two-way agonists, are drugs of compulsive drug seeking or addiction. They're certainly drugs of abuse; that is to say they can be used in a way that causes harm to the self and others, but doesn't appear that folks are jonesing for that next mushroom or LSD fix.

We published over a decade ago our recommended guidelines for essentially how you conduct this research safely, taking into account all of those risks and doing the research safely. Part of that is the comforting physical and interpersonal environment. This is kind of addressing the challenging experiences, the anxiety or the panic, that sometimes occurs. It occurs about a third of the time at a high dose of psilocybin that we use, but holding of the hand and

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words of reassurance seem to be pretty powerful in addressing that.

If no one's jonesing for their next psilocybin fix, why in the world would we expect it, though, to be able to treat addiction? A couple of threads there. One is in anthropological literature suggesting stories of addiction recovery from the sacramental use of these compounds. Those stories come from peyote use associated with the Native American church that contains mescaline, and also the use of Avahuasca. This South American concoction used ceremonially contains dimelthyltryptamine.

Of course, this is observational. Also, we know religious involvement is associated with addiction recovery as well, so by itself might be suggestive but certainly not conclusive. Another thread of evidence comes from this older research using LSD to treat alcoholism. There were a lot of studies. It was previously considered a mixed bag. Some studies didn't find an effect, some showed a significant effect, some showed a trend with a small number of subjects that wasn't significant.

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Several years ago, some Norwegian colleagues published a meta-analysis of the only six studies that randomized folks to either LSD or some other comparator condition. As you can see here, I'm showing the odds ratio, this side favoring LSD. These are the individual studies with the error bars. This is the aggregate meta-analysis effect size across those studies.

It was a clear significant effect in aggregate. More impressive is the effect size, essentially suggesting that there was nearly double the likelihood that folks were improved in their alcoholism outcomes at whatever the first follow-up visit was, suggesting something was there, although the rug was pulled out before we could follow up as a field on that.

This category is suggestive of potentially cross-compound anti-addiction. This is a single study that was published. In LSD in the treatment of heroin addiction, there were limitations that were some other differences besides the drug that were described in the original study published in '73, but nonetheless found

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some promising effects with increased biologically confirmed long-term success associated with LSD compared to a controlled condition. I'll say that, yeah, urine biological confirmation wasn't the norm back then, so that was an impressive component of that earlier research.

I just wanted to show you one quote from that paper, pretty interesting. These were inner city, Baltimore, heroin-using addicted participants, and they were asked to compare the drugs. One person said heroin has a numbing effect on you. It tends to relax you and somewhat takes you out in a way from your surroundings and yourself. LSD makes you more aware of yourself and puts you right into whatever has been troubling you.

I think that's a pretty good description anecdotally of what we tend to see in our various studies, that these drug experiences tend to prompt a confrontation with issues the person has been subjectively putting aside.

With this idea of cross-drug, potential anti-addiction efficacy, we tried our hand at smoking

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cessation. We had a little bit of money for an open-label pilot study. I had some background in smoking research. It's cheaply, biologically verifiable, so it seemed to be a good target to test the boundaries.

This was really just testing feasibility and safety, as it was an open-label study without a randomized control group. These were real smokers, smoking on average, over 30 years, about a pack a day, combining it with a 15-week program of cognitive behavioral therapy, not conducted during the actual psilocybin session -- those are largely introspective when they're wearing eye shades -- but the CBD being done in the preparation sessions and the series of follow-up sessions after the psilocybin exposures.

There were three psilocybin sessions over 8 weeks, starting at a moderate dose, then moving up to a high dose. We had the ability to adjust those later doses depending on the initial session response. But the first psilocybin session was actually scheduled on a target quit date. This is a big day for people, and not only are they going to quit smoking, but you're

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going to have this big old dose of psilocybin, and you've given them informed consent around everything that that means, particularly on the dark side, the difficult and challenging experiences.

Here are efficacy rates. I can't show causation as I said, but the question is, is this worthy enough for follow up, and these results would suggest absolutely. At 6 months, we found 80 percent of the folks were biologically verified to have a 7-day point prevalence abstinence rate. That held up in a very long-term outcome at an average of 2 and a half years at 60 percent.

Like the other research in healthy normals and in cancer patients with depression and anxiety, we found that long-term beneficial outcomes -- in this case, whether or not they were still smoking and also measures like smoking craving -- showed a relationship to the mystical nature, as Roland defined, of the psilocybin session; so involving that sense of unity, transcending time and space, sense of ineffability, overall positive mood.

We published a qualitative long-term interview

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with these people to kind of dig into whether we sort of missed something. They said the sessions left them with a sense of interconnectedness, all curiosity, and it reduced their withdrawal symptoms. They said it didn't seem addictive, psilocybin.

They said there were other increases. Aside from smoking, people kept saying, guess what, this was about so much more than quitting smoking, and they would report these benefits in their life, these changes in their lifestyle. Insights, idiosyncratic ones, their own self identity, and how smoking played a role into that and their own personal reasons for smoking.

I'd present this research early on, and people would keep coming up in different venues, sometimes scientific venues, and say, "This happened to me." Sometimes a year ago, sometimes like 40 years ago, they said they were doing a big psychedelic for fun at a party, and they said, "What the hell am I doing smoking?" and that was the last time they ever smoked. So we said, let's do a survey, and just capture the landscape of what people were reporting with these

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stories, how there are 1100 people that report such stories.

For the folks for whom there had been over a year since that reported psychedelic experience, the most interesting outcome came from this. We said if you had tried to quit other times before this, compare this to other times when you had quit smoking. We gave them a laundry list of withdrawal symptoms.

A big pop-out effect for me was that the modal response for all of the somatic symptoms tended to be, "Yeah, it was about the same." But for the affective responses -- anxiety, restlessness, depressed mood, irritability, craving, folks said it wasn't just less severe but much less severe. I think that's providing a potential link to -- [inaudible - mic fades] -- depression, anxiety, and cancer, and outside of cancer that Roland presented.

We're currently doing a randomized efficacy trial with 80 treatment-resistant smokers; 40 randomized to psilocybin and 40 randomized to nicotine patch, the same cognitive behavioral backdrop to both groups; scaling back to one psilocybin session. We

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still think more sessions is probably better clinically, but more for experimental reasons; scaling back to one session on their target quit date.

The study's in progress, but these are our current results, so note the different end as we get to these different lengths of long-term outcomes. But at 12 months, those people, what we're seeing right now is 56 percent are biologically confirmed as 7-day prevalence, biological abstinence, versus 17 percent in the nicotine replacement group, interestingly. We'll see if all of this holds up. It may not. None of it may hold up. But it seems like the difference between groups is getting larger as time goes on, and as more of the nicotine replacement folks are relapsing.

Very quickly, I'll say we studied fMRI pre- and post-quittings. This is not during the experience. We are looking here at a number of tasks, and we only have one analyzed so far with a subset of initial participants, but we administered the oddball task. This is a task of cognitive interference. People have to identify the oddball digit, and identify that digit with the finger number that corresponds to whatever

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that oddball digit is; if there's one 1 and two zeros, and 1 is the oddball.

Resist the urge to use the finger that's in the same spatial location. This is kind of like the Stroop task. You have to override a pre-potent response, and you get a difference in reaction times, which index is that interference effect. We're getting a significant improvement in that measure, dealing with that interference for psilocybin compared to the people 24 hours after quitting, who have gotten the nicotine patch treatment.

I don't want to make too much of a story out of it. This could change. But we are seeing an associated fMRI response, normalization of the task-associated response in the right lingual gyrus the day after. Again, we'll see if that holds up. But this might be kind of a clue into the more mindfulness type approach people are anecdotally reporting after they've quit with psilocybin; so this awareness that they have quit, less inclined to fall into automaticity.

Briefly, very similar results to our pilots;

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they were published by Michael Bogenschutz, who's with us here, who conducted this work at the University of New Mexico. He's now at New York University. In this study with 10 alcohol-use disorder participants, found strong reductions in drinking days and heavy drinking days after a series of psilocybin experiences. He, like us, is following up his data with, in his case, a large, I think, 100-person randomized, double-blind study, so we will see what results are there.

I'll go through this really quick. We've done a series of studies, again, like the smoking research, assessing the landscape, getting descriptors of these reports of people who have largely used for fun on their own, and they report quitting a drug. We did some of this work with alcohol, with some structural equation modeling.

I'll just briefly say it seems like -- we can't determine causation here, but the model suggests there may be a causal pathway involving both the mystical nature and the insightful nature of the experience, leading into how meaningful the experience was, and that predicting the change in alcohol-use

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severity.

We've published that. We haven't published this yet. We've done a similar thing with opioids, cannabis, and cocaine. I'll show you the opioid component here; 343 people said they quit or reduced opioids because of a psychedelic experience. These are all largely user classic psychedelics, largely psilocybin and LSD, is what people were using, and found the same model held up with these individuals in that study.

Just briefly getting into lessons for design and outcomes, in terms of the acute measures, certainly continuing to look at these with this trend of the nature of the experience that they have under psilocybin, predicting outcomes. We need to keep looking at that, and probably need to look at an additional number of measures; so mystical experience. We have psychometrically developed essentially a bad trip scale, the challenging experience questionnaire; weightings of how meaningful the experience is.

Peter Hendricks, who's with us, who's doing work using psilocybin to treat cocaine-use disorder, he

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has proposed, theoretically, the psychological construct of awe as being another mediator of these effects; so something else that can be measured. It's important to continue the assessment of persisting adverse effects.

These are kind of throwing and derailing people in their life. These anecdotes are bound out there in the wild. We're not seeing them so far in clinical research, but it's important to keep your eye out for them, people; essentially throwing them into an unresolved midlife crisis. That's kind of the way I think of it. These can be destabilizing experiences potentially. Then continue to look for those potential long-term perceptual disturbances that we haven't seen yet, but we've got to keep looking to understand, if they pop up, what their natures is.

The assessment of other persisting benefits and possible psychological mechanisms, so the commonality that we suggested between affective process and substance-use disorder treatment, there could be a common core. I kind of think of this stuff as addiction broadly defined, whether you're stuck in the

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rut of thinking about yourself in a certain way or in the behavioral rut of substance self-administration. There's a narrowed mental and behavioral repertoire, and this seems to be -- this is the idea -- that this is a powerful way to shake someone out of that and create a mental and behavioral plasticity that can be latched on to.

Looking at measures and also quality of life, we continue to do qualitative analysis. I should say Michael published a qualitative analysis with his alcohol-use disorder pilot work, finding similar things, that folks tended to say, "Oh yeah, and other stuff really improved in my life." Who knows? It could be that those things are a part of the package that helps the reductions in substance use.

Mechanistically, gosh; so much of this is speculative based on either acute effects -- [inaudible - mic distortion] -- or ideas. We need to look biologically at so much beyond receptor effects. A fascinating story that has emerged is the acute effects of these compounds under resting state fMRI. You see a really impressive -- [inaudible - mic

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distortion] -- that aren't well synchronized. You see an increase [inaudible].

At the coupling of synchronization -- [inaudible] -- change in the way that the brain acutely communicates with each other, and it very well could be that there are -- this is what we're looking at now in a smoking study, and other people are looking at. There's no answer yet, but one idea is that there is a long-term resetting, and to do these brain network dynamics fall back into a different pattern. This is interesting because we know a growing number of psychiatric disorders are associated with an abnormal or different resting state network effect, so we'll see if there's something there.

I suggested some data here that we may be seeing this effect dealing with cognitive interference. We need to continue to look at this and other specific forms of executive function that could be manipulated. There's some very fascinating animal work showing effects on neuroplasticity in the form of dendritic branching, synaptogenesis, and spinogenesis. It's yet to see whether this mediates these human effects that

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we're seeing and the long-term effects.

Then there's some really interesting work on inflammation with these compounds that Chuck Nichols is doing at LSU. We also know there's a thread of evidence suggesting that a growing number of psychiatric disorders are associated with neuroinflammation, so that's something to look at. There is more that I don't have time to get into. It's just such a mysterious thing. My bet is that there are multiple mechanisms that are going on.

Overall design, it's important to prepare people and to establish rapport. It is different than administering other drugs in the lab. There are unique risks and there are mitigation strategies, so we need to incorporate those into the designs. A lot of times we started with pilot studies; not because we want to do uncontrolled studies. It's because we don't have the big dollars. We've yet to get any substantial NIH funding for this work, so this has largely been philanthropic.

Thus, we're testing some new water. We want to test to see how does this look in a small sample

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when you're looking at something new. I think the ultimate answer is going to come from comparative efficacy studies, open-label studies, and double-blinded studies. I thought with smoking cessation, the next step, in terms of what we're doing now, is open label but a randomized comparative efficacy study to a known standard.

I think compared to other double-blinded medication studies, we are looking at something particularly bizarre with psychedelics in the sense that we're telling people this can be like this big experience in your life, including the most frightening experience, or you could be bored stiff on the couch all day.

That's probably something you're never actually going to get if this stuff is rolled out in actual medical use and we're modeling something that's kind of a Frankenstein you're never going to see. But again, we obviously need that, particularly for medication development and to fully understand what's going on. So I really think the ultimate answer comes through the triangulation of these methods.

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Then, big questions about the nature of the placebo. We've done a bunch within our group, and others have; a true placebo, an active placebo, another psychoactive compound. You've got to be careful or use something like ketamine for depression, and you might have a comparator that shows an efficacy, too.

You probably only want to throw in something like that if you also have a true placebo or something else; lower trivial doses of the same compound, the MAPP group, working with MDMA. I think they've learned some things there. There can be a danger in assuming that a low dose is not active because people differ in their sensitivity to these therapeutic effects. We have used, in the cancer work Roland showed, a really trivial dose that was really just controlling for instructional sets, so we can truthfully tell them you're going to get some dose of psilocybin.

So there's a lot going on there, a lot of room for creative thinking in terms of experimental design. Then obviously, the long-term assessment, like I said, it may be that that's where these treatments really shine, and certainly concerns about opioid-use laps.

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Even though you always have the potential for fatal relapse when you're dealing with opioid-use disorder, one extra concern, above the primary risk of hurting anyone, is that even if you have something that's not related at all in reality to psilocybin, this is such a sensational area, there might be this extra causal attribution to something that normally wouldn't be front-page news if it was more boring in terms of attention.

Medication, some real thought about -- yeah, as there should be for any study -- about really minimizing fatal outcomes with a relapse when people have lost their tolerance. Finally, a lot of thought around navigating the true believers. I've been doing this 15 years. Earlier on, I've always done some of both, but I've spent most of the time trying to convince people, yeah, there's something really credible and interesting here that we should invest in.

Now I think I spend most of my time arguing back to the people thinking it's going to be a panacea and that there aren't any risks. We really need to be thoughtful about how we model this stuff going forward

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in terms of mainstreaming it. These are sometimes and often described in mystical, spiritual language that can mean different things for many people. I've seen a lot of atheists go through this; they're still atheists. You can come to these experiences from a religious framework. It's not necessary.

So we need to really be thoughtful about how we're framing this for a broad audience and not fall into -- it's been called a cultigenic effect in the history of these compounds, that there can be an inclination for folks to form a religion around these kind of high-magnitude experiences. There's a lot of room for thought around how we mainstream these compounds.

I think that's it. Thank you to a whole lot of folks for the work that I showed you. I think we have a few minutes for questions. We have until 3:15.

(Applause.)

DR. JOHNSON: For Roland and I, if there's time for questions.

DR. STRAIN: Questions on this?

DR. JOHNSON: Michael?

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DR. BOGENSCHUTZ: I guess I have just a couple of general observations, and we'll have more time to talk tomorrow. Just in terms of opioids in particular versus other substance-use disorders, one of the key differences is that effective long-term pharmacotherapies exist and are really the standard of care. They can prevent overdose and death. So for the time being, it's hard to justify monotherapy trials, psilocybin for opioid-use disorder.

DR. JOHNSON: Right.

DR. BOGENSCHUTZ: So that being the case, is it better to combine with agonists, partial agonists, or antagonists? Do you give the psychedelic as an induction strategy prior to starting it? That helps prevent some potential drug-drug interactions. Or do you wait until they're stabilized and giving that? The goal of treatment and the outcomes would depend on that, too.

DR. JOHNSON: Right.

DR. BOGENSCHUTZ: I guess the only other general comment I had is you touched on a lot of the mechanisms as we know. It's complicated, and that's

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what one of the things that makes it so interesting. But in terms of target engagement, we have a receptor, but we have all of the psychological variables of preparation, intention, therapy, and the neuroplastic effects that can happen on all different time scales. It makes it a real challenge for grant writing.

DR. JOHNSON: We encourage reviewers and funding agencies to understand the challenges and the mechanisms.

DR. JOHNSON: Yes, it's going to take a lot of education. On the first point, I should point out, and I meant to point out during the talks, and I'm glad you brought it up, I think that's a critical question. Randy Brown, who's with us from University of Wisconsin Madison and is actually conducting a study with the interactions of buprenorphine with psilocybin, and paving the way for that type of combined treatment to make sure that's safe.

We have funding to do a study with opioid-use disorder using psilocybin to treat it, and we're still working with what the nature of that design is going to be. Of course there is depot naltrexone. There are a

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number of ways to kind of get at this and a lot of room for creativity.

Certainly, yeah. We know the 2A is the first domino in the chain, but I think it's a pretty safe bet at this point, the brain during a bad trip is not the brain during a mystical experience. So I think our biological understanding is just in its infancy, and it's probably not just agonizing the 2A receptor. Even at the biological level, getting to brain network dynamics might be a more appropriate level of analysis, but even that is very early on.

DR. STRAIN: Kurt, did you have a question?

DR. RASMUSSEN: Just real quick, in terms of commercialization, how is this going to get to -- even after the trials show that it's useful and effective, is there a company that's going to be marketing? How do you envision that?

DR. JOHNSON: Yes. This was a question for years, but now there are numerous entities. Yes, I think I'm aware of over 10 entities that have put substantial money into this space. Roland mentioned COMPASS Pathways. It's in the millions of dollars and

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they apparently expect some return on investment.

I would say it's a different treatment model. Folks have jumped out of the psychiatric drug space, and I think there's a recognition this is a potential niche. Maybe more of the opportunities are not along the model of selling the pill every day. I think there's plenty of opportunity for IP, for intellectual property, because there's a whole lot we know about structure and activity of relationships now and the potential for novel compounds here that can improve upon what we're seeing.

Even for compounds that lack the overt psychoactive effects, I don't think you're going to get the full efficacy there, but that's a guess at this point. I think there are business models that can rely on the treatment delivery. This isn't something you can just do anywhere. So I think there's a return on investment to be had and a relatively novel niche.

DR. STRAIN: Thanks, Matt, and thanks, Roland.

We're going to have to move on. I'm sorry, but we'll have some time tomorrow, certainly, as well, to further flesh out these ideas.

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We're going to turn to vaccines now. Sandy Comer is going to start. Sandy, the podium is yours. As you're going up, then Marco Pravetoni will do the last 10 minutes of this session

Presentation – Sandra Comer

DR. COMER: I'd like to thank Eric for inviting me here to give this presentation on a project that we're really excited about, and I'd like to thank NIDA for funding the bulk of the research so far.

This is our team. It's very much a collaborative effort. Marco, Paul, and Scott at the University of Minnesota, were the ones who originally developed this vaccine concept. Paul was the person who developed a nicotine vaccine that made it into phase 3 clinical trials, and Marco has taken over that program at the University of Minnesota. My team at Columbia will be conducting the first-in-human studies of the vaccine, and more recently, we've set up a collaboration with Clinilabs. It's a contract research organization who will help run that study.

When I first started talking to Paul about this concept of a vaccine, my immediate reaction was

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why a vaccine? I mean, we have naltrexone. Wouldn't it work in kind of the same way? The short answer is no, actually. Once we started discussing the ins and outs of what the vaccine would do, it became clear that there are certain clinical advantages of a vaccine over something like naltrexone.

There are unique concerns about using a vaccine that I will talk about today, and then there are certain regulatory hurdles as well. Hopefully, you can answer all of these questions in the course of the talk.

Just to give you a brief description of what the concept is, a person will initially get vaccinated and develop antibodies to a target drug. The first one that we're going to be working with is oxycodone. In a vaccinated person, if they end up using oxycodone, these antibodies will bind that substance and prevent it from getting into the brain. A series of injections are typically given with vaccines over a series of months in order to achieve maximal antibody production.

These are the two vaccines that we originally started working with. One is oxycodone vaccine and

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another is a morphine vaccine. The oxycodone vaccine targets oxycodone and other substances that are chemically similar to oxycodone, so hydrocodone and oxymorphone. The morphine vaccine would target heroine, 6-acetylmorphine, and morphine.

This is really a multivalent concept here, and I want to spend a little bit of time talking about that, because this is really important. The first vaccine that we're going to be studying is the oxycodone vaccine. Then, assuming all goes well with that, we'll look at the morphine vaccine, and the original concept was that it would be a bivalent vaccine. So both of the vaccines would exist in one vial that would be given to patients.

Then over the course of the last few years, of course, fentanyl became a problem, so Marco has developed a fentanyl vaccine as well, so this could be a trivalent vaccine, and it could be a multivalent vaccine more than just these three, which I think is really interesting. Whatever new opioid might come to be abused could be added to this vaccine.

To put it into context a little bit, we're

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kind of conceptualizing it almost like a flu vaccine. Every year the components of the flu vaccine change, depending on what strains of the virus might be prominent that year; so that's kind of the way we're thinking about this as well.

Just to remind you all to get your flu vaccine if you haven't done that yet.

(Laughter.)

DR. COMER: Here, I just want to show you some data briefly from the preclinical labs, Marco's lab. On the top are serum levels of oxycodone here; on the bottom are brain levels of oxycodone. The dark bars are the vaccinated animals and this is the control animals. When they received this 0.5 milligram per kilogram IV dose of oxycodone, serum levels go up and brain levels go down. Remember, I showed you that figure where the vaccine is supposed to prevent the drug from -- or the antibodies will bind to the oxycodone. With a lower dose of oxycodone, the same thing happens. Serum levels go up, brain levels go down.

This was a study that I thought was really

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interesting, where they gave animals the vaccine, and then started to train them to self-administer oxycodone.

These are across several sessions. The animals that received the active vaccine never acquired self-administration behavior. This is intravenous oxycodone. The animal presses the lever in order to get the drug. The control animals show this typical pattern of acquisition of oxycodone self-administration. So here it's preventing the acquisition of oxycodone self-administration.

Clinically, when I started thinking about these vaccines, I started to think of where it would fit in the treatment scheme. The progression of use goes from no use, to severe opioid use, to treatment, to relapse, unfortunately, in a lot of patients.

A typical progression of disease could be recreational use of oral prescription opioids progressing to daily use. Oftentimes, people switched to intranasal use of prescription opioids or they start dabbling into heroin or fentanyl. Then when the disorder gets really severe, they might start

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injecting. I know that people who love oral opioids also can have severe opioid-use disorder, but I'm just using this as an example.

Then, a subset of the patients will seek treatment, and they'll go onto buprenorphine, methadone, or naltrexone. Where I'm thinking the vaccine could be useful is in this situation where it might prevent the progression from recreational use to daily use. It can be used potentially as a stand-alone medication. We'll have to see after we run the trial how robust be effect is.

This is where I think it gets really interesting. In patients who are maintained on buprenorphine, methadone, or naltrexone, the vaccine could be used as an adjunct, actually, because the vaccine is really targeting a particular chemical structure. So the buprenorphine, methadone, and naltrexone have structures that are so different that it wouldn't interfere with their effects, and Marco has some data to show that this is the case.

In the patients who have been on medication-assisted treatment who end up relapsing to

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opioid use, the vaccine could be really helpful here because they might not experience much drug effect, so it would provide us with an opportunity to reengage them in treatment, and it could potentially provide a safety net for overdose at any of these phases. Again, Marco has some preclinical data to show that this might be the case.

These are the areas where I think it might be useful to prevent OUD, to use it as a stand-alone medication, to use it as an adjunct, to maybe prevent relapse, and to prevent fatal overdoses.

Here, I like doing this kind of exercise to think what are the pros and cons of different types of medication approaches compared to what's existing. This is agonist maintenance, this is sustained-release naltrexone, and then here's the vaccine. We know these two forms of treatment are effective.

For agonists, it's easy to get them on to the agonist maintenance from heroin. Buprenorphine has some unique challenges, but it's relatively easy once you kind of get the hang of it. With naltrexone, you have to detox patients. That's a hurdle for a lot of

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people. With the vaccine, it should be relatively easy because it should not precipitate withdrawal. This is something that's a big question mark. I don't know how we would transition patients onto the vaccine, so that's something that we need to answer empirically.

The risk of relapse is low if somebody relapses, and the same with naltrexone. I don't know if it's true anymore, now, with fentanyl on the scene. Medication compliance tends to be pretty decent for both forms of therapy. With agonist maintenance, patient convenience is poor, especially with methadone. There's a risk of diversion. Sedation can be an issue. There's a respiratory depression risk, especially with methadone during dose titration. There's child safety risks.

All of those are not the case with naltrexone, but as someone mentioned earlier today, patients don't like naltrexone, so that's the biggest hurdle with that one. With the vaccine, it should also have a lot of these same advantages as naltrexone has.

I to walk you through some of the interactions that we've had with the FDA in terms of discussing this

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trial with them. In 2014, we requested a pre-IND meeting with the FDA, which they granted. We originally proposed a phase 1 study in normal healthy volunteers with the oxycodone vaccine, and then later we were planning to run a phase 2 study in subjects with opioid-use disorder.

The FDA response was absolutely not. You cannot do this study in normal, healthy volunteers. So we're like, okay, we'll go back to the drawing board. They really insisted that we study the vaccine first in participants with opioid-use disorder. So in 2018, we wrote a grant, which was funded, thankfully. At a meeting that we had, where members -- so it's CBER, the group that we were working with at the FDA.

They recommended that we request another pre-IND meeting, partly because of the leadership change at the University of Minnesota, and because the design of the study was so dramatically different. So we did that earlier this year. We had another pre-IND meeting. We described our phase 1 A1B study in participants with opioid-use disorder, and they had a bunch of comments which we're addressing now.

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Their initial concerns -- and I think these are some of the things that are potentially unique with the vaccine approach, is they were worried about the vaccine blocking the effects of endogenous opioids. Marco ran a study to address that in rodents. They also were worried about the vaccine blocking the euphoric effects of opioids without blocking its respiratory depressant effects.

So again, Marco ran a study to address that concern, and the effects are blocked equally. If you kind of think about it, that wouldn't necessarily make sense because it's really just preventing the drug from getting into the brain, so it's basically the person getting a lower dose of the agonist.

They were worried about compensatory use of opioids that will result in increased toxicity. This was actually the same concern that we had with the sustained-relief naltrexones. Everybody said, oh my gosh. If somebody goes out and tries to override the blockade, they're going to just stop breathing; they're going to run into trouble.

So we were very, very careful about that with

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our sustained-release naltrexone studies, and it turns out that they don't do that. That doesn't happen. There were a few people who tried to override the blockade, but the doses that block the reinforcing effects or the euphoric effects of the opioids are also the same doses that block the respiratory depressant effects.

So while this is a theoretical concern, we don't think that this is going to be a real clinical concern, but we'll monitor that very carefully as well. Really, what happens is that people are just not willing to spend 100 bucks on heroin to get a very mediocre high. They're governed by laws of economics just like anybody else, and that just doesn't happen.

Another concern that the FDA had was the PK/PD profile in vaccinated individuals would be altered, so we've built some features into our study to address this concern. Then as I said, they really insisted on us studying people with opioid-use disorder.

This is the design of our study. The primary aim is to evaluate safety. This is a phase 1 study. We're monitoring all the kind of usual safety

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parameters. The second aim, which is very important, obviously, is to examine the immune response, so we'll look at titers, antibody titers, concentrations, affinity, and specificity of the oxycodone specific serum IgG antibodies.

We also will look at preliminary efficacy. The primary endpoint here is what the FDA usually expects to see in these types of studies, so our primary endpoint will be mean peak ratings of drug liking.

The inclusion/exclusion criteria for people in this type of study are different than what we normally. This is not different, actually; men and women 18 to 59 years. They have to meet criteria for moderate to severe opioid-use disorder and be physically dependent on opioids, but not physically dependent on any other substances of abuse, with the exception of nicotine. They currently will not be seeking treatment for their drug use because we're going to be giving oxycodone and fentanyl, actually, in the lab

The exclusion criteria, this is an important one. The opioid of choice in this population can't be

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oxycodone or structurally related opioids. This is one that I struggled with a lot when we were first talking about doing this study because the last thing I would want to do is take somebody who is just predominantly kind of popping pills and getting high off of them, and blocking the effect of that, and then pushing them in the direction of using heroin, or fentanyl, or something that's potentially more toxic.

So we're excluding people who are only using oxycodone. The other exclusion criteria are kind of the usual: sensitivity, allergy, or contraindications to opioids, alum, or any of the other components of the vaccine.

They can't have acute HIV, active tuberculosis, or any other immunocompromising diseases. They can't have any serious or unexpected reactions to a vaccine, including GBS, and then they can't use inhaled corticosteroids. We have a whole long list of exclusion criterion to ensure the safety of our participants.

Here's our design. It's a mixed within and between subjects design. Each subject will serve as

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their own control, so we'll collect endpoints before we start vaccinating them, and then we'll measure the same kinds of effects after they get the vaccine.

The between subjects part of it is that we'll look at three different doses of the vaccine. We'll have alum, which is the adjuvant as a control, and then 100 and 400 micrograms of the vaccine. We'll do it in ascending order. It will be roughly a 2-to-1 ratio of active versus control.

There's only one concentration of the vaccine, so we'll give a 0.25 milliliter amount here for both groups. Once we finish that, we'll make sure that everything is safe, and then proceed to the next dose, which is 400 micrograms, and we'll give 1 milliliter of the vaccine.

There will be both inpatient and outpatient periods. During the inpatient periods, we will be administering oxycodone, so that's the target drug that we're hoping to modify the effects of. We'll give them intranasally. Fentanyl will be used as the positive control. We thought about using heroin, but because fentanyl is so prevalent and it's much more dangerous

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now, we wanted to use fentanyl instead, then our placebo will be lactose powder. The study, as I mentioned, will be conducted both at Columbia and then also at Clinilabs. We'll be monitoring both immunological and pharmacokinetic responses, and those blood samples would be sent to the University of Minnesota.

Here's the design. We'll have a screening phase here for about a month. We'll admit them into the hospital for about 8 weeks. We'll stabilize them on oral morphine, and then start testing the effects of oxycodone and fentanyl. Then we'll start vaccinating while they're inpatient, so we can monitor them very carefully for any kind of adverse effects.

Then we'll give the first three vaccinations inpatient, and 2 weeks after each of the vaccinations, we'll measure oxycodone and fentanyl effects. Then they'll go outpatient for several weeks, and then they'll come back into the hospital where we'll give the last vaccination, and then test the effects of oxycodone and fentanyl again.

The oral morphine, we decided to maintain

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participants on this because it should not interfere with vaccine response. This is a very familiar dose range of oxycodone and fentanyl for us. We've actually given those doses intravenously, so intranasally is usually less potent -- or the potency of drugs is less lower for drug.

This is a study we conducted a number of years ago looking at intravenous doses of oxycodone, heroin, and fentanyl for visual analog scale ratings of drug liking, and these are the mean peak ratings. This is the primary endpoint that we'll be using in this current trial.

What we're expecting to see is a baseline dose-response curve of oxycodone that will look something like this, and then after vaccination, hopefully it will go down. With fentanyl, we're expecting to see no change in ratings of drug liking as a positive control.

These are just our study events table across the course of the study. We're working furiously with Bob Walsh and his group, and Marta De Santis at NIDA, to get our IND application in. Marco and I are burning

the candles at both ends, passing the application back and forth. It's really, really awesome that Bob and his group are helping us with this because it's a lot of work. So we're really grateful for that.

We hope to receive FDA approval sometime early next year; knock on wood. Hopefully, the pre-IND meeting was enough to address most of the FDA's concerns, so we'll see what happens.

We have conditional IRB approval now, and we hope that final IRB approval will happen sometime at the end of January maybe, and then we can start enrolling patients. We hope to finish that by the end of 2021, and then initiate the morphine KLH study some time in 2022, assuming all goes well and there are no issues.

I'd like to thank my colleagues at Columbia for being great, and helping, and working really hard, and then I'd like to invite Marco up to show some other data that are, I think, really, really exciting because this is Marco's brilliant idea that hopefully will help us with efficacy issues.

(Applause.)

Presentation - Marco Pravetoni

DR. PRAVETONI: Thank you for the introduction, Sandy, and thank you for the brilliant -- we don't know if it works yet, but hopefully. I thank you to the organizer to give me the opportunity to speak at this meeting.

Here, where I want to spend a little bit of time is, essentially, where the preclinical and the clinical program merge so that we can inform how to go about this clinical trial. One of the challenges in this field is being to identify immunological mechanisms and biomarkers that can predict the vaccine efficacy to accelerate translation.

From previous data, clinical data on evaluation in humans for nicotine and cocaine vaccines, we know a great deal of this. We know that, for instance, people that are vaccinated, against nicotine and cocaine, people that show the highest antibody levels also show vaccine efficacy. Roughly, in various trials of nicotine and cocaine, that corresponds to roughly about 30 percent of the subjects.

So the idea here is people that have the

highest antibody levels will also show the greatest efficacy. Roughly, that accounts for about 30 percent of the population that has been immunized. So what will happen if we can actually select patients a priori?

Here, when you're looking at antibody responses, even if you have not done analysis, you may appreciate that antibodies are the endpoint by a cascade of events that involve the immune system, both innate and the adaptive response. Prior to immunization, the naive new repertoire included a variety of immune subtypes that recognize different antigens, vaccines, infectious disease, et cetera. In that mix, there is the possibility that some of these cells will also recognize opioids or opioid vaccines.

After vaccination, a lot of these entities, whether they are innate or adaptive immunities -- so things like B cells/T cells -- are going to be activated. Lots of events will yield to an antibody response that may be characterized by IgG subclasses or by specific molecular pathways that are conducive to antidrug and antibodies that will then be effective in

reducing either drug distribution to the brain or behavioral toxicity. The idea here is by digging here in the weeds, we can actually point out where we can find biomarkers that are predictive of vaccine efficacy and whether we can apply that to our system.

Taking a step back here, what did we spent some time on is looking at various vaccine components. Each vaccine component is critical for optimization of this vaccine. As you can appreciate, as you improve your vaccine formulation, you may improve the vaccine efficacy. But on the other end, also these components are interfacing with a new system as soon as you vaccinate somebody.

This is a general schematic of our oxycodone vaccine. The molecule on the left is essentially the backbone of hydrocodone and oxycodone, that can be modified by various linker and attached to carrier proteins to actually make so that the new system will see it. These cells are generally thought to recognize this portion of the vaccine, so we we'll define them as Hapten-specific B cells. CD4 T cells are known to bind to the pertinacious part of the vaccine, so essentially

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the carrier protein, if you will. Then the old vaccine
Then the whole vaccine that is packaged and added on to a delivery platform will be recognized by antigen presenting cells, like just any other vaccine. Just to give context to this, B cells will make antibodies and that we can isolate monoclonal antibodies. So there are many ways to look at this.
We've spent quite a bit of time in the last few years looking in animals at the role of B cells and how that will correlate to vaccine efficacy. Taking a step back, we have to develop the technology. For example, in standard immunology, people have developed such techniques for looking at HIV vaccines and so forth; instead in our field, we sort of have to create this from scratch.
If you recognize this molecule here, it's still oxycodone. We create a set of reagents, and we've done this for oxycodone, nicotine, and so forth, that essentially are opioid ligands attached to fluorescent probes that allow us to essentially isolate immune cells that will bind to these things.
You can take blood, lymph nodes, spleens, and

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all sort of tissue from human models, primates, and so forth, and essentially enrich for B cells, they do recognize the opioid of choice or any antigen for that method. In a way, you can actually isolate the cells, the B cells of interest, that won't bind -- in this case oxycodone -- and then you can analyze by a flow cytometer or cell sorter. Essentially, you can take a lot of material and get down to a few cells. Just to give you a comparison in mice, we're able to look at a 200 microliter of blood and find 5 B cells that recognizes oxycodone.
Obviously, this is just mouse work, and that's where we've spent time in the last years. To give you an example of how this may apply to vaccines, here we have our oxycodone vaccine. The oxycodone KLH that Sandy was describing was given to mice, and here on my right is the individual variability. These are vaccinated animals versus control. The mean effect is obviously the vaccine will reduce the amount of drug that gets to the brain -- that is oxycodone -- but also you can appreciate there is a lot of individual variability.

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This individual variability can be predicted by early on antibody responses, so animals in this case that show an early response to oxycodone will also be the ones that a few weeks later will show greater efficacy against oxycodone. But in order to sample the antibody, you really have to wait until after vaccination.
What if you can sample prior to vaccination? Using our B cell analysis approach, we look at the pre-vaccination in mouse blood, and then we immunize animals. What we found was that prior to vaccination, animals that show the highest frequency of B cells that recognized the oxycodone, so the vaccine component, a month later, they're also the animals that would show the greatest efficacy.
Essentially, if you're looking at this kind of variability, and if you can predict, even prior to vaccination, who is going to be a good responder, that adds valued because that will inform you of the patient selection or therapy or if patients actually will benefit from this particular approach or would rather be served by naltrexone, methadone, or buprenorphine.

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We're here, and we're trying to bring this, I call them exploratory biomarkers, to the clinic. We are using this in technology. As I mentioned, that is non-species specific. You can look at oxy-specific B cells in pretty much any system.
In order to do that --
(Pause.)
DR. PRAVETONI: -- skipping the previous slide, story short, we're trying to bring this technology to the clinic, so we paired up with Sandy. The idea here, we don't have access yet to vaccinated individuals because the clinical trial hasn't started, but we have access to opioid users.
So the idea here is that we take blood from Sandy's lab [indiscernible] -- collecting blood from patients from her clinic. We're essentially comparing the frequency and other characteristics of opioid-specific B cells in either naive or opioid users.
For opioid users, we are using a very broad term, but, in general, on our consent form, we have people that have been using opioids for at least one

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year. By the technology I mentioned before, we are able to compare and see if these individuals have a higher frequency of opioid-specific B cells.

This is an output of what flow cytometry looks like. Most immunologists get very excited about things like that; most people don't. This is standard [indiscernible] cells used in clinical labs to standardize your blood measures. In the red box, we have two opioid users, and down here in green, we have no opioid users. Across, you are to look at the gates in the flow cytometry, where we look at opioid-specific B cells.

Story short, we are actually able to find opioid-specific B cells, and their frequency is higher in opioid users. That translates into roughly this type of data. If you don't like looking at a flow plot, this is just an overall estimate of some opioid-specific B cells, the number of cells that we found for amount of blood.

What we found is that people who have been using opioids for a given time, they show a higher number of opioid-specific B cells compared to people

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that have never used opioids. If you further down this analysis to look at specific B cell subtypes, results may come in many flavors, so antibody [indiscernible] cells, memory cells, et cetera. We show they have different roles in contributing to vaccine efficacy. But the bottom line is that we can find these things in opioid users and not necessarily in naive people, or at least the frequency's higher in people that use opioids.

The question here that we're going to try to answer is that opioid-specific B cells is a valuable marker that can help us to predict vaccine efficacy. We are gearing up to the clinical trial, and with the NIDA funding, we are able to start developing the technology that we will be able to apply to patients.

As you can appreciate, there are lots of logistics. Some of the flow cytometry analysis is done in fresh samples. We collect blood at sites. We ship it over and process it. There is actually a third lab on that slide that is also sequencing some of these B cell receptors, and that is done in Germany. So as you can appreciate, there are a lot of logistics

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involved with the different type of samples. We want to focus on what is actually doable and also cost effective that can be implemented in the clinic.

The biomarker, bridging what we learned from the preclinical studies, for years we've been working on different types of immunomodulator. Story short, we found that interleukin 4 would increase or is well associated with vaccine efficacy.

In this particular study, we co-administered the OXY-KLH vaccine with a neutralizing antibody of anti-IL-4. What we found is that we have increased antibodies and also increased the efficacy in blocking distribution of oxycodone to the brain. Some of these modulators are actually in clinical use for other indications, so there is value in that.

To validate the studies, we looked at animals that were genetically modified to not express IL-4. What we found was essentially the same story. IL-4 knockout animals vaccinated with the oxycodone vaccine, which showed an increase in antibody titers and also increased efficacy. This particular increase in efficacy was associated with a shift in IgG subclasses.

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IgG comes in many flavors, and some of them have a different function that contributes to vaccine efficacy.

We're hoping to bring some of these parameters into the clinical trial. Specifically, something like IL-4 can be simply sampled in blood. The idea here is that IL-4 could be a pharmacological target, a biomarker, and possibly both.

Looking even closer, we started implementing new techniques, like trying to look at the molecular signature of the vaccine. This was obviously done in the mouse, but some of these approaches can easily be done in people. This was sequencing of CD4-T cells, and we looked at animals that were either vaccinated with control, with OXY-KLH, or with OXY-KLH and the anti-IL-4 modulators.

Without going into details, you may appreciate this cluster of activities that are associated with vaccine efficacy. Obviously, if you bring this to a clinical trial, we will need some bioinformatic person to deconvolute the information so that you can actually correlate individual signatures through actual vaccine

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outcome. This is just a thought, and this is something that could be done as has been done for other vaccines against HIV, malaria, and so forth.

Finally, I tried to convey this idea that preclinical data supports the user biomarkers. What we learned about these vaccines in the past few years, from my lab but also other labs in the field, we can bring that and possibly improve vaccine design, or routine [indiscernible] like a design, or the vaccine, possibly preparing it for something like a phase 2 so that we can stratify patients.

One of the easiest biomarkers is sex. We've seen that female mice and rats have greater responses to vaccines, so that's something to keep in account. Frequency of hapten-specific B cells, as I just mentioned, by flow cytometry, we can analyze that, and that's doable. We can look at IgG subclasses; pretty much anybody can do that, and we see the value in that.

Also, there are other things that may be more on the genetic side. We've seen, in our studies or others, that toll-like receptors may be involved or uninvolving [indiscernible] the responses to vaccines.

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So humans have well-characterized polymorphisms for things like TLR. So those are things that we can look and maybe help us to better understand the data.

Finally, and I just mentioned, interleukin 4 and other cytokines might be something that can be sampled in blood. Of course, if you do approaches like sequencing, you can come up with other unknown targets.

For that, I thank the people in my lab. Obviously, we have this wonderful collaboration with Sandy. I'm not that clinical person, so she's the right person to move this stuff forward. Then, as you can imagine, we have lots of people at different institutions, and then of course we have NIDA to thank for the generous awards that are supporting this research. Thank you very much.

(Applause.)

DR. STRAIN: We have a few minutes before we open it up for a more general discussion, if there are questions for Marco or Sandy.

DR. KOSTEN: A couple of things.

DR. STRAIN: Tom Kosten?

DR. KOSTEN: We found out in our early cocaine

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studies that some of what's happened is there are people who have cocaine antibodies before you ever vaccinate them, then there are a couple of other groups that have the same thing.

I guess the one question that I might wonder about is when you're finding your B cells that are already activated before you vaccinated them in any way, they may do just the opposite of what you think; that is, they're in fact identifying people -- well, in this case, they're mice -- who are not going to respond to your vaccine.

That's in essence what we found with the human studies. They already had these cells activated, and they were making very low affinity antibodies, and the high affinity antibody-producing B cells had presumably already been eliminated, which is a way that you get immune tolerance.

So the first question I had was, do you have any idea whether those cells are making high-affinity IgG reads [indiscernible], let's say, rather than making a bunch of IgM or some of the other classes of that low affinity.

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The second question, we found the same thing with the genetic polymorphisms, and that was using toll-like receptor adjuvants. I think adjuvants are going to be critical. The alum just isn't good enough. We found that if people have the TLR4 polymorphism that led to dysfunctional TLR4 receptors -- they weren't totally gone but they were dysfunctional -- you in fact got an augmented response to the vaccine when you gave a TLR4 agonist as your adjuvant, which was the opposite of what we thought until we thought about it some more, and then realized what you were probably looking at was when you have a poorly functioning receptor in terms of its G-protein coupling, and then that whole sequence that follows, you get more of those receptors.

If you finally stimulate them with an excess amount of your toll-like receptor antigen, then you do in fact produce much more things.

Related to that, I think probably what you're going to find with the interleukins is it's the toll-like receptors that drive those interleukins and why you produce more or less of that. So you might want to think more about those toll-like receptors.

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They're clearly critical for vaccinology.
Now they're looking at 2 -- I guess, let's see, 4, 5, 9, 13, 6 and 7. The big guys in vaccines are doing a bunch of that. But it's terrific to see what you're doing, and I think that it will be interesting if it turns out the opposite of what you might expect. But maybe you've got some data on that.
DR. PRAVETONI: Yes, I pretty much agree on all your questions. They were very good points. Starting from the last, what we've seen, and other people have seen, is that there are, as you pointed out, different TLR agonists. So depending on experience and depending on which vaccine formulation. Some may work better than others. For example, for us, TLR9 works much better with oxycodone vaccine, while TLR4s, they don't work at all, to the extent that if we give the vaccine to a TLR4 [indiscernible] animal, you don't really see a good response.
As far as the other questions, I agree with you that preexisting antibodies may interfere with vaccine efficacy. We didn't find preexisting antibodies; we found preexisting B cells, which may

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have a different implication.
Also, one of the things to point out is each drug is slightly different, so perhaps if you have something like cocaine, that may be -- I don't know. I guess if it's bought on the street, that means illegal mixture and it's containing excipients. Those excipients may work just like a carrier. Therefore, if you have optimized cocaine, loosely optimized, not covering the bar, you may have [indiscernible] and so forth.
In terms of something like oxycodone, it may not be the same, so until we actually test it, we can't really see. But even if there is a negative correlation between [indiscernible] specific B cells and response, but if you have no correlation, you can still stratify patients, either by move them out or hold them in, I guess.
I don't know if I've answered all your questions.
DR. KOSTEN: Yes. Other than the people -- just like cocaine, there's a bunch of other crap mixed in. Most of the drug abusers on the street

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have a bunch of other crap mixed in with their heroin, or their fentanyl, or whatever they're using. So it will be quite exciting to see how this turns out with white blood cells from people.
DR. STRAIN: Other questions?
DR. WEISS: I may have missed this, but how long does the antibody last for? Similar to the Vivitrol question, if somebody had some sort of major accident where they needed opioids, if they were getting the multivalent vaccine that hit a lot of the commonly used opioids, is this something you can overshoot? How do you deal with that situation?
DR. PRAVETONI: Well, I can answer on the preclinical, and then Sandy can answer on the clinical. As far as vaccine antibodies, vaccine antibodies [indiscernible], we find antibodies up to 6 months in animals, so we cannot project that. Also based upon what groups, including Dr. Kosten here, we foresee doing essentially most immunizations every year with a vaccine like that. So depending on variability, antibodies may last from 6 months to 1 year.
As far as selectivity and interference with

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other drugs, these particular antibodies, they are very selective, so we made sure that did not prevent action of, things like methadone, naltrexone, naloxone, and so forth. As far as protections, he pointed out Vivitrol, and Vivitrol is like 1 month. If antibodies can offer protection for 6 months, that has implication for overdose.
Then to your point, Vivitrol, which as an opioid antagonist blocks pretty much everything, including endogenous opioids, these things, they're very selective. So even if you have a multivalent, you can still [indiscernible] some by their opioids, and maybe use in a clinical setting.
Also, antibodies can be surmounted [indiscernible], not easily, but can be surmounted [indiscernible]. Unless you do an actual comparison where you have extended-release naltrexone versus a vaccine, and see how much drug you need to surmount, it would be kind of hard to tell. But I would say selectivity, that would be the benefit of the vaccine.
DR. COMER: I completely agree with that.
Roger, thanks for that question because that

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was asked of us a lot when we were doing the sustained release naltrexone. With this vaccine approach, in some ways, it's easier to address that concern for the reasons that Marco gave.

With naltrexone, it blocks all mu agonists, so you'd have to switch to a non-opioid or something that might have higher efficacy like buprenorphine, and you hope to override the blockade with naltrexone. With this, you could use methadone. You could use buprenorphine. If somebody needed pain, you could use anything that was off target. Then as a second step, as Marco said, the antibodies ultimately would be saturated, so there would be a dose of the agonist that would be able to provide pain relief.

Group Discussion and Q&A

DR. STRAIN: Thank you.

We're on the home stretch. The afternoon sometimes can get slow. For the last 25 or 30 minutes, I wanted to open this up for questions and discussions of any talks that have come up today, especially this afternoon's talks. We're going to go back through in a systematic way tomorrow, each of the topics that we've

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heard about this afternoon.

I wonder if people have questions. You've been not just digesting the snacks but also the content that you've been hearing and have something that comes out of that.

Roger?

DR. WEISS: I have a question about the psychedelic presentation. I find the data very compelling, but I worry a lot about what if this thing became commercially available. I think if somebody were going to be treated at Johns Hopkins by this group, that's very different, with two people holding your hand for 8 hours that have done this for hundreds of patients versus Joe Dokes [ph] saying, "Here, take this."

This seems like a don't try this at home sort of operation. In the hands of probably the world's experts in this, it seems like a very exciting sort of thing. How that would get rolled out is a big question for me.

DR. KOSTEN: I can say something --

DR. STRAIN: Did you want to make a comment,

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Bob, about that?

DR. DWORKIN: Well, I was thinking the same thing. I think perhaps the example of what Roger is talking about is the ketamine infusion center a mile away from my house, where people, is my understanding, go in and get ketamine, and they go out. There's no preparation, there's no set and setting, and there's no follow-up. That seems, to me, a concern. How do you build set and setting into something that's commercially available? Is that a REMS program?

DR. JOHNSON: You read my mind. I think this is one of the very perfect examples. This is exactly what REMS is for. We've already included -- in our recent abuse liability paper of psilocybin that I mentioned, we made some recommendations about its potential medical approval and development, and said a strong REMS would be very much called for, including -- this is not take two and call me in the morning. This is like outpatient surgery. This is like an endoscopy. So it's mandated, much like this Spravato, esketamine use; not like the wild west of off-label ketamine use.

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So yeah, the requirement for preparation, the requirement for screening essentially models what we and our colleagues in the field are doing now. I think REMS is going to be absolutely critical, and we're going to be strong advocates for a strong REMS.

DR. STRAIN: Roland, do you want to comment as well?

DR. GRIFFITHS: Yes. Just to reiterate, the set and setting conditions are going to be critical. FDA, the companies that are developing this, the academic researchers are all very sensitive to this issue. I'm imagining, should it ever reach approval, it would be done so under conditions in which perhaps there was a central pharmacy dispensing drug to a clinic with clinical providers that are well trained in this, but that all needs to get worked out through the regulatory structure.

DR. STRAIN: In the back?

MR. BARROW: Rob Barrow. I work for Usona Institute, one of the commercial IND sponsors of psilocybin for major depressive disorder. We've spent a lot of time thinking about this, and I know that our

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colleagues at FDA have spent a lot of time thinking about this.

I think one of the challenges for the REMS is that there are bounds on REMS that are legislated by Congress. The delivery of medical care can veer outside of a REMS. So while we very much endorse the idea of a strong REMS, we also think that there is a intrinsic need for the delivery of the care side of things, for medical professionals to build an infrastructure around this that would enable them to be trained and support delivery.

We are working on models of how this would be funded, ultimately; how is someone getting a session of psilocybin going to be able to afford or get reimbursement for an 8-hour session. If it's two people, hours of preparation, hours of integration. That's a complex issue, which we're spending a lot of time thinking about.

I think it's going to require both guidance from FDA and input on a REMS as tight as we're allowed to make it, but also practitioners stepping up and state level organizations stepping up to really drive

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home the importance of this and actually delivering the care.

DR. STRAIN: If I could comment on that, I think it's extremely dangerous to count on practitioners to step up and do it, frankly. I mean, all the people in this room will step up and be responsible. The problems are the Lance Goodmans of the world, who was an anesthesiologist in Delaware who had big billboards saying, "Come get subcutaneous naltrexone for cash on the barrelhead." It's only going to take a handful of people like that.

I think, though, one possibility would be to say, okay, this can only occur in particular settings that have, say, the Joint Commission or CARF accreditation to do this. I think that's the way to get it forward so that you don't have the IV ketamine guy down the road from Bob, because, otherwise, there's going to be somebody who's going to say, "Oh yeah. I've got it. I asked the person, hey --"

FEMALE VOICE: Are you ready?

DR. STRAIN: "-- are you ready?"

(Laughter.)

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DR. STRAIN: There's a document to read about this. We'll send you a document. We've got a couch, just like Roland.

(Laughter.)

DR. STRAIN: Frances?

DR. LEVIN: I would think it's like in the setting the way methadone is, that you have regulations. You get certification. You'd be audited. If you had that kind of level, at least initially, I think --

DR. STRAIN: Well, that's the Joint Commission --

DR. LEVIN: Right.

DR. STRAIN: -- or CARF. Tom?

DR. KOSTEN: If you don't mind changing the topic a little bit about the -- the problem we have in opiates right now is getting people on naltrexone, and we've now had several studies to demonstrate once you do that, they in fact look like they do -- maybe even better than buprenorphine.

I don't know how. I guess they got my number from Herb Kleber. But I can't tell you the number of

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people that call me about ibogaine and that I should be giving ibogaine to opioid addicts. And if I did that, they would go through detox with -- they would just hallucinate it away, and it would all disappear.

Has anybody tried any of this to really markedly attenuate opiate withdrawal syndrome? Is that possible? Is that something -- I'm sorry. I don't mean to look at you and put you on the spot.

DR. GRIFFITHS: Are you asking about ibogaine?

DR. KOSTEN: No, no. I'm asking about real drugs, and ibogaine, as far as I know, rots your brain; maybe more ibogaine doesn't. But it's the concept that's here, which is you have something that might work for what is a real problem for us right now. We've got a wonderful blocker, but getting onto it has not been so easy.

DR. GRIFFITHS: That's certainly been one of the clinical targets that we've considered in talking about opiates. As Matt outlined, there are many different ways to go, but that's a very attractive one, and it also --

DR. STRAIN: I'm sorry. I didn't hear Tom's

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question. What clinical target?
DR. KOSTEN: Opiate withdrawal.
DR. STRAIN: Withdrawal.
DR. GRIFFITHS: And going on to naltrexone would have the advantage of protecting people from overdose, which is very attractive. There are a whole bunch of different ways to go; very interesting ones.
DR. KOSTEN: I think of that one as something that you can get your answer in a 10-day trial. It's a fast one. If it works, it works, but it's like clonidine or lofexidine.
DR. GRIFFITHS: And the answer is whether or not they go on naltrexone?
DR. KOSTEN: Yeah. That's the outcome. You don't need to show that naltrexone works. There's plenty of data that works.
DR. STRAIN: Kurt, did you have a question?
DR. RASMUSSEN: I love out-of-the-box thinking, but it sounds like to me opioid withdrawal on a hallucinogen is a recipe for a bad trip.
(Laughter.)
DR. KOSTEN: What you figure out, you'll miss.

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DR. STRAIN: I would propose that we actually can get people off opioids. The problem is not getting people off opioids; it's getting people to stay off opioids. Because if we had a way to get people off opioids and they would stay off it for 10 years, we would basically put everybody in the hospital for a week, get them off, if we can do that. Then if they could stay off for 10 years, we'd be great. The problem is that people relapse.
So I would propose -- and I think the three of us have discussed this, and we've talked about everything else, I think -- the model should be what happens if you can take somebody and get them off opioid, and give them a psilocybin session; can you decrease the risk of relapse? That would be a game changer.
DR. JOHNSON: That's, in fact, the direction that we're interested in. In fact, this whole idea that ibogaine does something special -- first of all, there's virtually no human research on that. There's very compelling non-human research with the normalization of the [indiscernible] response that's

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probably mediating the reductions and drug self-administration.
We don't know that this isn't going on with psilocybin and the other classic psychedelics; number one. Then number two -- this is my general ibogaine kind of answer; number two is exactly like Eric said. The action is all in the long-term response. If it takes putting people asleep for a few weeks or sending them to Club Med, it's easy. There are ways to get people off. But then also, you name the drug, and there are so many people that relapse long after the withdrawal has passed.
It strikes me that if we're on to something, the real power in these is really a fundamental change in the positive reinforcing potential of the drug of abuse, and the craving, if you will, the long-term, and the rewriting of the narrative surrounding that drug that can have an effect long term, after the withdrawal. But it's all an empirical question.
DR. STRAIN: Let me just --
DR. KOSTEN: No. You can't talk. You're only the moderator.

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DR. STRAIN: I'm the moderator, but I'm going to jump in.
Let me just make a quick economic point. Methadone treatment is probably something on the order of $45,000 a year. I remember having a conversation with Johns Hopkins' healthcare insurance provider years ago and saying, "Oh, it will run about $40,000 a year," and they said, "Oh, that's not bad. And then at the end of the year they're cured?" And I said, "No. Then it's another $45,000 the next year."
(Laughter.)
DR. STRAIN: And they go, "Well, how many years does that have to go on?" And I said, "Well, in some cases, it's 20-30 years." And they said, "Oh, that's not a sustainable economic model for us."
If you could say we've got a high probability of 5 years but they don't have to be in methadone treatment, you will have the methadone treatment community eating you alive because it's such a threat to them, because you can do it for much less than 20[000] or $25,000.
Tom, what were you going to --

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DR. KOSTEN: Just to follow up, how long after they're opioid free would this treatment be thought as -- after 5 days of acute detox? Do you have to be a month until you're really off it? Do you have any parameters with that? I guess I didn't quite understand that from the presentations.

DR. STRAIN: They haven't done the study yet; they don't know. They're still designing the study.

DR. KOSTEN: Oh, so you're still figuring that one out. No wonder I couldn't figure it out.

(Laughter.)

DR. KOSTEN: You don't know.

DR. STRAIN: Sandy?

DR. COMER: I wonder if, Matt and Roland, you can talk a little bit more about the potential abuse liability of psilocybin. I come from a generation where people were using mushrooms every weekend to get high, so I'm surprised that you're seeing so little of it. Did you have to be really selective in the participant population that you included in your trials, or what?

DR. GRIFFITHS: No. Let's see. In terms of

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abuse liability, again to reiterate what both Matt and I said, NIDA doesn't consider these to be drugs of addiction. They don't produce at least compulsive, repeated self-administration.

Do people use them intermittently of the type you say? I'm sure there are subgroups that do. Were we selective in picking people? No, most of the people who came into our studies -- except for a couple of studies that used psychedelic experienced people who were interested in psychedelics. But most people did not have histories of use, or if they did, it was just intermittently.

Under those conditions, when you expose someone to a high dose of psychedelic, this is really a challenging experience. For most of those people, they're not about to seek it out again. If they were going to do it again, they would want to do it under highly supportive conditions.

I think the kind of situation you're talking about, people using mushrooms on weekends, you're talking about relatively low doses, and then in a social context, that's going to be supportive of that,

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but this model looks very different from that.

I don't imagine, that the doses that we administer, that you'd have many people running back to seek it out again. If they're interested in re-exposure to psilocybin, they can look up on the internet how to grow mushrooms and do it themselves. Psilocybin mushrooms are almost freely available, although they're illegal.

Matt, do you have anything further?

DR. JOHNSON: If this is approved as a treatment and the numbers increase, you're going to get -- if you expose 2 million people to this, you're going to get people that never used before, and then they do use every once in awhile. We haven't seen it so far. I think that's got to be part of the landscape.

The typical response is, so many times -- and some people are just so compelling when they say it -- "Holy cow! People do this for fun? You've got to be kidding me." They just can't imagine it and part of that I think is the really substantial dose.

We so often get the feedback -- and I'm sure

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Michael, and Peter, and Randy can speak to this, too, from their experience -- that folks will say, "I can't imagine having done this without the preparation. I would have been completely lost, and it would have been dangerous."

Part of that is our whole framing, to really encourage that, the importance of this framework. I think it's largely been successful. But in the grand scheme of things, I think it's likely there's going to be some of that.

Fortunately, we know it's a drug that even if they do get into extra medical use, it's not going to be a daily use habit, and probably not going to be a whole lot of disordered use, and hopefully it's kept to a minimum. But in the risk-benefit ratio, if you're looking at getting them off, if it's effective -- a big if for opioid-use disorder -- yeah, it still might be a positive intervention.

DR. COMER: Do you think it would be like an unintended consequence of what you're doing? You're publishing your data on these really high doses of psilocybin. Somebody who has used mushrooms before,

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they may say, "Oh wow. Maybe if I take 10 mushrooms, I'll be able to stop smoking, I'll be able to feel less depressed," and do it on their own. I don't know. I'm a worry wart.

DR. GRIFFITHS: No, we worry about it, too. And the cultural narrative around this now seems to be so skewed positively, and it's an issue and concern. We have these state level decriminalization and legalization initiatives for psilocybin and other compounds. I don't know how to manage that, frankly. I don't think diversion of chemically synthesized psilocybin is going to be an issue at all. But they're very powerful change agents, and unless we want to keep it a secret from the culture and the world, that information is going to be out there.

DR. STRAIN: We've got others. We've got Peter, then Tanya, and then Roger. Peter?

DR. HENDRICKS: I'll just add to that a little bit. We're about half-way done with a pilot trial of psilocybin facilitated treatment for cocaine dependence. We do ask our participants if they'd be willing to participate in a medication session like

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this again, and almost universally the response is I'd rather not, or no, "but I might consider it if at some point in the future I felt like maybe I really needed it, and of course only under very similar conditions."

Many people have reported that it feels like a lot of work. It's not especially pleasant, which is interesting because these mystical experiences can be very positive and experienced as a very positive event, but at the same time not the kind of experience that people wish to repeat. We had one participant liken it to running a marathon. They might say it was meaningful to me, and I'm glad I did it, but it's just not something I'd want to do on a regular basis.

DR. STRAIN: Interesting. Tanya?

DR. RAMEY: I have some small concerns. It seems to me that the discussion that we are having is around superficial things, such as, for example, like, oh, there are good changes; people have changed. We don't know how they have changed, how their lives have changed; not based on self-report, but, really, based on real data, functionally, what changed in their lives.

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Then again, I don't hear the discretion about cognitive changes, which are common to, actually, not only opioid users, but to other addicts. It's far above and beyond just executive functioning, and it affects the high levels of cognition. Apparently, that's what is changing, but you need to name that. What are those mystical experiences?

It's kind of a overarching feature of an addict, is they change in the higher level of -- they start to become conscientious. The first thing, when you deal with an addict, he or she changes -- changes goes to zero, practically. Maybe there is something on that level, and maybe it's not a mystical experience, that we call mystical experience, but what is it?

A window opens up into the self-perception. Everybody who's dealing with addicts, they know that their self-understanding, based on even psychometric scales, is impaired, so that's what you're repairing, practically. And whether it's mystical experience, or how, it translates to a higher level of consciousness. Conscientiousness is a very important trait, and if you're having all those long-term positive

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consequences, maybe that's where you need to focus.

DR. GRIFFITHS: There are just so many questions to be asked about the nature of these experiences. We're just scratching the surface. In Matt's presentation, he went through a number of the mechanistic possibilities.

You're absolutely right. Under the conditions in which we administer it, the appearance is that it skews very positively, and certainly people are reporting these positive changes in moods, attitudes, and behavior. Nonetheless, I think we should be extraordinarily sensitive to downside risks and adverse effects, and this all needs to get worked out in research over time.

DR. STRAIN: Roger, then Kit. I'm going to interject myself.

Let me just, Tanya, say when we've had these internal discussions about the opioid study, for example, I said, well, what we want to see is we want to see people stop using illicit opioids. That's what we really want.

If we've got an opioid user who says, "Well,

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I'm still using, but I've had one of the top five most powerful experiences I've had in my life," that's good, but at the end of the day, I want him to stop using.

In that vein, what I'd come back to is the pilot study of smoking cessation because if you can get smokers who have failed 2 quit attempts -- wasn't that the pilot study, failed 2 quit attempts?

DR. JOHNSON: They all to have tried, yeah, multiple times; right.

DR. STRAIN: Multiple times, at least two. And you've got 50-60 percent cessation at 6 months, that's a game changer. Chantix, which is our best, did something like 20 percent, so my head explodes when I think about that because that's a behavior change, not to denigrate having a truly wonderful experience.

Roger, then Kit.

DR. WEISS: I want to change the subject to cannabis.

DR. STRAIN: Yes!

(Laughter.)

DR. WEISS: Trying to study medical cannabis is so difficult because there are hundreds of thousands

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of pre-/post-studies going on every day with people using all kinds of things on their own to treat whatever it is they're trying to treat; whether it's CBD that they buy at the gas station, or whether it's cannabis.

I think of medical cannabis sometimes like if someone said we have medical food; well, what kind of food? Because it could be anything. The problem is the tortoise and the hare, that these natural experiments are going on a mile a minute and research moves at this glacial pace.

There's this study recently, a European study, that talked about adolescent cannabis use and its negative effects during adulthood. It said people with high THC content did the worst, defined as greater than 10 percent, when average now is 16 percent.

So by the time something is done and is published, it's so far behind the time, that it becomes irrelevant. I just don't know how we deal with that. If there was some opportunity for some big data solution, that would be great, but we can't get access to any of the data.

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DR. STRAIN: Let's see. Ryan, did you want to respond to that? Did you have any thoughts?

DR. VANDREY: I don't really have a response to that; I agree. It's a big issue because cannabis is not cannabis, is not cannabis. We're using one umbrella term for something that describes a massive array of products that have different effects, different pharmacologies, and different time courses. There's so much variability.

The term "cannabis" doesn't mean anything anymore. It's not useful from a scientific perspective, so we have to drill down and talk about it, about a THC product, a CBD product, a CBG product, and we have to talk about it with respect to formulation and route of administration.

DR. STRAIN: Kit?

DR. BONSON: These cognitive questions are really fascinating, especially when we're dealing with the psychedelics. But those are really intellectual questions; they're academic questions. And hopefully, if there is continued interest in psychedelics, it's something that NIDA would want to -- but let me finish.

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This is not a regulatory question. For regulatory purposes, we don't need to know what the mechanism of action is. This was like a shock to me when I first started working at FDA because you didn't need to -- like it was good; we kind of wanted to know, but maybe we didn't know.

All we need to know is that it's safe and that it's effective. And if we can show those two things -- all of these other things are fascinating, and they lead to other directions for new research, but for the particular product that we're talking about, it's not a regulatory question. I just wanted to make that distinction.

DR. RAMEY: For example, there would be an endpoint that is related to change in social cognition, not an executive function because cognition is not like a car. Executive function, there's something beyond executive function, which is really important in addiction.

For example, there are measures on psychometric scales, which has a social cognition, that could be very important for psilocybin because it seems

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to me that there's something there that changes, like what he's described as a positive change in life, and that's what it is.

DR. BONSON: Right, but in the end, we're going to be asking does it tell somebody get off this drug. That's the bottom line.

DR. STRAIN: Let me let Dr. Dworkin have the last word.

DR. DWORKIN: It's not interesting enough to be the last word. It's a question for --

DR. STRAIN: Then step up your game, Bob.

(Laughter.)

DR. DWORKIN: It's a question for Ryan.

In Canada, of course, Sativex is approved for neuropathic pain associated with multiple sclerosis. I was just wondering, given that we know exactly what Sativex is, is there any anecdotal experience, among Canadian psychiatrists, I suppose, and addictionologist, with using Sativex for OUD? Because we know what it is.

DR. VANDREY: I'm not aware of anybody using Sativex to treat opioid-use disorder. Part of the

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issue, too -- and you're not seeing any off-label prescribing of Epidiolex here in the U.S. because it's prohibitively expensive, and insurance isn't covering it for anything, except for Dravet or Lennox-Gastaut.

So we have a problem there of how do you get it out there making a fit? But that approach where you have a defined product, it's manufactured GMP, you know the dose, and it's going to be the same every time is really what we want, and I think we're going to start to see more of that emerge.

But again, it's picking. Well, do you pick Epidiolex, do you pick Sativex, or do you pick some other thing? Do you pick Charlotte's web? What do you pick, and how do you do it, and what makes the most sense?

I think we need to, again, come back and look both at preclinical data and look at these observational studies, and not epidemiological observational studies but longitudinal observational studies, where you look at changes within the same individual.

We're a part of a research program that's

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doing that. Stacey Gruber is doing it. Mark Ware is doing it. There's a group in Arkansas doing these similar kinds of longitudinal natural history type studies, where we can gather data on, well what happens to people using cannabinoids for any different reason?

Then we can pick people with pain or opioid-use disorder; what are they using, how are they using it, and how often, and try to glean some information from them to then try to say, "Well, let's pull this into the lab and then go to the clinic from there." But we need some sense of where in the array of products to start, I guess. Then it becomes dose finding, and then efficacy.

DR. STRAIN: Thanks. That was alright.

(Laughter.)

Adjournment

DR. STRAIN: We've gone over a little bit, but there's a sense of some of the discussion we may be starting to get into tomorrow.

Thank you to our speakers throughout the day today. Thanks to all of you for your participation. Dinner will be from 7:00 to 9:00 on the first floor.

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If you were here last night for dinner, I think it's in that same space back there. Otherwise, we'll see you at breakfast tomorrow morning, as well. Thanks, everybody, and have a good evening.

(Whereupon, at 4:37 p.m., the meeting was adjourned.)

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