

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

November 21, 2019

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6	TREATING OUD (B-MOST-O)
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12	Thursday, November 21, 2019
13	9:05 a.m. to 4:37 p.m.
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1	P R O C E E D I N G S	
2	(9:05 a.m.)	
3	Overview, Introduction, and Goals	
4	DR. STRAIN: I realize just now standing up	
5	here that there's a big mirror behind me.	
6	Does it show my bald spot?	
7	(Laughter.)	
8	DR. STRAIN: That's my biggest concern right	
9	now.	
10	(Laughter.)	
11	DR. STRAIN: I'm Eric Strain, and I will be	
12	moderating this session, this meeting, along with my	
13	distinguished colleagues, Dennis Turk and Bob Dworkin	
14	from ACTTION.	
15	Welcome to this meeting, Beyond the Mu Opioid	
16	System for Treating OUD, or as we call it, B-MOST-O, is	
17	the acronym that's been used here. I'm going to just	
18	do a few housekeeping things, but before I get started,	
19	maybe I'll ask Bob Dworkin to come up and say a few	
20	words about ACTTION. Many of you are familiar with it,	
21	but perhaps not all of you, and Bob can explain to you	
22	the organization.	

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1 Bob?

2 DR. DWORKIN: I'm Bob Dworkin, half of Dennis

3 Turk, who's over there. My colleague Dennis Turk and

4 the ACTTION public-private partnership with the FDA, I

5 want to welcome all of you to this meeting.

6 ACTTION launched by the FDA in 2010, so we're

7 almost 10 years old at this point. I want to start

8 off, even though they're not here, by acknowledging the

9 steadfast support of Dr. Sharon Hertz and Dr. Allison

10 Lin over the last 10 years in supporting ACTTION and

11 all of its activities.

12 The mission of ACTTION, it's evolved over the

13 past 10 years, but it's currently to accelerate the

14 development of treatments with better efficacy and/or

15 safety tolerability in four different therapeutic

16 areas, which is where ACTTION started, but then was

17 expanded to include substance-use disorders, peripheral

18 neuropathy, sedation, and anesthesia. Those are the

19 four areas that ACTTION covers.

20 Substance use disorder, part of ACTTION, has

21 been led from the beginning by Eric, and it is

22 completely accurate to say that we would not be here

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1 and we would have accomplished absolutely nothing with

2 regard to substance-use disorders without Eric's help,

3 mentorship, and leadership of that part of the ACTTION

4 public-private partnership. So thank you very much.

5 What ACTTION does is to really focus on how to

6 optimize the design, analysis, execution, and

7 interpretation of randomized clinical trials across

8 those four therapeutic areas. We've done a bunch of

9 things, ranging from systematic reviews and consensus

10 meetings to actually sponsoring various types of

11 studies and developing novel clinical outcome

12 assessments.

13 So ACTTION is willing to consider anything

14 that could help move forward the development of better

15 treatment in those four diverse therapeutic areas.

16 There have been multiple stakeholders over the

17 last 10 years for ACTTION; obviously professional

18 societies; government agencies like FDA, NIH, DEA,

19 et cetera; academic clinical researchers; patient

20 advocacy organizations; foundations; and definitely

21 pharmaceutical and device companies. I'm sure I've

22 left some stakeholders out. The general public, of

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1 course, is a stakeholder when we're talking about the

2 development of improved treatments.

3 The funding for ACTTION, in case you're

4 wondering, has come from grants and contracts from the

5 FDA -- the FDA started ACTTION -- and also unrestricted

6 support from pharmaceutical and device companies; a

7 little bit philanthropy; and a little bit of royalties.

8 Those funds are supporting this meeting and all of

9 ACTTION's other activities.

10 Have I left anything out?

11 DR. TURK: What the end product is going to

12 be; what we're working toward.

13 DR. DWORKIN: This meeting or in general?

14 DR.. TURK: This meeting.

15 DR. DWORKIN: I'm going to defer that question

16 to Dr. Strain. That's out of my wheelhouse.

17 ACTTION has a website updated on a very

18 regular basis, and it's a simple website address. It's

19 www.action, with two T's, .org. Let me say, because

20 it's so important these days to do self-promotional

21 things, I'm going to promote ACTTION by saying we're

22 all very pleased that at some point in the middle of

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1 last year, ACTTION surpassed 100 publications in

2 peer-reviewed journals. So that's one measure of our

3 success over the last 10 years, though I think not the

4 only measure.

5 Any questions from any of you about ACTTION,

6 how it works.

7 MALE VOICE: Our website.

8 DR. DWORKIN: www.action, with two T's, .org.

9 Alright. Thank you all very much. Take it

10 away.

11 Presentation – Eric Strain

12 DR. STRAIN: Thank you, Bob.

13 This meeting is focused on -- I'm going to

14 just go over some of the big picture aspects of this

15 meeting. We're going to be focusing on examining

16 outcomes measures, risk-benefit assessments, and trial

17 designs for studies of the treatment opiate-use

18 disorder that may need to be modified or developed as

19 the field identifies and studies novel non-mu opioid

20 treatment interventions. As you'll see, we're going to

21 hone in on four particular topics over the course of

22 the day and a half.

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

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

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

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1 interactive and thoughtful that way.

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

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

22 I will maybe do a little sidebar on ACTTION in

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

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

14 DR. STRAIN: Did you bring your checkbook?
 15 Let's see. A few housekeeping things.

16 Needless to say, silence your phones. I was saying to
 17 Valorie, who's helping to staff the meeting, one of the
 18 best ACTTION meetings we ever had was in a basement of
 19 a hotel where there was horrible WiFi service.
 20 Everybody was really engaged in active because nobody
 21 could look at their email, but it sort of dank and
 22 dungy down there.

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

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

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

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1 peer-reviewed paper come out of it. Sometimes they're
2 commentaries. We just did one on craving in JAMA
3 Psychiatry. We did one on a scoping review that
4 Annie's had; a review on cannabis outcome measures that
5 Dustin Lee published.
6 So I'm not exactly sure what the product will
7 be from this meeting because we have four different
8 topics; as I mentioned, sleep aids, vaccines,
9 psychedelics, and cannabis. But I think that we will
10 be trying to produce some form of a paper out of this.
11 That's usually our goal for these things. Often, and
12 typically, we'll look at who's attended, and these do
13 turn into papers that have 20 or 25 or 30 co-authors,
14 so there are opportunities in that respect as well.
15 I think that was my last slide for this. Does
16 anybody have any questions about any of that, ACTTION,
17 the meeting, meeting, what we're trying to do?
18 DR. KOSTEN: Are there minutes that are going
19 to come out of this or is there going to be some sort
20 of -- everybody's presentation gets put on line, or
21 what's going to happen with that?
22 DR. STRAIN: Often, we do put the PowerPoint

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1 presentations on the ACTTION website. I think we've
2 been doing that regularly, right, Dennis?
3 DR. DWORKIN Yes. So the standard is the
4 presentations will all go online, and the speakers can
5 take out any slides that they want to take out. So the
6 presentations go online; names and affiliations of all
7 the participants; the agenda for the meeting. And
8 typically, we do put the transcript of the recording
9 that's being made online. So you should all watch what
10 you say because it's quite possible it's going to be
11 available on the Web in a couple of months.
12 That's not a decision we've made. We've been
13 encouraged by FDA to put transcripts online, so we do
14 that almost always.
15 DR. KOSTEN: The next question to that is it's
16 one thing for the speakers to get all their stuff
17 online and be careful; it's something quite different
18 for me to be careful when I ask a question, and ask it
19 in such a way that the New York Times finds it
20 interesting. So when we say stuff as participants --
21 DR. DWORKIN: It's a great question. There
22 has not been, to my knowledge, anyone who's dug through

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1 the transcripts that are available online and written
2 about it in the New York Times or any other
3 publication.
4 As you can imagine, the transcripts of a day
5 and a half, two-day meeting like this are extremely
6 lengthy, and it would be a challenge, I think, for
7 anyone to read through them. That's, of course, not to
8 say that it couldn't happen, so it's possible, but to
9 my knowledge, it's not ever happened. We actually have
10 wondered, given preparing the transcripts is not
11 inexpensive, is there anyone who's actually looking at
12 them. But yes, it's possible that could happen.
13 DR. KOSTEN: We are in the city where they
14 seem to read 800-page documents overnight.
15 DR. STRAIN: And Tom, that comment is now in
16 the transcript.
17 (Laughter.)
18 DR. TURK: I don't know if you're aware of
19 this. Since we do the transcripts, and since they are
20 recorded and someone tries to type out, we ask people
21 to say their name before they make a comment, at least
22 the first time until we sort of know your voice.

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1 Therefore, you could, quote, "be identified" and you
2 should be identifiable if someone really wants to track
3 you down.
4 DR. STRAIN: Well, my name's Eric Strain.
5 (Laughter.)
6 DR. KOSTEN: And I'm Tom Kosten, and I think
7 that Eric Strain guy is just --
8 DR. STRAIN: Does somebody else have a
9 question or comment?
10 (No response.)
11 DR. STRAIN: Let's, obviously, try to
12 keep -- and I think we all will -- a collegial
13 discussion. This is not an opportunity to take
14 political stands in inflammatory ways, despite what
15 might be going on just a few miles from here.
16 Anything else?
17 (No response.)
18 Presentation - Eric Strain
19 DR. STRAIN: If not, without further ado, I
20 will introduce the first speaker who is me. I'm going
21 to be talking about an overview of the futures of
22 clinical trial designs for traditional mu agents. I'll

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1 try to move briskly. As the moderator, I'll try to
2 keep things on track.
3 The goal today, briefly, is to review some of
4 the study designs used today, and we should be thinking
5 about whether some, or all, or none of these should be
6 used when looking at non-mu therapeutic agents. I'm
7 going to be talking about clinical trial designs. Kyle
8 Kampman's going to be talking about outcome measures.
9 We'll have a break, and then Kenzie Preston's going to
10 be talking about risk assessments. So I will try not
11 to bleed into their discussions, although it's hard to
12 sometimes.
13 My own line is actually agents that have been
14 studied, I'll talk about briefly. Aspects of trial
15 designs, I'll go into a little more detail. Then
16 summary and final thoughts actually turned into sort of
17 a wastebasket for me as I was putting this talk
18 together because I discovered there were more and more
19 things I wanted to draw out. I've never done this
20 before, but I actually have figures in my summary and
21 final thoughts section on this talk. I apologize.
22 When I get to the summary and final thoughts, you may

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1 think I'm at the home stretch, but I'm not necessarily.
2 Let's start with agents that have been
3 studied. I think people are probably pretty familiar
4 with this. Basically, we've got mu agonists, mu
5 partial agonists, and mu antagonists, the three
6 categories to consider.
7 For mu agonists, things that have been studied
8 as I was thinking about this, obviously there's heroin,
9 or what has been rebranded as diacetylmorphine, not in
10 this country so much but in other countries, Canada,
11 Europe, European countries; hydromorphone, which has
12 typically been done as a control condition in some of
13 the heroin trials; LAAM, or l-alpha-acetylmethadol,
14 which is no longer marketed; methadone of course;
15 morphine in extended release form, and there were some
16 studies done in the UK. Tramadol has been studied, and
17 that's a weak mu agonist.
18 There may be others as well. I put this list
19 together, and then I would think of something and I
20 would add it. So there's been a wide variety of mu
21 agonists I would describe.
22 Now, on the mu partial agonist side, obviously

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1 the medicine is buprenorphine. There are a number of
2 other mixed agonist/antagonist opioids. They may have
3 partial agonist effects. I don't think any of those
4 have been really studied as therapeutic agents in any
5 meaningful way, beyond buprenorphine.
6 Then antagonists, there's of course
7 naltrexone, which comes in both an oral and an
8 extended-release form. Nalmefene and naloxone have
9 been studied in various ways; naloxone, not really, but
10 I felt for completeness sake, I would put it up here,
11 and nalmefene has been studied as an agent.
12 So for all three of these, I think there's
13 unique features to the design of trials for each of
14 these categories, especially when you -- and I'm going
15 to do this. I'm going to lump together these two and
16 contrast it with a mu antagonist because they're really
17 sort of two different categories, and in the Venn
18 diagram, the circle virtually doesn't overlap on them
19 in many ways.
20 With that in mind, let's dive into the aspects
21 of the trial designs that have been used when studying
22 these agents traditionally. Studies have been both

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1 inpatient and residential, as well as outpatient
2 studies. The residential studies, or inpatient ones,
3 are often within subject studies. They can test safety
4 and efficacy, assessing outcomes such as withdrawal,
5 suppression, or blockade efficacy. There have been a
6 number of these, especially with buprenorphine, as it
7 was being developed.
8 On the outpatient side, these are often group
9 designed studies. They're closer to the real world but
10 still can be quite different, and I'll come back to
11 this certainly. But they're closer to what might be
12 going on in clinical practice, although they still have
13 features that contrasted markedly from the real-world
14 experience with a medication.
15 Most efficacy and safety studies have
16 generally been these outpatient, randomized and
17 controlled clinical trials, and I'm going to primarily
18 focus on outpatient group design studies. We may want
19 to return to talking about within subject studies as
20 well as some point on our discussions over the course
21 of the next day or so, but for the moment, I'm going to
22 talk about the group design studies, the outpatient

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1 ones. As I mentioned, Kyle and Kenzie will be talking
2 more about outcomes and risk assessments.
3 So as I think about this, there are a number
4 of issues you have to consider when you're doing these
5 studies. Obviously, one is what's your control
6 conditions going to be, placebo versus active controls;
7 the dosing, fixed versus flexible dosing; the blinding
8 or masking; the transition on to the medication -- and
9 I'm going to come back and elaborate on these in a
10 moment -- the psychosocial support, the type of
11 support, the intensity of it, the inclusion and
12 exclusion criteria, especially with respect to
13 comorbidities and other drug use; and stratification
14 variables. Some of these can be more specific for
15 opioid-use disorder.
16 Let me go back, and I'm going to first talk in
17 a little bit more detail about the general aspects of
18 trial designs, and then I'm going to talk about aspects
19 that are specific to agonists, partial agonists and
20 antagonists. So let's start with general aspects of
21 trial designs. In particular, I want to talk about
22 three things: inclusion and exclusion criteria and

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1 psychosocial support and dose selection. We can talk
2 about more as well as stratification, for example, is
3 one that comes to mind, but I'm going to focus in on
4 these three for the moment.
5 So when thinking about inclusion and exclusion
6 criteria, the issue is whether you include or exclude
7 other drug use with opioid-use disorder. If anybody
8 tries to do an outpatient clinical trial of pure opiate
9 users, you'll probably need 20 years to find enough
10 people to populate it. Nobody's a pure opioid user the
11 way they might've been 50 years ago. Even 20 years
12 ago, we looked at subjects enrolled in an outpatient
13 clinical trial for opioid use, and at the day of
14 application, two-thirds of the urines were positive for
15 cocaine. So it's just not out there.
16 Then you get into this issue of balancing
17 feasibility, rigor, and generalizability, and I think
18 this is going to be something -- not to jump too far
19 ahead, but this is going to be something that we've got
20 to think about when we're talking about doing things
21 like psychedelics, for example, and who's going to get
22 enrolled in a psychedelic study; and if it's for

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1 opioid-use disorder, what else? Is it just opioid use
2 or is it all drug use, or is it nothing else, something
3 besides that?
4 I think it's also going to impact other
5 studies as well. For example, sleep aids, when we were
6 talking about sleep aids, are you going to exclude
7 people who are abusing benzos from a study?
8 There's other criteria that can impact
9 generalizability as well. Comorbid, psychiatric, and
10 medical conditions, these are very common in this
11 population. High rates of psychiatric comorbidities,
12 certainly hepatitis C, very common; HIV, not uncommon.
13 There's also this issue of past experience and
14 treatment and in studies, so certainly a lot of
15 people -- and I'm going to come back to this at the
16 end -- cycle in and out of treatment. Do you want to
17 exclude people who have been in treatment before or
18 should they be allowed in?
19 There's been a lot of concern now in the
20 broader field of clinical trials with people who are
21 professional research participants, who cycle in and
22 out of studies, and certainly do we want to exclude

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1 people who've been in past studies? The INSIG trials,
2 which are multisite trials of pharmacotherapies for
3 alcohol-use disorder, have been increasingly raising
4 the bar on excluding people who have been in past
5 alcohol pharmacotherapy studies, which makes it more
6 and more difficult to recruit.
7 The second thing I want to reflect on is
8 psychosocial support. This is generally overlooked in
9 clinical trials of pharmacotherapies for OUD,
10 especially the older studies that were done. Some
11 studies have attempted to standardize the treatment
12 provided, and we certainly tried to do that. We
13 created a manual at one point that our counselors would
14 use.
15 We've certainly seen standardization in other
16 trials. It's sort of weird or peculiar because, on one
17 hand, we're not necessarily doing a good job in our
18 clinical trials here. On the other hand, when you do a
19 clinical trial that's looking at psychotherapeutic
20 interventions, there's high rigor for what's being
21 provided. So you'll see further psychotherapies for
22 substance-use disorders such as alcohol-use disorder.

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1 This is something that I think we probably will need to
2 be considering as well going forward.
3 There's this risk of the loose cannon effect,
4 I call it. It's a therapist or counselor who provides
5 highly effective treatment that is superior to others
6 in a clinic, but that's not assessed; or the reverse, a
7 very ineffective therapist or counselor.
8 I got worried about this 25 years ago, where
9 we had a counselor in our clinic, and it was a research
10 clinic, and he was horrible with documentation. He was
11 horrible at doing what he was supposed to do. But he
12 would be out in the hallway all the time talking to all
13 the patients, not just his, encouraging them, slapping
14 them on the back, asking how they were doing, all these
15 things. And I just thought, "Oh, my gosh; this guy's a
16 loose cannon. You can't track what he's doing, and
17 he's going to be helping people in a way that I can't
18 quantify." So I'm aware of this effect.
19 Some non-OUD studies have simply dropped
20 in-person therapy. Again, the INSIG trials for
21 alcohol-use disorder are basically using a
22 computer-based treatment module. So rather than having

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1 any counseling services by a person, the participant is
2 put in front of a computer and has to complete certain
3 modules regarding their alcohol use.
4 Then dose selection, I want to talk about this
5 for a moment. OUD clinical trials often use fixed
6 doses. Everyone gets the same dose of the medication,
7 which may confound a medication effect with a dose
8 effect. Some studies have tested different doses, and
9 it's more rare, but some clinical trials have used
10 flexible dosing as an approach, double-blind flexible
11 dosing.
12 This, for example, is a study that Walter Ling
13 did about over 20 years ago now. He randomized
14 patients, opioid-use disorder patients, to 148 or
15 16 milligrams a day of buprenorphine. He's not just
16 saying, well, does buprenorphine compared to placebo
17 work, which was the study. The primary study was
18 8 milligrams primary outcome versus 1, with one being
19 an active placebo, but he also had these other
20 conditions as a way to try to look at dose effects.
21 This is a study that we did, again, 20 some
22 years ago, 25 years ago now, that used a double-blind,

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1 flexible dosing, and compared buprenorphine and
2 methadone. We flex people between 8 and 16 milligrams
3 a day of bup and 1590 milligrams a day of methadone,
4 because we were looking to test the medication effect
5 rather than a dose effect. So unbeknownst to people,
6 they could get dose increases if they were still having
7 positive urine samples in this study. There are
8 strategies to do that, and there have been other
9 studies that have done that as well.
10 Let me then turn to talking about aspects that
11 are specific to agonists, partial agonists, and
12 antagonists in these designs. I'll start with agonists
13 and partial agonists, and lump them together, because
14 they often overlap.
15 Most agonist and partial agonist studies,
16 they're using an agent that essentially replicates the
17 receptor effects of the abused drug such as heroin or
18 oxycodone or fentanyl. That's what buprenorphine and
19 methadone do. Generally, these agents have lower abuse
20 potential. They have something like a slower onset of
21 effect, a longer duration of action. There are easier
22 modes of administration than the abused drug. They're

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1 producing the same receptor effects, but in a way that
2 doesn't have quite the same profile of abuse liability.
3 When considering clinical trial designs with
4 mu agonists, placebo conditions become a challenge in
5 persons with physical dependence on opioids, which is
6 who's typically enrolled in these studies. As you
7 start to think about it, if you do a double-blind,
8 placebo-controlled study of methadone, anybody who's
9 assigned to placebo with the first dose, within a few
10 hours is going to say, "Hey, wait a second. I'm in the
11 placebo condition," because they're going to be going
12 into withdrawal, so that becomes obviously an issue.
13 There are strategies to address this. For
14 example, we did a study many years ago that looked at
15 periods of an agonist to achieve withdrawal before
16 transitioning to placebo dosing. This was this study
17 design. This was done back in the early 1990s.
18 Everybody who came in was put on 25 milligrams of
19 methadone, double blind. One group over 6 weeks was
20 titrated up to 50 milligrams, which in the early '90s
21 was considered a robust dose of methadone in the
22 Baltimore area, where we did it.

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

9 You can also use an active control that is
10 placebo like as another strategy. This goes back to
11 that Walter Ling paper again, where, as I mentioned,
12 they used a 1-milligram dose of sublingual
13 buprenorphine as an active control condition. The
14 thought was, well, people experience something with
15 1 milligram. So it isn't that they're just getting
16 placebo, but it's a low, and they expected it to be a
17 poorly effective dose.

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

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

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

16 The studies that were done with buprenorphine
17 25 years ago, the pivotal trials, may be harder to do
18 today, given the higher levels of physical dependence I
19 think we're seeing in populations now with the
20 widespread use of fentanyl.

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

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

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

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

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

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

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

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

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

1 took naltrexone in the first month of treatment. By
 2 month 4, it's down to -- not 86 percent; 86 people;
 3 6 people were on it by a month into it, so you see
 4 these dramatically high dropout rates.

5 This is another report from the same author on
 6 oral naltrexone, which is just really striking to me;
 7 386 patients expressed an interest in naltrexone; 242
 8 were withdrawn off opioids and got a dose; 153 got
 9 6 days of doses; 60 got 2 months; 3 took it for one
 10 year. So less than 1 percent of the people expressed
 11 an interest in oral naltrexone.

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

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

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

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

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

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

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

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

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

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

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

8 (Applause.)

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

14 Presentation - Kyle Kampman

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

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

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

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

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

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

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

19 The second trial here is much larger. It is a
20 600-plus patient trial. Patients were admitted and
21 were randomized to either 1 of 2 doses of lofexidine or
22 placebo, and again received the 7-day detoxification.

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

4 Other withdrawal management trials,
5 buprenorphine or methadone for the treatment for
6 withdrawal management; 45 subjects admitted to either
7 2 milligrams of buprenorphine, 30 milligrams of
8 methadone for 3 weeks, followed by 4-week dose
9 titration and 6 weeks of placebo medication. That was
10 in this trial. It's an old trial back from 1988.

11 Again, the primary outcome measure was the Subjective
12 Opiate Withdrawal Scale with secondary outcomes of
13 treatment retention and use of ancillary medicines for
14 withdrawal symptoms.

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

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1 analog scale.

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

11 Now, I'm moving up a little bit in here,
12 closer to the present day. We have studies of very
13 low-dose naltrexone. The first one, a Manneli trial,
14 and again, that was 127 subjects. They were put on a
15 6-day methadone detox and supplemented either with low
16 doses of naltrexone versus placebo. The primary
17 outcome, again, were the SOWS and the OOWS; with
18 secondary outcomes of treatment retention and use of
19 ancillary medicines.

20 Very low-dose naltrexone studied plus
21 buprenorphine. This is was a Sullivan trial. This was
22 150 subjects either randomized to a single dose of

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1 buprenorphine and then a gradually increasing dose of
 2 very low-dose naltrexone over a week versus a standard
 3 buprenorphine 7-day taper, followed by a 7-day period,
 4 and then followed by an injection of extended-release
 5 injectable naltrexone.
 6 Again, the primary outcome was simply
 7 transitioned to extended-release naltrexone, who got
 8 the naltrexone shot, and also looked at who got the
 9 second shot of extended-release injectable naltrexone
 10 after a month. They looked at the proportion of
 11 patients completing detoxification measured in an ad
 12 hoc way, and then the typical withdrawal measure, SOWS,
 13 COWS, and they also looked at depression scores using
 14 the Hamilton Depression Inventory.
 15 Then finally, a much larger trial with very
 16 low-dose naltrexone. This was a multicenter trial and
 17 involved about 380 subjects, and patients received
 18 either 3 days of reducing dose of buprenorphine plus
 19 extended-release naltrexone -- I'm sorry, plus oral
 20 naltrexone; so oral naltrexone plus a few days of
 21 buprenorphine, or placebo, buprenorphine, and oral
 22 naltrexone, or placebo, both of the naltrexone and the

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1 buprenorphine. They were tapered and transitioned on
 2 to extended-release injectable naltrexone.
 3 The primary outcome was a well-tolerated
 4 transition to extended-release injectable naltrexone.
 5 So not only did they have to get the Vivitrol shot, but
 6 they had to demonstrate that they weren't in severe
 7 withdrawal; so a COWS less than 12 and a SOWS less than
 8 10 was a successful transition. I also looked at some
 9 visual analog scales, desire for opiates, looked at the
 10 Clinical Opiate Withdrawal Scale, and then abstinence
 11 during the trial. This was an outpatient trial.
 12 Those are your withdrawal management trials,
 13 mainly standard measures of withdrawal and treatment
 14 retention being the main outcomes there.
 15 Let's move on and look at antagonist trials.
 16 Again, you have oral naltrexone, which I won't talk
 17 about at all. I'm going to mention some of the
 18 implantables, the Go Medical implant; there are several
 19 trials of that; Prodetoxone, the Russian implant, we'll
 20 talk a little bit about that; and I'm going to ignore
 21 the New Jersey implant and the Chinese implant since I
 22 couldn't find papers on those, but they are out there.

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1 Then we'll talk a little bit about injectable
 2 naltrexone, mainly talking about extended-release
 3 injectable naltrexone, Vivitrol. I also mention the
 4 Depotrex trial; that was done as well.
 5 For antagonist trials, first implants,
 6 Prodetoxone. This was a trial done in Russia,
 7 306 subjects randomly assigned to either an active
 8 implant plus active oral naltrexone, a placebo implant
 9 plus active oral naltrexone, or placebo implant and
 10 placebo naltrexone.
 11 So there were 3 groups followed for 6 months,
 12 and the primary outcome measure was retention and
 13 treatment without relapse, and relapse being defined as
 14 a return to physiological dependence. So anybody with
 15 positive urine drug screens received a naloxone
 16 challenge.
 17 Secondary outcomes included just percent urine
 18 negative drug screens, which they received twice a week
 19 and then relapse at 9 and 12 months follow-ups, and
 20 they looked at liver function test as well as a
 21 secondary.
 22 The Go Medical implants, there were two

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1 trials. The first one done in Australia involved 72
 2 subjects followed for 6 months on that, double-blind
 3 placebo controlled, active implant versus placebo
 4 implant. There's an interesting primary outcome. It
 5 was actually maintenance of therapeutic naltrexone
 6 levels; 2 nanograms per milliliter tested monthly was
 7 the primary outcome level and measure of that trial.
 8 The second primary outcome level and measure
 9 was also kind of interesting, the number of overdoses
 10 that required hospitalization at secondary
 11 [inaudible - mic fades]. The secondary outcomes in
 12 that trial was returned to regular heroin use more than
 13 4 days a week by self-report. Other heroin use was
 14 also a secondary outcome of that.
 15 The Go Medical implants were also studied in a
 16 Norwegian trial, and this was 56 patients randomized
 17 either to the naltrexone implant or treatment as usual,
 18 and again followed for 6 months. The primary outcome
 19 was self-reported opiate use, although they did verify
 20 that with hair testing, interestingly. Also, another
 21 primary outcome measure was the number of overdoses at
 22 the end of the 6-month period.

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

10 Depotrex, another injectable naltrexone
 11 product studied in a human lab trial as well as a
 12 clinical trial. In the human lab, 12 subjects were
 13 admitted, detoxed, given Depotrex, and then challenged
 14 with various doses of IV heroin. The primary outcome
 15 was the ability to block the opiate high and
 16 physiological effects of opiates; 26-item subjective
 17 effect of heroin visual analog scale; the SOWS; and a
 18 13-item opioid symptom checklist, and the Drug Effect
 19 Questionnaire. Secondary outcome: performance tasks
 20 and some neuropsych testing.

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

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1 actually. Patients were assigned to receive 2 doses of
 2 injectable naltrexone versus placebo and followed for
 3 8 weeks. It was a short trial. The primary outcome
 4 was number of weeks in treatment and percent opioid
 5 negative urine samples. The secondary outcomes, time
 6 to drop out; percent of urines negative for other drugs
 7 besides opiates; severity of opiate and cocaine use;
 8 CGI, both subject and clinician; and a visual analog
 9 scale rating opiate craving; and depression measured
 10 about by the Hamilton Depression Rating Scales.

11 That brings us to the last group of naltrexone
 12 trials, which are the injectable naltrexone trials.
 13 The first one was the Krupitsky trial done in Russia,
 14 250 subjects, 6 months, double-blind placebo control.
 15 The primary outcome was abstinent from opiates during
 16 week 5 to 24 of this 24-week trial, with secondary
 17 outcomes of number of opiate-free days; an opiate
 18 craving visual analog scale; number of days retained
 19 and relapsed to physiologic dependence, but again
 20 identified by a naloxone challenge.

21 The Lee trial, this one was written up in
 22 2016. This was a probationer trial, opiate-dependent

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

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

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

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

4 The other trial, the Tanum trial, was a
 5 12-week multicenter trial done in Norway, 159 subjects
 6 randomized to either sublingual buprenorphine or
 7 extended-release injectable naltrexone. The primary
 8 outcome was retention in the study and also the
 9 proportion of total number of urine drug screens
 10 without illicit opiates, and the number of days of
 11 heroin use and other illicit opiates.

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

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

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1 this case using the Drug Use Questionnaire, urine drug
2 screen results, and treatment retention, and measured
3 adverse events, secondarily.
4 The methadone trial that I'm looking at here
5 was an interesting trial, 179 subjects randomly
6 assigned either 12 months of methadone maintenance or
7 6 months of an extended methadone taper, followed by
8 6 months a psychosocial treatment. The primary outcome
9 was treatment retention, opiate use by self-report and
10 urine drug screen, and a bunch of secondary scales, ASI
11 again, risk of AIDS behavior, and treatment services
12 review.
13 Trials comparing buprenorphine and methadone,
14 the first one, the Johnson trial, randomized,
15 double-blind, controlled trial, looking at 8 milligrams
16 a day of buprenorphine, high dose of methadone,
17 60 milligrams or a low dose of methadone, 20 milligrams
18 a day. Patients followed for 17 weeks in this
19 particular trial, with the primary outcome being
20 treatment retention, percent opiate negative urine drug
21 screens and relapse, with a secondary outcome looking
22 at other drug use.

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1 Another trial looking at methadone, and in
2 this case comparing low-dose methadone, versus
3 high-dose methadone, versus LAAM, versus buprenorphine;
4 another 17-week trial with the primary outcome being,
5 again, treatment retention, percent opiate positive
6 urine drug screens, and then 12 weeks of continuous
7 absence by both self-report and urine drug screen data;
8 secondary outcomes looking at other drug use and
9 severity of a drug problem, visual analog scale.
10 Then finally, the last of these, the Hser
11 trial done in 2014, which was fairly huge, about 1200
12 patients randomly assigned to receive methadone
13 maintenance flexible dose versus buprenorphine, with
14 the primary outcome being simply treatment retention;
15 secondary outcomes being urine drug results obtained
16 weekly.
17 We're almost to the end of this, and then
18 we'll sum it all up and try to make some sense out of
19 it. I apologize for some of the repetition, but you
20 see the outcome measures are very similar across the
21 trials. The two injectable buprenorphine products have
22 very similar studies. CAM 2038 had a blockade trial

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1 and a clinical trial, and sub-blockade, the same.
2 First we'll talk about the CAM 2038, the
3 blockade trial, 47 subjects admitted, started on
4 CAM 2038 the weekly 1 of 2 doses, and then challenged
5 with hydromorphone. The primary outcome would be the
6 maximum rating on the drug liking visual analog scale.
7 The goal was to see if CAM would block the subjective
8 effects of the hydromorphone; the secondary outcomes
9 was drug high and desire to use, visual analog scales,
10 COWS, OOWS, and physiologic measures of withdrawal.
11 The clinical trial of CAM 2038 was 428
12 subjects randomly assigned, double-blind, double-dummy
13 to either CAM 2038, weekly for the first 12 weeks,
14 monthly for the second 12 weeks, versus sublingual
15 buprenorphine over the same period of time. The
16 primary outcome was the mean proportion of opiate
17 negative urine drug screens over 24 weeks, and there
18 was a responder rate, and the responder rate was
19 required by the FDA. No illicit drug use at
20 prespecified times while participants received either
21 weekly or monthly injections.
22 Secondary outcomes, urine drug screen results

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1 starting at week 4 and going on to week 24, visual
2 analog scales for craving opiate withdrawal symptoms,
3 supplemental buprenorphine, and supplemental
4 counseling, whether or not they were required during
5 the trials.
6 For extended-release buprenorphine
7 sub-blockade, the blockade trial was similar to the one
8 done from CAM 2038, but had a little change in that
9 they added a drug versus money choice task. Patients
10 were stabilized on the extended-release buprenorphine
11 and then received hydromorphone challenges during this
12 time. The primary outcome is the same as for CAM 2038,
13 which was maximum rating, and a drug liking visual
14 analog scale with a secondary outcome, which was a drug
15 money choice task, a progressive ratio task looking at
16 how hard they would work for a drug or money.
17 The clinical trial, which was published in
18 2019, 504 opiate-dependent subjects randomly assigned
19 to 2 extended-release buprenorphine conditions, 300
20 milligrams monthly for the first 2 months, followed by
21 100 milligrams monthly, or patients continued on 300
22 milligrams a month for the entire 6 months of the

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1 trial.

2 The primary outcome was percentage of
3 abstinence from opioid use defined as the percentage of
4 negative urine samples and self-reports of illicit
5 opiate use from week 5 to week 24 with a secondary
6 outcome of treatment success, in this case defined as
7 at least 80 percent opioid abstinence during weeks 5 to
8 24; also looked at treatment retention, withdrawal
9 scores on the COWS, and opiate craving visual analog
10 scale.

11 The last of the review slides, this is for
12 buprenorphine implants, three trials. I'm going to
13 talk about the first trial, the Ling trial published in
14 2010, which is 163 subjects randomized either to
15 placebo or to active buprenorphine implants and run for
16 6 months. The primary outcome was the percent of urine
17 drug screens negative for illicit opiates during the
18 first 16 weeks of the trial.

19 The secondary outcomes was the percent of
20 urine drug screens negative during the second half of
21 the trial and treatment failure; patients were allowed
22 to have rescue doses of sublingual buprenorphine during

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1 the trial under a schedule, and if you exceeded that
2 schedule, then you were considered to be a treatment
3 failure. So the number of treatment failures was a
4 secondary outcome, looked at opiate withdrawal
5 symptoms, craving on a visual analog scale, and CGI
6 severity and improvement.

7 The second trial of buprenorphine implant,
8 similar to the first, except they added a group that
9 received open-label, sublingual buprenorphine, and they
10 tightened the criteria for who was allowed to getting
11 rescue doses of the sublingual buprenorphine; ran it
12 for 6 months again.

13 The primary outcome was the same as the first
14 trial, was the percent of urine drug screens negative
15 for illicit opiates during weeks 1 to 16, with
16 secondary outcomes including urine drug screens during
17 the second half of the trial for completers, opiate
18 withdrawal symptoms, a craving visual analog scale, and
19 the CGI.

20 The third trial was markedly different from
21 the first two trials because the target was different.
22 It was sent to identify patients who would benefit from

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1 being placed on the implants who are already stable on
2 a lower dose of buprenorphine.

3 So you had to be stable on 8 milligrams of
4 sublingual buprenorphine for about 6 months. You had
5 to have 90 days of no drug use prior to being
6 randomized into that trial. And when you were
7 randomized into the trial, it was double-blind,
8 double-dummy, sublingual buprenorphine versus
9 buprenorphine implants, followed for 6 months.

10 The primary outcome was the proportion of
11 responders, and that was defined as participants with
12 at least 4 out of 6 months without evidence of illicit
13 opioid use, based on your urine tests and self-report;
14 urine test once a month with 4 random ones during the
15 6-month trial for a total of just 10 urine drug screens
16 over that 6-month trial. The secondary outcomes would
17 be retention, time to first use, opiate withdrawal
18 symptoms, and as almost always a craving visual analog
19 scale.

20 So what does this all mean? Efficacy outcomes
21 used depends on the goal. You have withdrawal
22 management trials, you've got blockade trials, and

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1 you've got maintenance trials. Again, I'm not going to
2 talk at all about the safety and adverse events that
3 were universally measured in all of these trials and
4 will be discussed later today, is my understanding.

5 For opiate withdrawal, or withdrawal
6 management trials, detox trials, the main outcomes,
7 almost always, obviously, opiate withdrawal signs and
8 symptoms with the Subjective Opiate Withdrawal Scale
9 being a favored withdrawal Scale, with a close second
10 being the Objective Opiate Withdrawal Scale, the COWS
11 somewhat third down the line in preference.

12 The Modified Himmelsbach Opiate Withdrawal
13 Scale was used in the one trial but not in the others.
14 Completion of detoxification is a clear primary outcome
15 measure, and in the more recent trials, it's initiation
16 of extended-release injectable naltrexone as the
17 primary outcome measure of choice.

18 Blockade trials, subjective effects of opiates
19 using drug liking visual analog scales was the two that
20 I looked at, the primary outcome in both of those; also
21 tend to measure withdrawal symptoms; visual analog
22 scales measuring high desire to use. People usually

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1 identify that differently in their particular trials.
 2 And of course, there was a drug versus money task in
 3 this one.
 4 In the clinical trials, the most common
 5 primary outcome by far was opiate use measured by urine
 6 drug screens. That was number one. Several trials
 7 used the combination of measuring opiate use by both
 8 self-report, supported by urine drug screens, and then
 9 retention was a distant second as to being a favorite
 10 outcome in the clinical trials.
 11 Relapse was a common trial, especially if
 12 you're looking at antagonist trials. Overdose was an
 13 interesting outcome in the Australian trials. Visual
 14 analog scales are used almost universally and mainly
 15 for craving, but other phenomenon show up on visual
 16 analog scales as well.
 17 The CGI is commonly used, but there was
 18 actually not a whole lot of instruments, like the
 19 Hopkins Symptom Checklist, the Temporal Satisfaction
 20 with Life. Those were used in some of the trials, but
 21 generally tended not to be primary outcome trials and
 22 not favored as outcomes, in general, in the clinical

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1 trials. And that I think is all I've got for you.
 2 (Applause.)
 3 DR. STRAIN: We have a couple of minutes
 4 before we go into a break. Are there questions?
 5 DR. DUNN: Eric, I have general thoughts about
 6 outcome measures and how they relate to retention
 7 withdrawal. Should we save those for the discussion
 8 after Kenzie's talk.
 9 DR. STRAIN: I think so, although I likewise
 10 have similar thoughts, but, yes, maybe focusing on
 11 this. We're going to have, before lunch, a chunk of
 12 time for general questions.
 13 DR. KOSTEN: I've got a question --
 14 DR. STRAIN: Tom Kosten, and that was Kelly
 15 Dunn that just asked.
 16 DR. KOSTEN: Yes, Eric Strain, that's right.
 17 When you look at these outcomes, the ones that
 18 we're doing, like 4 randoms during the month and then
 19 just one other, was there any way of looking at the
 20 validity of that, or reliability of that, or anything?
 21 DR. KAMPMAN: All you had were self-reports,
 22 and 1 urine a month and 2 urines a month, and 4 out of

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1 6 times. So you got 1 or 2 urines a month and
 2 self-report, so I don't think there's any way to look
 3 at validity.
 4 DR. KOSTEN: One of the things that happens
 5 when people come in for treatment for opiate dependence
 6 is that they only come into treatment when they're
 7 using pretty much every day, all the time, and they
 8 meet every criteria, 8 out of 8, in terms of having a
 9 diagnosis, and how much of that was true in these kinds
 10 of studies?
 11 The question we always have is experimenting
 12 when you have a blocker is very common. Rats learn in
 13 two trials, don't self-administer, but people, it takes
 14 20 before they get the point.
 15 DR. KAMPMAN: We'll see in a couple of those
 16 trials, they specifically eliminated looking at people
 17 during the first month, so they picked weeks 5 to 24.
 18 Krupitsky did it in his Russian trials, and the implant
 19 trials did the same thing.
 20 DR. KOSTEN: Is there any way to see if that's
 21 a good idea or a bad idea?
 22 DR. KAMPMAN: Not that I know of. Eric?

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1 DR. STRAIN: I don't know. I got stuck in my
 2 head, actually, thinking about something, which
 3 is -- maybe this relates to what you're asking,
 4 Tom -- we've got data sets where we collected urine
 5 samples like 3 times a week around a clinical trial,
 6 and it seems like -- maybe somebody's done this -- you
 7 could go back and look at, well, what's your
 8 sensitivity to detecting drug use if you drop that to
 9 just one randomly a week, picking at random one from
 10 each week out of the clinical trial?
 11 DR. KAMPMAN: You know, in the cocaine trials,
 12 Tom, there's a lot of controversy between how real is
 13 self-report, and a lot of people believe that it's very
 14 valid. In Philadelphia, it doesn't seem to be quite so
 15 valid.
 16 (Laughter.)
 17 DR. KOSTEN: We have a lot of liars in Texas,
 18 too.
 19 At any rate --
 20 DR. STRAIN: Philadelphia football fans,
 21 there's no Santa Claus training, only Eagles' games.
 22 DR. KAMPMAN: So true.

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

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

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

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

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1 versus external validity of these things. We would
2 like to have the same outcome measures for every study
3 so that we can compare studies, but it doesn't always
4 work, and I think that's a real challenge for the
5 field. Now, particularly when you get into different
6 kinds of treatments, it may even be more variable how
7 people measure the same thing.
8 DR. STRAIN: Next question?
9 DR. COMER: One thing that I think has not
10 been paid attention to enough, really, especially in
11 the withdrawal studies, is the use of ancillary
12 medications. There's always a background of other
13 medications that are allowed, or not allowed, or
14 whatever, and that can potentially have pretty big
15 impacts on the outcome measures, and there's no
16 consensus, I don't think, on that.
17 DR. KAMPMAN: I agree, because I'm a big
18 believer now on non-narcotic detox, based on my
19 experience in one of the very low-dose naltrexone
20 trials, where the placebo group just did great in
21 Philadelphia, and they got clonidine, trazodone, and
22 Imodium --

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1 DR. COMER: Exactly.
2 DR. KAMPMAN: -- and clonazepam, which made a
3 big difference.
4 (Laughter.)
5 DR. STRAIN: That was Sandy Comer for the
6 transcript.
7 We've gone over a few minutes, but we've got a
8 generous break time. So let's take a break now, and
9 we'll reconvene at 10:45. Thanks.
10 (Whereupon, at 10:22 a.m., a recess was
11 taken.)
12 DR. STRAIN: We are now going to go into a
13 talk by Kenzie Preston for our program. Kenzie's going
14 to be talking about an overview to risk assessments
15 used when studying traditional mu agents. So without
16 further ado, Kenzie?
17 Presentation - Kenzie Preston
18 DR. PRESTON: Good morning. I actually have a
19 cold, so hopefully, my voice will hold out. I'm going
20 to cover risk assessment in four areas: adverse
21 events, dependence potential, opioid antagonist
22 activity, and physical dependence potential.

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1 Adverse events, do undesired, harmful,
2 unintended effects result from taking the medication?
3 We know that there are mu receptors all over the body,
4 in both the central nervous system and the peripheral
5 nervous system.
6 If we give a medication, for example, for
7 analgesia, it's likely going to have effects on all
8 these other mu receptors. So indeed, if we look up the
9 list of adverse events associated with morphine, you
10 can see that the list is quite extensive.
11 It's also important to note that not all mu
12 agonists have the same set of adverse effects. Some
13 drugs have off targets of non-mu agonist activity such
14 as methadone, which causes QTc prolongation by blocking
15 the flow of potassium ions through the hERG channels,
16 and this can lead to even more serious adverse events.
17 Then there are also a set of molecule-specific
18 adverse events that relate to metabolism and allergy.
19 Codeine, for example, interacts with drugs that affect
20 the cytochrome P450 isoenzymes and has a higher than
21 expected rate of allergies. Meperidine is another
22 example of an opioid agonist, but it has a metabolite

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1 that has serotonin effects, which can lead to serotonin
2 syndrome.
3 This is a list of typical safety assessments
4 that are done in clinical trials with opioid drugs.
5 The only one I'm going to talk about a little bit are
6 the treatment-emergent adverse events. One approach to
7 collecting these is through spontaneous reports. The
8 research staff would ask the participant how have you
9 been feeling since your last visit? And if the
10 participant reports something, then they record it
11 appropriately.
12 They also would report anything that the
13 participant just spontaneously brings up outside of
14 being asked that question, or if the clinic staff
15 notices a participant, say, has an arm in a sling, then
16 they might ask about it. There are very specific ways
17 of what to report, the reporting procedures, and
18 following regulatory requirements.
19 Another approach is to actually have a
20 questionnaire. I took this from the NIAAA studies.
21 They use a modified safety questionnaire, which
22 includes three general inquiry questions, which they

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 analog scale, and then the MBG scale, which is a
2 16-item true/false subscale. I put some of the items
3 on here because none of them actually say I feel
4 euphoric. They're all a little more subtle than that.
5 This is a slide that shows the effects of
6 prototypic opioids with high abuse potential. That
7 includes drugs like morphine and heroin. They increase
8 ratings of drug effect, feeling high. They reliably
9 increase ratings of liking on the MBG scale. They also
10 increase ratings on the sedation scales, PCAG, and they
11 have a very specific constellation of affects that they
12 produce, including things like nodding. As I
13 mentioned, participants can identify them as being an
14 opiate under double-blind conditions.
15 The other kinds of drugs that they typically
16 studied at the Addiction Research Center were these
17 non-morphine like opioids, which we now know probably
18 have some kappa agonist activity, things like
19 nalorphine and cyclazocine. They also increase drug
20 effect and high, but they don't reliably increase
21 liking. They increase ratings on this dysphoria scale,
22 as well as the sedation scale, and the subjective

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1 affects that people reported included things that
2 aren't typically seen, like heroin, including feeling
3 drunk or nervous. When participants were tested with
4 them, they identified them as being like a barbiturate.
5 This results from a typical addiction research
6 center study that compared heroin, morphine, and
7 methadone. The top panel shows the objective measures
8 and the bottom panel shows the subjective measures.
9 You can see that the effects of these three drugs are
10 virtually identical on these measures. The only
11 differences is that heroin is about twice as potent as
12 morphine and methadone.
13 These are a result of a study that looked
14 compared morphine and pentazocine, and now morphine
15 being agonist/ antagonist opioids. You can see that
16 pentazocine didn't produce the level of liking that
17 morphine did. It also didn't increase the MBG scale to
18 the extent that morphine did, but it did increase the
19 LSD scale.
20 Back when tramadol was being considered for
21 marketing in the United States, Don Jasinski and I did
22 a study comparing tramadol to morphine by the

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1 intramural administration route, and tramadol did not
2 increase liking and it did not increase the MBG scale.
3 But it turned out we were looking at the wrong route of
4 administration, and the subsequent studies, such as
5 this one that compared tramadol to oxycodone, we did
6 find that tramadol increased liking to the same degree
7 that oxycodone did.
8 There were still, nevertheless, some
9 differences. For example, when they looked at the
10 maximum time, how long did it take for that high effect
11 or that liking effect to come on, for oxycodone, that
12 was about an hour, whereas for tramadol, it was about
13 2 hours.
14 In yet another study that compared tramadol to
15 oxycodone and codeine, what was noted is that tramadol
16 also increased ratings as having some bad effects as
17 did codeine, but you can see that oxycodone, that's on
18 the left, did not produce increases in ratings of bad
19 effects.
20 That's going to switch to drug
21 self-administration. This is a procedure in which
22 participants are given the opportunity to take drug in

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1 the laboratory. It's a behavioral response. It's
2 often required for them to earn a dose of drug, so that
3 work requirement can then increase with each successive
4 dose that they earn. It's called a progressive ratio
5 system. The point at which people say I'm not going to
6 work anymore for that dose of drug is called the
7 breakpoint.
8 These studies often include the opportunity to
9 choose between the drug and an alternative reinforcer,
10 and that could be a different drug, it could be money,
11 and it could be food. The outcome measures that are
12 used for these can be the proportion of test drug that
13 the participant chose to take or the breakpoint, or
14 sometimes both.
15 They're often done in two phases. So the
16 person gets the opportunity to sample the drug that
17 they're going to then have the opportunity to work for,
18 and then they have that opportunity; so there's the
19 sampling and then the self-administration. In these
20 kinds of studies, other kinds of measures can also be
21 collected within the context of the study.
22 This is a paper from Sandy Comer's lab. They

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 100 milligrams and placebo. They tried it in five
2 different people, and only three of them were actually
3 able to learn that discrimination and meet that
4 acquisition criteria that I mentioned.
5 When they tested the three patients who got
6 the discrimination, 2 out of 3 of them discriminated
7 hydromorphone as tramadol, and then they did a
8 naltrexone pretreatment intervention, and they found
9 that that shifted the response curve to the right. The
10 investigator suggested that the results showed that the
11 discrimination was based on mu opioid effects, and
12 that's actually consistent with that previous study
13 that I just showed you.
14 I thought I'd go through advantages and
15 disadvantages of each of these. For the single-dose
16 studies, the advantages are that the methods are very
17 well established, and it really takes a minimum of
18 number of sessions to do the study. You just need
19 enough to do a good dose-response curve.
20 Disadvantages is it relies entirely on
21 self-report. And if you have a mix of good effects and
22 bad effects, you kind of have to interpret what's going

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1 to predominate when the drug's out and available.
2 For self-administration, the advantages are
3 that it has faced validity. After all, drug taking is
4 what we're generally concerned about, and it's a
5 behavioral or objective measure. You can get other
6 kinds of self-report measures at the same time that
7 you're collecting the self-administration data.
8 Disadvantages are that it can take more
9 sessions than the single-dose studies. For example,
10 the tramadol self-administration study I told you
11 about, it took 7 sessions to get subjective reports,
12 that was the sampling, but it took 14 sessions to get
13 the drug self-administration data. So that's time,
14 money, and exposure of the drug to research
15 participants.
16 While it sounds kind of simple, in fact, it's
17 harder to get right than it seems, and there are a lot
18 of factors that can affect a participant's decision to
19 take drug. So they might come in, and they're there to
20 earn money, and it doesn't matter what you offer them,
21 they'll choose money. Or they might come in, and
22 they're there to get drugs. And it doesn't matter what

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1 the alternatives are; they're going to choose to take
2 drug. I think a lot maybe more parametric work needs
3 to be done to get a very reliable procedure.
4 For drug discrimination, advantages are that
5 it's a behavioral measure, again, and it gives one
6 answer to similarity, so it assimilates across those
7 divergent kinds of measures. So you don't have to
8 decide; the participant tells you what is it most like,
9 and you can get those other kinds of measures at the
10 same time.
11 The disadvantage for drug discrimination, it
12 takes many more sessions than it would for a
13 single-dose study. Also, I didn't have time to go
14 through it, but in fact it does matter what you choose
15 for your training drugs and the doses of those drugs.
16 I next want to jump to opioid antagonist
17 activity, and will administration of the drug
18 precipitate withdrawal symptoms in the patients taking
19 opioid agonists? It actually is really important, and
20 I found many papers where they talk about having to
21 deal with buprenorphine precipitated withdrawal. So
22 you'd want to know in advance whether your drug

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1 produces precipitated withdrawal.
2 Among the many things that were done at the
3 Addiction Research Center, it was actually
4 characterizing physical dependence. What were the
5 effects of these opioids when they were given over long
6 periods of time? At the top there are the
7 physiological and at the bottom are subjective
8 measures. Then they looked at what happened when they
9 abruptly stopped them.
10 Believe it or not, there was a time when
11 people didn't believe that opiate withdrawal was real,
12 so they did a lot of work in this area characterizing
13 it and developing scales. In fact, that Himmelsbach
14 scale that Kyle mentioned was developed. I think he
15 was one of the early scientific directors of the ARC.
16 One of the things they also found when they
17 would say test one of the novel drugs while people were
18 on repeated administration of morphine, that it would
19 produce withdrawal-like effects. So they developed a
20 method for looking at precipitated withdrawal. This is
21 the dose-response curve for four different drugs:
22 cyclazocine, naloxone, nalorphine, and pentazocine.

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

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

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

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

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

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

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

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

13 (Applause.)

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

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

22 DR. PRESTON: I looked at several

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

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

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

18 DR. PRESTON: Right.

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

22 DR. PRESTON: Right. The trial that was done

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1 at Hopkins specifically noted that. If you're treating
2 opiate withdrawal, there's not like a switch where you
3 say, yes, that's definitely opioid withdrawal or not;
4 it's a series of symptoms and signs. I know in that
5 trial, they decided to just collect all of those as
6 possible adverse events, and then they looked at the
7 proportion of them that were likely related to opiate
8 withdrawal. And I think in that trial, half of the
9 adverse events that were reported were actually
10 symptoms of opiate withdrawal.
11 So that is something that you need to
12 consider, is the effects of the indication that you're
13 trying to treat.
14 DR. STRAIN: Sandy Comer?
15 DR. COMER: I know that assessments of
16 dependence potential is one of the standard things that
17 we do for evaluating the abuse potential of a drug, but
18 this is a little bit off target from what you're
19 talking about. But what about for non-opioid
20 medications? We don't really focus on the issue of
21 tolerance development to medication effects. I'm just
22 wondering if that's something that we should be

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1 thinking, especially in the context of a non-opioid
2 medication for treating opioid-use disorder.
3 DR. PRESTON: I personally think that's an
4 underreported problem. There are some medications like
5 clonidine, which do have a discontinuation syndrome.
6 The SSRIs, I think there are lots of people who are put
7 on SSRIs who are not aware that when they try to stop
8 them, they're going to have withdrawal symptoms, and
9 that actually more attention needs to be paid to that.
10 DR. COMER: That's an excellent point. That's
11 not kind of the one I was thinking of. For something
12 like clonidine, I absolutely agree with you, that if
13 you use it too much, then there might be this rebound
14 hypertension that should be evaluated clinically.
15 What I was sort of thinking about was -- and
16 the reason I'm thinking about it at all is that I
17 reviewed some grants recently and this was a topic that
18 came up in the data, where these medications were being
19 evaluated as potential maintenance medications for
20 treating opioid-use disorder, but when you look at the
21 preclinical data, the effect of suppressing opioid
22 mediated responses was pretty good in the beginning,

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1 but then it sort of dissipates pretty rapidly.
2 DR. PRESTON: Yes.
3 DR. COMER: So I'm thinking that maybe we
4 should think more about tolerance development to
5 therapeutic effects for non-opioid medications that we
6 don't really think about with opioid-mediated
7 medications. You know what I mean? Naltrexone doesn't
8 seem to produce tolerance to its therapeutic effects;
9 methadone and buprenorphine don't either.
10 DR. PRESTON: Yes. Well, certainly among the
11 opioid mu effects, there are different rates of
12 tolerance that develop. So I think it's a pupillary
13 response; supposedly the tolerance doesn't develop to
14 the same degree that it does for other, like feeling
15 good effects.
16 So, yes, I agree with you that that would be
17 something that should be tested. A lot of the
18 preclinical studies, they kind of ignore that effect of
19 repeated administration, and they can say, Oh yeah,
20 that drug blocked self-administration of cocaine, but
21 does it do it the next day, and the next day, and the
22 next day?

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1 DR. COMER: Right.
2 DR. STRAIN: Right. Or sleeping.
3 DR. PRESTON: Yes.
4 DR. STRAIN: Patrick Finan.
5 DR. FINAN: Kenzie, I'm wondering in the work
6 reviewed, how often at all are you running into abuse
7 liability being assessed based not so much on the
8 positive agonist effects, but more on the relief of
9 states like pain, particularly non-withdrawal pain and
10 non-withdrawal related aversive states, like negative
11 affect?
12 DR. PRESTON: I can't think of any. I mean, I
13 know that people talk about that. People take opioids
14 to reduce the withdrawal that they're getting from
15 something else, but I don't know.
16 DR. STRAIN: Kit, do you have --
17 DR. BONSON: Kit Bonson. I'm with the FDA.
18 So use different patient populations. That's the main
19 way you don't confound that issue. In assessing abuse
20 potential, you would use recreational opioid abusers
21 who are not physically dependent and are not pain
22 patients, so there is no question about that.

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

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

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

1 outcomes that would support medication development.

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

8 Even if we look at just self-report versus
 9 observer-rated reports, we get very different outcomes.

10 We're starting to dig into this a little bit in the
 11 context of a trial that Eric ran that compared
 12 clonidine, tramadol, and buprenorphine for detox
 13 outcomes, and we're looking at the time at which people
 14 self-reported.

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

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

5 DR. STRAIN: Thanks. Did we clap for Kenzie?
 6 Let's clap for Kenzie.
 7 (Applause.)
 8 Group Discussion

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

16 Go ahead, Kelly. Say something.

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

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

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

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

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1 can be modified by numerous other things, and the FDA
2 has actually recommended against it in their guidance
3 to industry on this topic, because you can incentivize
4 retention. So to use that as a formal indication
5 driving outcomes seems problematic, but it's the one
6 thing that we all have for all of our trials, reliably.
7 I think we're in this kind of unique state
8 with opiate-use disorder, where it's very challenging
9 to know what the right outcomes should be, so we're all
10 using multiple different things, and some consensus I
11 think would be helpful.
12 DR. STRAIN: Els?
13 DR. HOUTSMULLER: I'm Els Houtsmuller from the
14 Patient Centered Outcomes Research Institute, and I
15 just want to say that I really agree with your point,
16 and I was struck by how much this is the case, that the
17 outcome measures, they're all sort of measuring the
18 same thing, but there's really a wide variety. And
19 there is an interdisciplinary group that is actually
20 trying to establish core outcomes across all these
21 studies.
22 I think they go by the name of COMET, and

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1 they're doing this in a number of different fields. I
2 think it would really help the field because it would
3 allow for meta-analyses much more easily, et cetera,
4 and that might be something to connect with.
5 DR. STRAIN: El, it was called COMET?
6 DR. HOUTSMULLER: COMET, C-O-M-E-T. They
7 started in England. They are also connected to a
8 number of American groups, CMTF in Baltimore, and
9 others.
10 DR. STRAIN: They flew across the ocean?
11 DR. HOUTSMULLER: They did.
12 DR. STRAIN: Okay, like a comet. Sorry.
13 DR. BROWN: Randy Brown from the University of
14 Wisconsin. Great points, and I think one of the
15 challenges becomes that in some of these cases, I don't
16 think we have complete clarity around the construct.
17 We really want to measure. I'm referring specifically
18 to lapse, relapse, retention, and craving, and whether
19 the instruments used or the measures put forward in a
20 lot of these studies are really validating what we
21 understand as those things [inaudible - mic fades].
22 I think if we were to ask a number of people

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1 in this room to write a definition of any one of those
2 things, we'd get a lot of different answers. So I
3 think at some level, the step needs to be taken back
4 around validation with some of these things, too. But
5 Roger had also brought up the point earlier about what
6 that looks like may also depend on the context and
7 design of the study and the goal of the intervention
8 when we're talking about something like relapse or
9 lapse. But that's an additional challenge when we're
10 talking about consistency between studies and what
11 measurement should look like.
12 DR. STRAIN: That certainly
13 resonates -- thanks, Dr. Brown -- with our last ACTTION
14 meeting on craving, where we concluded that we don't
15 know what it is. So despite Kyle's point that there
16 are all these visual analog scales asking about
17 craving, it's not really clear that the craving I
18 experience is the craving that Bob experiences; that's
19 the craving that Dennis experiences.
20 Els?
21 DR. HOUTSMULLER: I want to add a point to
22 that, and that is that it would be, I think, very

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1 helpful to really represent a patient voice in the
2 discussion about which outcomes to include because
3 there's a risk of this being in its own world, and when
4 you look at -- I mean, the FDA meeting was really
5 interesting in that respect because it really had an
6 enormous group of people who are talking about what
7 matters to them.
8 There are ways to do that that actually can
9 work very well. I used to be very skeptical about
10 this, but now having been involved in some of this, it
11 can work very well. And it would make for a good
12 connection to effectiveness studies because currently
13 there's such a disconnect between what happens in
14 efficacy trials that are very rigorous, and they have
15 to be, and they have to be done. But I think there
16 could be more of a connection by including some of
17 these more patient-centered outcomes earlier on.
18 DR. STRAIN: Thanks. Brian, and then Kit.
19 Your name, by the way, even though say your names.
20 DR. KILUK: I'm Brian Kiluk from Yale. A
21 related question along this, which is actually a more
22 basic question for a meeting like this and thinking

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

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

20 DR. STRAIN: Kit?

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

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

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

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

22 So staff as well that are working with the

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1 patient population can often share a great idea.
2 Sandy?
3 DR. COMER: This is Sandy Comer. I think
4 that's a really interesting point that was raised about
5 focusing on opioid use per se versus opioid-use
6 disorder, and I have a lot of thoughts around that.
7 One is, I think, unlike for other drug classes, opioid
8 use is sort of inextricably tied to opioid-use
9 disorder, which kind of differs from cocaine.

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

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

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

5 DR. STRAIN: Let me follow up. I felt myself
6 thinking -- I just wrote it down -- are we ready for
7 treatment of opioid use and opioid-use disorder 3.0?
8 In other words, if you think of methadone as
9 the first wave of pharmacotherapy for opioid-use
10 disorder, kind of a revolution, and then the next
11 revolution in some respects was buprenorphine, that
12 really impacted the treatment of opioid use and
13 opioid-use disorder, are what we say is we're ready for
14 3.0? Which is something different and something beyond
15 simply getting people to reduce or stop their opiate
16 use, which maybe kind of a variant of what you're
17 saying.

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

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1 urine positive rates down, but maybe that's where this
 2 is at. Obviously, that also fits with the afternoon
 3 session, so I may be self-serving in proposing that.
 4 Tom had something, and then Els.
 5 DR. KOSTEN: Along with what Sandy Comer and
 6 you are both saying, I think that the opiate field
 7 offers us an opportunity to actually open up the other
 8 areas of substance abuse improvements that have been
 9 quite valuable for alcohol, where heavy drinking has
 10 now become a reasonable FDA outcome to have, based on
 11 other aspects of wellbeing that have gone on with the
 12 patient. Whether that's psychological status, medical
 13 problems, getting arrested, paying your taxes, getting
 14 employed, all of those things, we have excellent data
 15 with opiates, and methadone maintenance in particular,
 16 but also with buprenorphine, that those things improve.
 17 The fact that this is an illicit drug, you
 18 could say, the way alcohol is, but the standard in the
 19 community for alcohol is that everybody drinks some,
 20 and the standard in the community is not that
 21 everybody's taken opiates all the time, it seems to me
 22 that we could learn something from opiates that builds

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1 and is applicable to those drugs that are traditionally
 2 viewed as not so good for you, like stimulants,
 3 amphetamines, cocaine.
 4 If we can carry that system of looking at that
 5 type of outcome, that's psychosocial, not just total
 6 abstinence, that will move us a long way with
 7 [inaudible - mic fades] the pharmaceutical companies,
 8 at least, willing to go into the stimulant area and
 9 other areas, where right now criteria just seems
 10 totally unrealistic, which is completely stopping. And
 11 it's almost like smoking, where you're supposed to
 12 completely stop for a year, for example. And even
 13 after you stop your treatment, which is ridiculous,
 14 most things are not approved on that basis.
 15 But there's a standard that I think we can
 16 make sense out of. It's just like opiates and urines,
 17 where we can look at this question of how good are the
 18 self-reports. We can look at this question of is it
 19 good enough if you only get once a week, and carry that
 20 over to the other area, where we have nothing right
 21 now, and where, in fact, we're not likely to get
 22 anything with big pharma support because they don't see

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1 a road forward.
 2 So long speech, but that's how I see this as
 3 useful; not so much for opiates. We've got treatments,
 4 but we've got some other areas. We need better
 5 agreement from the FDA that these are reasonable
 6 outcomes, as happened with alcohol, and that happened
 7 from data within alcohol. We're not going to get that
 8 same level of data from cocaine, or methamphetamine, or
 9 anything. We have it with opiates.
 10 Can we analogize it and move it over to make
 11 some of the other drugs of abuse more amenable to
 12 participation of investors that it's going to take to
 13 jump this 100 million dollar barrier that you have to
 14 putting something in the market?
 15 DR. STRAIN: Els?
 16 DR. COMER: I just think there are two ways of
 17 approaching this, one looking forward and one looking
 18 back.
 19 DR. STRAIN: Sandy Comer speaking.
 20 DR. COMER: Looking forward, we need to
 21 develop instruments that can capture quality-of-life
 22 type issues, or sort of clinical indicators of

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1 improvement, of functioning, of life; that kind of
 2 thing. I know that Walter Ling has developed this
 3 T questionnaire. There are others that are also being
 4 used.
 5 Looking backward, I was thinking there's a
 6 little pot of money for somebody who has time to do
 7 this, but we could analyze some of the existing data
 8 that we have of buprenorphine maintenance, methadone
 9 maintenance, and try to tease apart individual
 10 patients' outcomes. Because there are a variety of
 11 people who have complete abstinence to total relapse,
 12 and if we have CGI data, for example, that are included
 13 in the trial, then we can go back and see whether or
 14 not people who have reductions in use show improvements
 15 in functioning.
 16 DR. STRAIN: Els?
 17 DR. HOUTSMULLER: So a related point is that I
 18 think it's important to think about different
 19 populations for different outcomes, or different
 20 outcomes for different populations, because the opiate
 21 using, and abusing, and addicted population is very
 22 different from twenty years ago, as we all know.

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1 Things that work or matter for people who have been on
 2 pain medication are now being moved off in this effort
 3 to reduce that kind of prescribing and may be
 4 interested in very different outcomes than people who
 5 have been using heroin and a lot of other drugs for the
 6 last 30 years.
 7 DR. STRAIN: Tanya?
 8 DR. RAMEY: Tanya Ramey. Since we started to
 9 talk about alcohol and what's happening in the alcohol
 10 field, we haven't touched upon that. Sandy maybe tried
 11 to move in the direction. It's the direction of
 12 endophenotypes. That is a field that is not so much
 13 addressed right now. As we are here, at the present
 14 day, we are not discussing that yet.
 15 The patient's that is [indiscernible] drug
 16 developed is pointed into the direction of what to
 17 focus on as an endophenotype. The previous speaker was
 18 just talking about that in a certain way. That would
 19 open up a whole new approach. I the alcohol field is
 20 now doing several endophenotypes testing. So maybe
 21 that's the future or one direction of the future.
 22 DR. STRAIN: Thank you. Roger?

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1 DR. WEISS: This was the subject of a previous
 2 ACTION meeting, or a couple of previous ACTION
 3 meetings, and led to a paper that Brian was the first
 4 author on. To quickly summarize that, the way that the
 5 alcohol field got no heavy drinking days as an
 6 acceptable outcome for medication approval was by
 7 showing that having no heavy drinking --
 8 [inaudible - mic fades] -- to an absence of negative
 9 consequences.
 10 The drug field has traditionally not measured
 11 negative consequences. The ASI asks about problems,
 12 but they don't say have you had family problems as the
 13 result of drug use in the last month? They just say
 14 have you had family problems in the last month? Which
 15 may or may not be related to your drug use. The more
 16 chronic those problems are, the more likely they are to
 17 continue, even if you stop using drugs; whereas the
 18 alcohol field, their use of the sip and the drink asks
 19 have you had family problems related to your drinking.
 20 I think that it's a big leap to expect
 21 functioning necessarily to increase quickly, but you
 22 can potentially make negative consequences go away by

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1 reducing substance use. I think that's something that,
 2 when we design clinical trials, could help lead the way
 3 to figuring out whether there are a certain amount of
 4 reductions that can reduce negative consequences enough
 5 to be meaningful.
 6 DR. STRAIN: Thanks. Bob Dworkin?
 7 DR. DWORKIN: I'm sure this is a naive
 8 question. For a clinical trial, you need a primary
 9 endpoint, a single primary endpoint. There are
 10 co-primary endpoints, multiple primary endpoints, but
 11 that's going to increase your sample size
 12 significantly.
 13 So at the end of the day, why isn't the
 14 primary endpoint the incidence of OUD at some follow-up
 15 time point as diagnosed by DSM-5 in your active arm
 16 versus your control arm? And if you show a
 17 statistically significant reduction -- that's really
 18 point prevalence -- in that follow-up prevalence that's
 19 also clinically meaningful, that's your primary
 20 endpoint. But it sounds like we're all disagreeing.
 21 Everyone else in the room disagrees that that's a
 22 meaningful primary endpoint.

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1 DR. STRAIN: Let me take a crack at that. One
 2 of the dilemmas has been -- and I should know
 3 this -- has been the window of time, typically, that
 4 DSM-4 and 4-TDR [ph] uses for the criteria that can
 5 qualify for the diagnosis. Now, you could change that,
 6 of course.
 7 Does anybody know offhand what is in DSM-5?
 8 DR. DWORKIN: Twelve months.
 9 DR. KILUK: There is an early remission
 10 qualifier, which is the absence of the criteria for a
 11 3-month period. It's considered early remission, which
 12 could potentially be useful as an outcome, if everybody
 13 entering the trial has the disorder.
 14 DR. DWORKIN: And you could also do 6 months.
 15 DR. STRAIN: Or 1 month, or whatever, 6 weeks.
 16 Yes, you could tailor to it. But we've had this
 17 discussion as well in some other ACTION meeting, and
 18 they all blur together sometimes. We also thought
 19 about looking at the number of DSM criteria that a
 20 person fulfills. Brian, maybe you had that in your
 21 paper. You're saying yeah.
 22 DR. KILUK: Yeah. I've actually been doing

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

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

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

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

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

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

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

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

7 (Whereupon, at 11:50 a.m., a lunch recess was
8 taken.)
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2
3 AFTERNOON SESSION
4 (12:48 p.m.)
5 DR. STRAIN: We're going to go ahead and get
6 started with the afternoon session. I think there
7 are a few people still trickling in, but for the sake
8 of trying to stay on time.
9 We're now moving into mu agents that can be
10 potentially used for the treatment of opioid-use
11 disorder. We're going to start with the cannabinoids,
12 and it's my pleasure to introduce Ryan Vandrey, who
13 will be giving this talk.

14 Presentation - Ryan Vandrey
15 DR. VANDREY: Thanks, Eric.
16 This is a really interesting thought exercise
17 because this isn't something that I would necessarily
18 think about or even endorse prior to this week, but
19 it's been fun to think about this. Here are my
20 disclosures. This isn't something new. There's a lot
21 of talk in the media about cannabis opioid interactions
22 and the concept of using cannabis to treat opioid

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1 disorders. In Maryland here, it's actually been pushed
 2 for as being approved as a therapeutic use of cannabis.
 3 Just a quick background here, cannabis was
 4 legal initially, then it was made illegal. Now we're
 5 in this process of slowly moving back towards
 6 legalization. It started at state levels with
 7 California, and now we're rolling in, I think, 34 U.S.
 8 states of legalized medicinal use of cannabis. Several
 9 of them actually have opioid treatment or pain relief
 10 as an indication for medical use of cannabis.
 11 Recently, we've got the legalization of hemp
 12 at the federal level. Hemp is a subcategory of
 13 cannabis defined by the THC concentration of being 0.3
 14 percent or less. This map shows you the areas in which
 15 you have legal cannabis. In the dark green states is
 16 where any use of cannabis is legal for adults; the
 17 slightly less green states are medical cannabis law
 18 states; and then the really light green states don't
 19 have medical cannabis.
 20 As we go through this, I think part of the
 21 exercise here is to understand what we mean by cannabis
 22 versus cannabinoids because what used to be a very

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1 simple term that described the dried flowers from the
 2 cannabis plant that would be smoked by individuals is
 3 now very, very different, so it requires some
 4 distinction and level of understanding. So I'll go
 5 through this a little bit and kind of come back to this
 6 several times throughout the talk.
 7 Cannabis as a botanical is a very complex
 8 entity. It's composed of over a hundred different
 9 phytocannabinoids, which are chemical contents that are
 10 specific and unique to the cannabis plant, in addition
 11 to hundreds of other chemical entities that are not
 12 necessarily unique to the cannabis plant but could have
 13 behavioral or physiological effects.
 14 This should be distinct from cannabinoids
 15 globally because there are synthetic cannabinoids that
 16 interact with the endogenous cannabinoid receptor
 17 system that are not part of the cannabis plant. So
 18 there's a lot of diverse pharmacology that can happen
 19 with all of these compounds. When we're talking about
 20 botanically derived versus synthetic, there can be very
 21 different effects based on those pharmacological
 22 differences.

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1 As I mentioned, there's this distinction
 2 between cannabis and hemp. Hemp is cannabis, but not
 3 all cannabis is hemp. In addition, when we think about
 4 these phytocannabinoids and some of these differences
 5 in pharmacology, the two main players here are THC and
 6 CBD. THC, up until recently, was universally the most
 7 predominant phytocannabinoid, or the most abundant
 8 phytocannabinoid in the cannabis plant.
 9 THC is what drives most of the hallmark
 10 effects of cannabis. When you think about acute
 11 cannabis affects, you feel high, you get giddy, you
 12 laugh a little bit more, you appreciate music a little
 13 bit more, you get the munchies, and things like that.
 14 Those are THC-driven effects.
 15 CBD is kind of the new guy on the scene and
 16 has really been promoted as driving a lot of the health
 17 promoting and therapeutic effects of cannabis. It's
 18 important to note and to remember, though, that both
 19 THC and CBD are part of FDA-approved products. THC is
 20 available as an FDA-approved medication for the
 21 treatment of wasting syndromes or nausea due to
 22 chemotherapy or advanced AIDS wasting syndrome.

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1 CBD is part of a formulation that was just
 2 recently approved to treat rare childhood seizure
 3 disorders. THC and CBD in their therapeutic use is not
 4 a totally novel and new idea, but in both of those
 5 cases, these molecules have been kind of isolated and
 6 provided in a vehicle of some description, whether it
 7 be sesame oil or some other kind of oil. They're also
 8 limited to oral consumption.
 9 Whereas THC tends to drive a lot of these
 10 hallmark, intoxicating, euphoric experiences of using
 11 cannabis, CBD tends to not have the same properties,
 12 and it's because of a differential pharmacology. CBD
 13 works as an allosteric modulator of the endocannabinoid
 14 system, whereas THC is a partial agonist. It has a
 15 number of other off-target pharmacological targets as
 16 well, and we're still figuring out and determining
 17 which ones those are.
 18 Contrary to popular belief, CBD does not
 19 mitigate the acute effects of THC in most circumstances
 20 for most types of effects. We see a little bit of a
 21 signal there for it mitigating some anxiogenic effects
 22 of THC, but not much else.

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1 In addition to these two, there are several
2 other minor cannabinoids that we don't know a lot
3 about, and there have been no human controlled studies
4 of cannabigerol, cannabiniol, cannabichromene, chromium
5 and some of these other things. The reason I bring
6 that up is that with the advent of legal retail
7 cannabis sales in the U.S., we're starting to see these
8 products pop up.
9 This is an example over here of a CBG oil
10 that's on sale right now. So we don't know a lot about
11 what that kind of a product is going to do, what it's
12 going to have, but given the retail environment and the
13 kind of loose regulations about cannabis products right
14 now, and given the wide stake from the business sense,
15 we're seeing companies come up with a lot of diverse
16 products trying to kind of corner a market or create a
17 unique niche market, and they make a lot of claims
18 about what these things can do.
19 I've kind of gone into this -- and I'm going
20 to skip over and not drill too far down into the
21 pharmacology of all of these different cannabinoids,
22 partially because it's not terribly important to this

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1 discussion, but it's important to know that there is
2 this diversity. You get partial agonism. You get full
3 agonists with the synthetics. Then, with CBD, there's
4 some preclinical research indicating that there might
5 be some direct interaction with opioid receptors or
6 modulation as an allosteric modulator. But again, we
7 can have dose-specific agonism/antagonism, and just a
8 lot of differences in terms of effects here.
9 So where does that bring us and where do the
10 opioids come into the picture? Why do we think that
11 cannabinoids might be a useful target to look at
12 treatment of opioid-use disorders? Opioid receptors
13 have multiple subtypes and, basically, what we can look
14 at, when we look at cannabinoid opioid receptor
15 similarities, they're G-coupled protein receptors, and
16 they inhibit neurotransmitter release. They have
17 comparable distribution in the central nervous system.
18 There's a lot of indication of crosstalk
19 between these two receptor systems. The acute
20 administration of agonists for cannabinoids or opioid
21 receptors have some comparable types of pharmacodynamic
22 effects, including analgesia, catalepsy, hypothermia,

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1 motor depression, hypertension, immunosuppression, and
2 sedation. They also are common among drugs of abuse in
3 that they increase dopamine release in the reward
4 pathways of our brain; so they are both drugs of abuse
5 in terms of agonism.
6 A number of preclinical studies have been
7 conducted that look specifically at how these two
8 systems interact with each other and how administration
9 of exogenous cannabinoids and opioids intersect with
10 each other. Some studies have demonstrated
11 cross-tolerance. If you train an animal up on
12 administration of an opioid, and then give a high dose
13 of a cannabinoid, you see evidence of tolerance to the
14 cannabinoid and vice versa. You see some evidence in
15 some studies of antagonist precipitated withdrawal.
16 So if you get an animal dependent on an opioid
17 and then give a cannabinoid antagonist, you can elicit
18 some withdrawal symptoms, and again, vice versa. There
19 is some substitution for self-administration in
20 preclinical studies, but these studies tend to be a
21 little bit mixed and depends a little bit on the
22 species, the medication, and the dose that you're

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1 using.
2 With respect to receptor knockout models or
3 what might be the interplay here, how required is the
4 interaction of these two receptor systems? If you look
5 at models of opioid self-administration and dependence
6 in cannabinoid knockout mice, you can still get
7 self-administration and condition place preference, but
8 it seems to be modulated to some degree. Similarly,
9 cannabinoid models of dependence, they seem to be
10 attenuated in mu opioid knockout mice. So there's some
11 interaction there in terms of modulation of one
12 receptor system and drug abuse on the other.
13 With regards to analgesia, one of the main
14 pushes for the therapeutic use of cannabinoids within
15 the context of the current opioid crisis is the
16 argument that cannabinoids can replace opioids for
17 treating pain. In preclinical data, we do see evidence
18 of synergistic interactions between cannabinoids and
19 opioids, where you can use smaller subtherapeutic doses
20 of the two medications and get super therapeutic
21 effects.
22 What's interesting there is that we focus in

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1 and we really drill down on that analgesic effect, and
2 we're not really looking at the other effects. So one
3 thing that we have to keep in mind going forward is, is
4 there synergy in potential adverse effects and other
5 types of pharmacodynamic effects like impairment?
6 We do see neurobiological adaptation. If you
7 give chronic high doses of cannabinoids, you see
8 altered expression of the endogenous opioid system; and
9 the same thing if you give chronic doses of opioids,
10 you see altered expression of the endocannabinoid
11 system.
12 From a mechanistic standpoint, acute
13 administration of cannabinoid agonists have shown to
14 increase the synthesis and release of endogenous
15 opioids, so that might be another way in which dosing
16 of a cannabinoid can modulate the opioid system and
17 maybe help in the treatment of opioid-use disorder.
18 To summarize this preclinical data, what I
19 think we see are very clear indications from
20 preclinical studies of an interaction between the
21 cannabinoid and opioid systems in our bodies. Both
22 drug types can induce analgesia, and there's evidence

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1 of substitution effects in preclinical models of drug
2 taking. The mechanism of the analgesia appears to be
3 different. We do see some signals of exogenous
4 cannabinoids modulating opioid effects and endogenous
5 opioid release. But again, there's variability across
6 studies, and we need to see how much that translates
7 from the preclinical to the human work.
8 I'll take a little bit of time now and talk
9 about some of the human data that we have. There's a
10 study by Donald Abrams that looked at the impact of
11 vaporized cannabis in combination with morphine or
12 oxycodone. This was a lab study with patients
13 maintained on these opioids. What they did is they ran
14 a laboratory session with them before dosing, and then
15 they gave them vaporized cannabis for 5 days, and they
16 ran additional tests.
17 I don't know if you'll be able to see this,
18 but on the top, up here, these are pain reports by
19 opioid medication. What we see is the difference in
20 pain ratings from day 1 -- this is before cannabis, and
21 day 5 is after 5 days of cannabis -- go down, overall,
22 across the study, and pain is reduced, so the addition

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1 of cannabinoids to the opioid maintenance doses were
2 comparable across morphine and oxycodone. So cannabis
3 added analgesic efficacy in this patient population.
4 What's interesting is that here you see
5 morphine plasma levels on day 1 and then on day 5. You
6 can see the addition of the cannabinoid for 5 days
7 reduce plasma levels of morphine, and they're
8 maintained on their stable level of morphine. We
9 didn't see any impact on the pharmacokinetics of
10 oxycodone. This translated to a little bit of a
11 difference in peak subjective ratings of feeling high
12 when they were exposed to cannabis in the laboratory on
13 day 5.
14 What's important to note here is that when
15 people are taking their opioids, they don't really feel
16 high, but when they smoke cannabis, by and large, yes
17 they do. So something to keep is we're reducing pain,
18 but we're producing a very discriminative drug effect.
19 Yasmin Hurd has got a lot of press recently
20 for her research looking at cannabidiol all as an
21 impact on opioid-use related outcomes. What she did is
22 a pilot study, then followed by a larger study, looking

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1 at heroin cue reactivity in the laboratory. In her
2 pilot study, she showed that when showing people
3 heroin-associated cues and given a placebo, you see the
4 appropriate expected increase in craving and cue
5 reactivity to heroin-associated cues versus neutral
6 cues, and that this was attenuated by cannabidiol.
7 She followed that up and replicated it in a
8 larger study, with longer term exposure to CBD that was
9 just published recently. Here she showing that, again,
10 this is kind of a replication of that pilot study here,
11 where neutral cues do not increase reactivity, but
12 heroin-associated cues do, and you see dose-related
13 suppression of cue reactivity with 400 milligrams of
14 oral CBD and 800 milligrams of oral CBD.
15 Interestingly enough, this pattern was
16 maintained 24 hours after exposure but seemed to wash
17 out a week later. The other important thing here, in
18 contrast to the Abrams study, you don't see acute
19 self-reported drug effects in this study, and you don't
20 see much in the way of adverse events.
21 Stacy Gruber has run a longitudinal
22 observational study with patients initiating the

1 medicinal use of cannabis up at her lab in Harvard.
 2 This is an interesting cohort study, where she's
 3 getting people with no history of cannabis use.
 4 They're looking to initiate cannabis use for
 5 therapeutic purposes for a variety of reasons.
 6 One of the key outcomes from her early work
 7 here is that she's seeing a 42 percent reduction in
 8 self-reported opioid use, not elimination, but a
 9 reduction in dose. In addition to reduction of opioid
 10 use, she's seeing reductions in self-reported use of
 11 benzodiazepines and a number of other prescription
 12 medications and increases in sleep, depression, quality
 13 of life, and cognitive functioning.
 14 Now the increase in cognitive functioning can
 15 mistakenly be interpreted, in some cases, as being that
 16 the cannabis is improving cognitive functioning, but I
 17 think if you're reducing opioid and benzodiazepine use,
 18 that's probably more likely mechanism.
 19 There have been a couple, really high profile,
 20 epidemiological studies, evaluating the rate of opioid
 21 overdoses in states that have adopted medical cannabis
 22 laws. The first study conducted by some of our

1 certain states was associated with a reduction in the
 2 number of opioid dependence admissions in those states
 3 by 23 percent and prescription opioid overdoses by 13
 4 percent.
 5 So again, this is kind of pointing towards
 6 medical cannabis laws having these really positive
 7 effects on opioid-related harms, but again,
 8 correlational.
 9 Some folks in Australia did an interesting
 10 study, where they looked at a community sample of
 11 individuals who were prescribed opioids for chronic
 12 pain. They found that 16 percent had used cannabis for
 13 their pain and an additional 25 percent of this
 14 population said that they would use cannabis if it was
 15 available to them. So at the time, Australia did not
 16 have an active medical cannabis program. They do now,
 17 and it's just kind of getting going.
 18 What they found and what they report is that
 19 the cannabis users in this population were younger, had
 20 greater pain, more pain-related problems, and also had
 21 more out-of-control opioid use. Now again,
 22 interpretation is tricky here and needs to be evaluated

1 colleagues at the Hopkins school of public health made
 2 a big splash a couple of years ago by showing that
 3 medical marijuana states had drastically reduced opioid
 4 overdoses after the passage of their medical cannabis
 5 laws, but a reanalysis of the same data set by other
 6 folks this year, and looking at more recent data, have
 7 shown that that trend is actually reversed.
 8 So it's important that when we look and we see
 9 data like this, that we think about, carefully, that
 10 this is correlational, and that there are a lot of
 11 other things happening. And that while early on, we
 12 did see a reduction in opioid overdoses and that data
 13 is real, there might be other things that were
 14 happening at the prevention level, at the treatment
 15 level, that might be driving this other than the new
 16 availability of medicinal use of cannabis.
 17 Thinking about other kind of big, broad public
 18 health impacts of this stuff, there's a study by Shi
 19 and colleagues, showing that the rate of hospital
 20 admissions related to cannabis and prescription opioids
 21 increased dramatically from the period of 1997 to 2014,
 22 and that the medicinal cannabis law implementation at

1 carefully. This was a cross-sectional study, and I've
 2 seen people look at these data and think, well, the
 3 cannabis use is driving up more reckless opioid use,
 4 but they're not accounting for the fact that the people
 5 who are using cannabis may have been more problematic
 6 and had greater pain to begin with.
 7 This was not a longitudinal study, so you
 8 can't really look at the individual patient level,
 9 whether the addition of cannabis use to the
 10 prescription opioids was improving, making things
 11 worse, or keeping it the same for these people.
 12 There's another big kind of convenient sample
 13 study done in New England, as is Massachusetts, Maine,
 14 and a couple of other states up there legalize cannabis
 15 for therapeutic purposes, where they interviewed a
 16 bunch of people who are using cannabis for their pain,
 17 and they said, by and large, most of them said it was
 18 really helpful. It was helpful for a variety of pain
 19 conditions, and that they had significantly reduced
 20 their use of opioids.
 21 This kind of goes in contrast, a little bit,
 22 to the National Academy's report that kind of

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

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

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

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1 thinking about this working in an actual practical
 2 place?
 3 Are we thinking about replacing opioids with
 4 cannabis for pain to prevent the onset of prescription
 5 opioid-use disorders and transition to heroin?
 6 Are we thinking about cannabinoids as a way of
 7 suppressing opioid withdrawal in early treatment
 8 seeking?
 9 Are we thinking about it as a mechanism of
 10 reducing craving and then a relapse prevention measure
 11 for people who are already detoxified and out in the
 12 world?
 13 Do we promote cannabis as a substitute for
 14 illicit opioids? Do we just take a harm reduction
 15 approach here and say, you know what? Cannabis isn't
 16 great but it's better than heroin. People aren't going
 17 to OD. Maybe we should just encourage everybody to
 18 just smoke as much weed as they can.

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

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

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

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

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

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

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

10 Shown up here is also Epidiolex, which is an
 11 oral dose of cannabidiol, and we have Sativex, which is
 12 not approved by the FDA in the U.S. but is approved in
 13 a number of other markets, which is kind of a balanced,
 14 1-to-1, THC-CBD solution.

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

22 Literally, insanity, but when you think about

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

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

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

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

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

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

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

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

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

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

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

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

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1 you've got a difference in improvement from placebo,
 2 but far substandard compared to methadone or
 3 buprenorphine, what's going to be your recommendation?
 4 Do we compare it to naltrexone? Naltrexone's
 5 got a different safety profile, but nobody likes to
 6 take it. THC is reinforcing and rewarding; CBD is not.
 7 If CBD ends up attenuating some anxiety and helping
 8 craving a little bit, can you get people to take it if
 9 it doesn't get you high?

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

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

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1 Key safety and feasibility concerns. I think,
 2 by and large, we can say that for most individuals,
 3 cannabis is safer than heroin, but it's not safe,
 4 necessarily, and it's not equally safe for all people.
 5 My biggest concern, and I've been asked about this a
 6 lot of times, is that methadone and buprenorphine have
 7 demonstrated capabilities of reducing the likelihood of
 8 an opioid overdose because of its pharmacology.
 9 Cannabis doesn't. So are we putting people at greater
 10 risk of opioid overdose by not giving them an opioid
 11 maintenance medication?
 12 There's a high rate of psychiatric
 13 comorbidities in people with opioid-use disorders, and
 14 we know from really well-conducted studies in cannabis
 15 that cannabis can exacerbate psychosis, and long-term
 16 use of cannabinoids -- again, THC in this particular
 17 case -- can be harmful to the disease progression for
 18 people with anxiety or depressive mood disorders.
 19 There's tolerance to the effects of cannabis
 20 over time. How likely is this going to be sustained?
 21 How high do they have to increase the dose? What's the
 22 long-term health ramifications of that? Cannabis-use

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1 disorder is real. We've studied it for a long time. A
 2 lot of people in the room are better experts on that
 3 than I am and have been doing it for longer than I
 4 have.
 5 So how do we reconcile the likelihood of
 6 development of cannabis-use disorder with a high THC
 7 product? Is that acceptable with a trade-off of
 8 opioid-use disorder?
 9 We've got the cannabis quality control issues,
 10 and there are adverse events associated with cannabis
 11 use. The other thing at the very bottom here -- I
 12 don't know if you can see it -- is there's an
 13 increasing concern about drug-drug interactions. I
 14 showed you the slide earlier about how cannabis can
 15 affect the pharmacokinetics of one opioid and not
 16 another.
 17 We don't know enough about this. One of the
 18 studies we're trying to do in my lab is a really
 19 careful analysis of drug-drug interactions at CYP450
 20 enzymes, and we hope to get that started in January or
 21 February of the coming year.
 22 I've mentioned quality control issues. They

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1 are abundant. We see contaminants. We see improper
 2 labeling of all of these products. We need
 3 standardization if we want to look at this from a
 4 pharmaceutical standpoint. Impacts on cognition. You
 5 guys have probably all heard this. Early onset
 6 cannabis use can lead to a number of cognitive
 7 impairment issues, acutely. Acute doses, high doses of
 8 THC impairs working memory, attention, psychomotor
 9 functioning; a lot of things that are key for
 10 day-to-day functioning.
 11 There's some indication that it's sustained
 12 for some period of time for some individuals and
 13 earlier onset is worse outcomes. But a number of
 14 studies have showed that you can reverse with
 15 abstinence, but if you are looking to switch people on
 16 to a maintenance medication, what's the impact here?
 17 So I think it's something to think about.
 18 Then we have the current regulatory
 19 environment, which is super complex. Right now, to
 20 summarize as of today, and it will probably be
 21 different next week, and different again the next
 22 month, and different again next year, cannabis,

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1 synthetic CBD, and multiple synthetic cannabinoids are
 2 all Schedule I in the Controlled Substances Act.
 3 Hemp derived from CBD is now legal. THC
 4 exists in both Schedules I, II, and III, depending on
 5 the formulation. Terpenes are all legal and mostly are
 6 generally recognized as safe by the FDA, but that's all
 7 for oral consumption. We're talking in a number of
 8 these situations about inhaling the drug, and we don't
 9 know the safety or toxicology of those things there.
 10 Epidiolex is Schedule V.
 11 So if we're thinking about doing something
 12 that's Schedule I, which is a lot of this stuff still,
 13 trying to do a phase 2 or higher study in a Schedule I
 14 drug is near impossible; so that has to be factored in
 15 as well.
 16 What are our key trial types or approaches to
 17 this? You've got preclinical, kind of
 18 mechanism-oriented studies that still need to be done.
 19 A lot have been done, but there's a lot more that can
 20 be done specific to treatment of opioid-use disorder.
 21 I think longitudinal observational studies of people
 22 doing this in the states where it's approved as a

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1 treatment for opioid-use disorder is something where we
2 can get a signal and maybe get some initial sloppy
3 evidence of efficacy, safety, and type of product used,
4 and route of administration and things like that, that
5 we could then translate into a clinical trial.
6 We've got human lab studies that were talked
7 about this morning, where we can apply a purchase there
8 to look at reductions in craving, reductions in self
9 administration, in models of safety and efficacy, and
10 then the outpatient RCTs, and, again, phase 4 type
11 modeling kind of goes along with those longitudinal
12 observational studies.
13 Key trial design features; if we're going to
14 go down this road, my recommendation is you get a
15 standardized product, and you have it manufactured like
16 a pharmaceutical, and we evaluate that product at a
17 specific dose, but allow some flexibility in the
18 dosing, again, as was discussed this morning; because
19 based on the cannabis use history of an individual, you
20 can respond very, very differently to a dose of THC.
21 We've shown in my laboratory that 25 milligrams will
22 take somebody who's not tolerant and send them on a

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1 crazy, crazy adventure and a daily user barely feels 25
2 milligrams.
3 The design should be randomized, placebo
4 controlled. Again, I think a positive control with an
5 evidence-based treatment is important; I just don't
6 know which one it is. We want to have a foundational
7 psychosocial treatment layered on top of a medication
8 so that everybody gets it, and it helps with the
9 placebo control.
10 We've been one of the folks that have adopted
11 the computerized therapy to avoid Eric's loose cannons.
12 I think any trial needs to be powered for sex
13 differences. In the cannabis world, every time we look
14 for sex differences, we see them. I think the other
15 thing that's important is that any trial needs to be of
16 sufficient duration to carefully evaluate long-term
17 health impacts, relapse, and risks of opioid overdose.
18 Inclusion/exclusion criteria are key here.
19 Again, the psychiatric disorder comorbidities is a
20 concern. Again, I don't know enough about what kind of
21 impact opioid use has on those, but we do see negative
22 impacts of long-term chronic cannabis use on a number

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1 of psychiatric disorders.
2 As I mentioned before, cannabis use history is
3 going to be important for tolerance and dose selection.
4 How do you differentiate use of the therapeutic
5 cannabinoid products from other cannabis use?
6 Cardiovascular health is an impact for high THC
7 products. Drug-drug interactions might impact other
8 medications and then pregnancy. So in the opioid world
9 you do have Andre Jones' work, looking at the safety of
10 buprenorphine and methadone for pregnant women. We
11 don't have that data for cannabis.
12 In terms of outcome measures, we've got,
13 again, differentiating; being able to differentiate use
14 of the therapeutic cannabis product versus other
15 cannabis use. If you give somebody a high CBD product,
16 and they go off and they smoke a bunch of high THC
17 cannabis throughout the trial, how do you draw any
18 conclusions about that, and can you differentiate your
19 product from other products that they can get on the
20 market or on the illicit market?
21 We need to evaluate the acceptability of the
22 study drug and study retention. Obviously, you need to

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1 look at opioid use, but in addition to opioid use,
2 you're looking at craving and withdrawal. And, again,
3 I think the most important thing, aside from opioid
4 use, is the overdose risk; use of other medications,
5 other substance use and substance-use disorder
6 severity, including opioid-use disorder severity, and
7 the development or onset of cannabis-use disorder.
8 Looking at adverse events, looking at broad
9 health. Again, if we're going to take this
10 substitution approach, we need to be looking at broad
11 health outcomes, both mental and physical health;
12 again, given the risk for anxiety, depression,
13 psychosis, but also looking at quality-of-life
14 functioning, pain, sleep, and things like that if we're
15 looking at more of a harm reduction approach here.
16 Healthcare utilization; in the opioid-use
17 disorder world, these guys that are chronic heroin
18 users show up to the ER every chance they get. If they
19 switch to cannabis, does that go down or does it stay
20 the same? It'd be interesting as an outcome.
21 To wrap up and summarize here, can cannabis
22 help with the opioid epidemic? As this guy says,

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1 "There's nothing wrong with cannabis; it's just all
2 good, right?" So what do know? We know that cannabis
3 is really complex, so it's going to be a challenge to
4 figure out a single product type, a dose, things like
5 that.
6 It's neither benign nor an ideal from a
7 medicinal standpoint. It's tricky moving from what's
8 currently available in the retail world to a
9 pharmaceutical clinical trials approach. Observational
10 studies suggested it's relatively safe and associated
11 with reduced opioid use. But we need clinical trials.
12 Currently, there's none where opioid-use disorder or
13 opioid use is a primary outcome.
14 So what do we need to know? Pretty much
15 everything else, which is a lot. My recommendation, as
16 far as where we go from here, is that we try to funnel
17 money into more preclinical work, evaluating these
18 mechanisms and interactions; do more observational
19 studies to look at how things are playing out in the
20 world right now because things are happening in the
21 natural laboratory; that anything moving forward should
22 have appropriate product standards.

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1 We want to minimize unwanted adverse effects;
2 so again, thinking about daily functioning and people.
3 You don't want to give them a whole bunch of really
4 high doses of THC, and that we have to evaluate
5 comparative efficacy with other effective treatments.
6 And that's it.
7 (Applause.)
8 DR. VANDREY: I think I'm down to two seconds.
9 DR. STRAIN: That was great. Thank you, Ryan.
10 Staying on time, we're going to move on, but
11 we do have some time for discussion later. I think our
12 heads are going to explode with all the questions that
13 Ryan has put out.
14 Our next speaker is Dr. Andrew Huhn, who's
15 going to be talking about sleep aids. Andrew, take it
16 away.
17 Presentation - Andrew Huhn
18 DR. HUH: Thank you, Dr. Strain.
19 About an hour after we've had lunch, it's a
20 good time to either go to sleep or talk about sleep.
21 (Laughter.)
22 DR. HUH: So some of you might be interested

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1 in listening about it, and some of you might do the
2 former; I'm not really sure.
3 My research is focused treatment outcomes for
4 opioid-use disorder, generally predictive models of
5 relapse risk. Through that research, I've become
6 interested more broadly in what treatment outcomes are,
7 not just opioid relapse or continued drug use, but also
8 mental health, general health, and quality of life.
9 Sleep affects all of those things, and I think in its
10 own right could be a treatment outcome.
11 This is an outline of the next 45 minutes of
12 your life. First, we're going to talk about OUD
13 treatment options. We'll talk about outcomes for sleep
14 medications and clinical trial designs for sleep
15 medications. As I'm imagining, most of us in the room
16 are experts in addiction and might not double over as
17 experts in sleep medicine, as well; how can we
18 incorporate sleep measures into OUD clinical trials;
19 the role of sleep and stress and treatment outcomes for
20 opioid-use disorder; and then some non opioid receptor
21 targets that could also treat sleep disturbance.
22 This is treatment in America right now for

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1 opioid-use disorder. It's like one of those choose
2 your own adventure books. Remember those? If I'm a
3 person who is suspected to have diabetes, I know what
4 to do. I go to my primary care physician. He or she
5 can probably manage my diabetes, and if it's kind of
6 out of control, I might go to an endocrinologist; but
7 the point of entry into treatment and what happens next
8 is all clearly laid out. That's really not the case
9 for people with opioid-use disorder, and it varies
10 wildly based on where you are geographically and state
11 level policy.
12 There's the big three medications for
13 opioid-use disorder: buprenorphine, methadone, and
14 extended-release naltrexone. People might also opt not
15 to use any medication for opioid-use disorder. In
16 fact, a lot of people opt not to use that, and they go
17 straight into 12-step meetings or other kinds of
18 counseling. There's residential or hospital-based
19 treatment facilities, 1-on-1 counseling or psychiatry.
20 Most of these options have different treatment
21 philosophies. It makes it challenging to think
22 about -- especially for something like sleep

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1 medication, even like a treatment for depression, et
 2 cetera, and how does that work into this, into what's
 3 currently going on?
 4 This is perhaps a more orderly way to look at
 5 it. For somebody with opioid-use disorder, they're
 6 either going to go on opioid maintenance therapy or
 7 they're going to go through opioid withdrawal. We know
 8 that the majority of people going into treatment are
 9 not getting opioid maintenance therapy at this time. I
 10 think that's changing for the better, but it's maybe
 11 not changing quickly enough.
 12 On top of the different medications that act
 13 directly on the mu opioid receptor, there's also
 14 different levels of care, intensity of treatment. Some
 15 of those are around-the-clock supervision like you
 16 might find in an inpatient or residential setting;
 17 outpatient group counseling. Some people will go
 18 through opioid withdrawal and just do
 19 meetings -- [inaudible - mic fades] -- what the
 20 community's recommending right now because it's not
 21 been too successful, but that is a reality out there.
 22 The different treatment options, especially

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1 the medications for opioid-use disorder, we don't know
 2 a lot about how these impact biological systems that
 3 might in turn impact treatment outcomes or the
 4 propensity to continue drug use or relapse, and of
 5 course, sleep falls into this.
 6 We know a lot about opioid-use disorder and
 7 stress, that there's increased stress reactivity,
 8 especially early in recovery, that stress is an issue.
 9 There's not as much research about sleep and opioid-use
 10 disorder, but there is a clear connection between
 11 stress and sleep, and especially via the hypothalamic
 12 pituitary axis, which follows a [indiscernible] rhythm
 13 throughout the day.
 14 Your cortisol levels, which is the downstream
 15 product of the HPA-axis, are highest when you wake up
 16 in the morning. They fall throughout the day, and they
 17 get lowest right after you go to sleep at night, and
 18 then they build up in your system, and that helps you
 19 wake up again in the morning.
 20 There's plenty of research on stress
 21 reactivity in OUD and practically no research on
 22 circadian rhythms in OUD. Here's what we do know. An

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1 acute dose of an opioid reduces subjective feelings of
 2 stress, produces HPA-axis signaling, and interestingly
 3 disrupts sleep architecture. Even though, generally,
 4 if you were taking an opioid, like in an acute
 5 situation, that might be to relieve pain, so thus you
 6 might actually sleep better in that one instance. Your
 7 sleep architecture is disrupted.
 8 But chronic opioid use increases stress
 9 reactivity, and I'll say alters HPA-axis function. So
 10 it could increase HPA-axis signaling. It could also
 11 flatten out the curve so that your cortisol levels are
 12 lower in the morning and higher in the evening.
 13 There's persistent sleep disturbance in this
 14 population. There are very few studies about sleep
 15 quantity and quality in OUD.
 16 This is data from a study done by Kelly Dunn
 17 out at Ashley Addiction Treatment, which is a
 18 residential facility. We just ask people coming in to
 19 fill out the brief addiction monitor and looked at
 20 sleep disturbance in the past 30 days as it related to
 21 opioid use for the past 30 day, and, in fact, there was
 22 a correlation between those two. So more opioid use is

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1 more sleep disturbance.
 2 There's also a very strong correlation between
 3 sleep disturbance, feelings of depression, and anxiety
 4 and anger in the past 30 days. These things likely
 5 have a cumulative effect. Anxiety and depression
 6 disrupts sleep, makes it harder to sleep, and then that
 7 in turn makes you feel worse the next day.
 8 This was kind of a retrospective analysis of a
 9 first pass attempt. Medications for sleep studies, in
 10 general, have much better defined outcomes probably
 11 than we have in studies of opioid-use disorder. It's
 12 probably worthwhile to go over what some of those
 13 outcomes are.
 14 If you just take a minute and think about your
 15 actual experience of sleep, usually you get ready to go
 16 to bed at night. You turn out the lights. You
 17 actually get into bed. You don't fall asleep
 18 instantly, at least probably not. There's some kind of
 19 period of time that you get into, and then you actually
 20 fall asleep. You might wake up in the middle of the
 21 night once or twice, get up, and get out of bed in the
 22 morning.

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

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

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

1 is a little bit questionable because you don't usually
 2 sleep with a whole bunch of wires hooked to you; at
 3 least I don't sleep like that, but very good for
 4 mechanistic studies; probably not something you're
 5 going to do repeatedly night after night.

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

18 A secondary measure of sleep that's also good
 19 because it's objective is to use wrist-worn actigraphy.
 20 There are of course companies that make -- like Fitbit,
 21 Apple watch, these have applications that automatically
 22 monitor your sleep. The downside of using these in a

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

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

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

21 The level of data you get from this is really
 22 deep, but the actual, I don't know, ecological validity

1 research study, to my knowledge, most of these
 2 applications, they just autoscore your sleep, so
 3 there's no ability for you as a researcher to go in and
 4 set your own parameters for what you define as time
 5 asleep and time awake. We've typically use these
 6 actigraphs that give us more options with the data, and
 7 we set our criteria before the study of what counts as
 8 sleep and what doesn't.

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

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

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1 what that might look like; what time did you go to bed;
 2 what time did you get up in the morning; did you wake
 3 up at all; and how restful did you feel?
 4 Some of our sleep studies, we're using a much
 5 more detailed sleep diary, and you can find several
 6 examples of these in different trials.
 7 We've also used ecological momentary
 8 assessments to measure sleep. EMA has briefly
 9 delivered surveys that are given throughout the day,
 10 generally on a smartphone. You can ask all sorts of
 11 questions with these. You can actually incorporate a
 12 sleep diary into EMA assessments. You can incorporate
 13 measures of daytime sleepiness into ecological
 14 momentary assessments and nighttime sleep diaries.
 15 This can further be used not only to look at sleep but
 16 also this complex relationship between sleep, mood,
 17 stress, craving, et cetera.
 18 The EMA is becoming, I think, more common in
 19 trials of opioid-use disorder because you can get a lot
 20 of data and I think have a much more granular
 21 understanding of what's going on with your participants
 22 compared to a traditional trial design; where maybe

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1 they're coming back once a week to give a urine sample
 2 and fill out a couple of questionnaires, here you're
 3 sampling them throughout the day, and it eliminates
 4 recall bias, which is a problem with folks with
 5 opioid-use disorder as well.
 6 There are other wearable technologies that are
 7 making it onto the market for sleep as well. One is
 8 Oura Ring. This is literally like a ring that you
 9 wear. It has an accelerometer like an actograph. It
 10 also measures pulse, which could be an important
 11 secondary outcome and could be a secondary measure of
 12 stress throughout the day.
 13 There's a new one called the Watchpat. This
 14 one's actually pretty interesting. The base of it has
 15 actigraphy just like the actographs that I showed
 16 earlier, but it also has this finger cover that
 17 measures oxygen saturation and peripheral arterial
 18 tone. You can't get full sleep architecture from the
 19 Watchpat, but you can get time in deep sleep, and you
 20 can also get apnea events throughout the night. So it
 21 adds a few more outcome variables to your study and
 22 gives you actually a pretty robust number of outcomes

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1 for how low maintenance it is.
 2 I will say that I've actually tried this
 3 before, too, and I found it a little bit disturbing
 4 because to get the peripheral arterial tone, it
 5 tightens around your finger periodically through the
 6 night, and that was a little bit disruptive to me, but
 7 it's another option.
 8 Of course there are retrospective
 9 questionnaires. Most commonly used is the Pittsburgh
 10 Sleep Quality index, and that's like a measure of past
 11 30 days sleep. This has been used in thousands of
 12 studies, literally. If you look up the PSQI, you'll
 13 see thousands of citations for that one paper. Beyond
 14 that, there's the Stanford Sleepiness Scale, Epworth
 15 Sleepiness Scale. These measure daytime sleepiness.
 16 These are pretty low maintenance to work in. Your
 17 study doesn't have to actually be on sleep for you to
 18 give these and be able to compare that to other
 19 research.
 20 Clinical trial designs for sleep medications
 21 follow the same general designs as we use for
 22 medications for opioid-use disorder. After you get

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1 past phase 1, there's typically a dose-finding study
 2 versus placebo to see which dose is most effective, and
 3 then there's usually a larger trial that's active sleep
 4 medication versus placebo. Then you might see a series
 5 of studies that puts one active sleep medication versus
 6 another, either within the same class, so like a
 7 benzodiazepine versus a benzodiazepine, or maybe a
 8 melatonin receptor agonist versus a benzodiazepine to
 9 look at the relative effectiveness and also side effect
 10 profile.
 11 Other things to consider in studies on sleep
 12 and clinical trials for sleep medication is the time
 13 duration of the study, so how long do you actually want
 14 to put somebody on this sleep medication. This
 15 actually varies quite a bit in the sleep literature.
 16 You see some trials that are very short, only
 17 a few weeks. You see other trials that are up to a
 18 year on multiple doses of a sleep medication to see if
 19 there's any long-term effects of that medication. It
 20 reminds you somewhat of trials on opioid-use disorder
 21 as well, but I feel like we don't have as many studies
 22 that go out to a year. Most of our outcomes are like

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1 3-month outcomes, and that's the most typical.
 2 It's also important to consider the
 3 environment. Did these folks live at home? Are they
 4 homeless? Are they inpatient? How does that affect
 5 their sleep and other secondary outcomes? Do you allow
 6 self-titration in the study; so can people up their
 7 dose? Can they reduce their dose if they don't like
 8 the side effects? What's the relationship to stress?
 9 Also, I think importantly for studies in opioid-use
 10 disorder, what's the relationship to relapse? Relapse
 11 is still our primary outcome for most trials.
 12 I'm going to talk about a couple of studies
 13 that I've been involved in, where we did measure sleep;
 14 one we did in an inpatient facility in Pennsylvania
 15 called Caron Treatment Center. It's important to put
 16 this in context because Caron is a residential
 17 facility. They have a primary care unit where patients
 18 can stay for 28 days, and then after that, some
 19 patients will go on to stay for an additional 90 days
 20 inpatient; not the typical experience for somebody with
 21 opioid-use disorder, which is usually outpatient
 22 therapy but still can get some interesting data like

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

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1 diaries every morning.
 2 Within that 12-day period for 3 days, we took
 3 samples of salivary cortisol at 4 points throughout the
 4 day so we could look at diurnal rhythms of cortisol.
 5 Then within that, we did a neurophysiology session,
 6 which I'm not going to talk about; but I'm happy to
 7 talk about if anybody asks me later.
 8 The first data burst happened about 15 to
 9 27 days after they had entered treatments, so they're
 10 all the way through withdrawal. The second data burst
 11 was in month 2; third data burst month 4, and then we
 12 followed up with some of these patients for 90 days
 13 after they left treatment to determine if they relapsed
 14 or not.
 15 This data is under review right now. This is
 16 data from 96 patients and controls. It's cortisol
 17 throughout the day. In the first month of treatment,
 18 you can see that at every time point, cortisol is
 19 higher in the OUD patients than it is in controls. I
 20 think one of the things we're really interested in was
 21 does this HPA-axis reregulate, or is there at least
 22 some evidence of that? And that is what we found.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 One of the neurotransmitter systems that we've
2 been really interested in is orexin system. The orexin
3 system is actually really interesting. There's only
4 10[000] or 20,000 orexin-producing neurons in your
5 brain, and they're pretty much all in the lateral
6 hypothalamus.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 studies, and it might be relevant to folks with OUD,
 2 especially people who are already in recovery, as a
 3 tool for relapse prevention, improving sleep and
 4 generally improving health and mental health outcomes.
 5 We do have a couple of ongoing studies with
 6 people with opioid-use disorder. These are clinical
 7 trials on suvorexant. Suvorexant is a dual orexin
 8 receptor antagonist. The first study we have uses
 9 suvorexant during opioid withdrawal. We're examining
 10 the effect on sleep, of course, but also whether it
 11 reduces withdrawal and addresses some of the issues
 12 with craving and mood. I'm not blinding us to the
 13 actual drug, but I'm blinding us to the doses. You can
 14 probably guess that one dose is higher than the other,
 15 but you'll have to wait to see which doses we use until
 16 the end.
 17 This is a dose-finding study. It's three
 18 arms, so people would get either suvorexant low dose,
 19 high dose, or placebo. First, they come in and they
 20 get stabilized -- this is all inpatient -- for 3 days
 21 on buprenorphine, and then they have a 4-day taper, and
 22 then a 4-day post-taper period. We start the

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1 suvorexant right before the taper.
 2 In this one, we're using the sleep profiler to
 3 monitor sleep architecture, actigraphy as a secondary
 4 measure of sleep, and, of course, sleep diaries as
 5 measures of daytime sleepiness. It's a way to follow
 6 what's a traditional clinical trial for an opioid
 7 withdrawal medication, but with the twist that it's a
 8 sleep medication, and that this is a really significant
 9 problem for folks with OUD.
 10 The second study we have is looking at sleep
 11 during opioid recovery. Again, we're using suvorexant
 12 in this trial as a probe of the orexin system. This
 13 trial is for people who are either on methadone or
 14 extended-release naltrexone. It was kind of
 15 conceptualized as a mechanistic study, not just to look
 16 at suvorexant but also to look at a full agonist versus
 17 antagonist medication-assisted treatment and how that
 18 might impact sleep and stress.
 19 For folks coming into the study, they have to
 20 be abstinent from opioids for 3 to 6 weeks. So we're
 21 getting people who have some initial success in
 22 treatment and looking at this in terms of relapse

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1 prevention. I don't personally think a sleep
 2 medication on its own is going to affect drug use
 3 behaviors enough to get people off of opioids, but as a
 4 way to tip the scales in their favor. For relapse
 5 prevention, I think it could be very useful.
 6 The aims we're looking at here are the
 7 relationship between orexin signaling and sleep
 8 disturbance in OUD and also orexin signaling and
 9 diurnal measures of stress. People are going to be out
 10 in the community. This is an outpatient study.
 11 They'll be wearing actigraphy every day, doing
 12 ecological momentary assessments, and giving salivary
 13 cortisol samples throughout the trial, then also, to
 14 look at the relationship between sleep and stress on
 15 treatment outcomes in people who are in recovery and
 16 actually in the community.
 17 This is the kind of rough design of the study.
 18 Folks will come in and do a screening visit. We'll do
 19 what we term, again, a data burst, where they're doing
 20 ecological momentary assessments for 7 days and also
 21 giving salivary cortisol for 3 days within that 7 days
 22 before they start taking the study medication, then

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1 they'll be randomized to either suvorexant or placebo
 2 for an 8-week trial. Once weekly, they'll come in and
 3 do an outcomes assessment with us and also monitoring
 4 through the smartphone.
 5 So we covered a lot. My voice didn't hold up
 6 through the whole thing, but we did make it through.
 7 Sleep disturbance is a big issue in people with
 8 opioid-use disorder. We see this firsthand. Patients
 9 are reporting this to us anecdotally. The FDA has had
 10 a patient listening session, where it was brought to
 11 light that sleep disturbance is a major issue, in
 12 addition to craving and anxiety. These were things
 13 that people wanted treatments for.
 14 It's a big issue in withdrawal, especially for
 15 folks who are in very severe withdrawal and can't sleep
 16 for one or two nights at a time. Sleep assessments on
 17 their own, especially the self-reported stuff could
 18 easily be incorporated into clinical trials for OUD
 19 medications and doesn't have to be a sleep trial to
 20 incorporate some of these measures and start recording
 21 this stuff across several different studies. But then
 22 I also think -- and I think this because I'm doing

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1 it -- that sleep is really important, and it should be
 2 actually be the focus of clinical trials in this
 3 population.
 4 With that, I'm done. I think I have a couple
 5 minutes if there are any questions.
 6 (Applause.)
 7 DR. STRAIN: Thanks, Andrew.
 8 There's a question in the back. I can't see
 9 who it is. Can you identify?
 10 DR. HENDRICKS: It's Peter Hendricks, UAB. I
 11 think I have a question that dovetails with what
 12 Patrick asked a bit earlier. And that is, I'm curious
 13 what we know about pain and how that might relate to
 14 sleep disturbance. I think, Patrick, you're an expert
 15 in his, so I probably shouldn't say much more, but it's
 16 just interesting that we don't know much about that,
 17 from what I can tell.
 18 DR. HUH: Patrick's the pain guy.
 19 DR. STRAIN: What is your question?
 20 DR. HENDRICKS: I think there's an emerging
 21 literature on not just opioids and pain, but a range of
 22 addictive substances and pain and how there could be a

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1 reciprocal relationship there. I'm curious if pain
 2 could be a mediator of this relationship; in other
 3 words, if people are having trouble sleeping because
 4 they're in pain. This is regardless of whether chronic
 5 pain is there. It seems likely or possible that pain
 6 would be an issue even for those who don't have a
 7 chronic pain condition.
 8 DR. FINAN: These are great observations. I
 9 can tell you what we know, pretty well, at this point
 10 in the sleep and pain field, is that, yes, sleep and
 11 pain are definitely reciprocally related. In the past
 12 decade, we've started to learn that there appears to be
 13 more of a predominant focus in the data that's being
 14 presented on sleep disturbances driving pain problems
 15 to a greater extent than the reverse.
 16 It's definitely not a unidirectional
 17 relationship, and we'll see both patterns, but as
 18 longitudinal designs, EMA designs, cross-panel analyses
 19 have become more prominent in the literature. We're
 20 seeing this kind of more consistent effect of sleep
 21 problems begetting pain problems.
 22 So if we're thinking about how to

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1 conceptualize mediators versus moderators, I think
 2 you're on the right track there to think that pain may
 3 be an important mediator in the relationship between
 4 sleep disturbance and opioid-use outcomes.
 5 DR. STRAIN: Interesting. Thanks.
 6 Kelly?
 7 DR. DUNN: It's Kelly Dunn. I'll just add
 8 that I think it's notable that sleep disturbance is one
 9 of the few symptoms that is evident across all forms of
 10 drug withdrawal. It seems that there's this kind of
 11 underlying mechanism. I don't know that the opioid
 12 field knows enough about the relationship in terms of
 13 whether or not sleep contributes to withdrawal severity
 14 or if withdrawal severity contributes to sleep
 15 problems, but it certainly seems that there's value,
 16 and that there would be cross-translation across drug
 17 classes.
 18 DR. STRAIN: Tom, did you have a question?
 19 DR. KOSTEN: It's a practical question. I
 20 don't know if those are allowed here.
 21 DR. STRAIN: Absolutely.
 22 DR. KOSTEN: Okay. The sleep profiler itself,

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1 how good an outcome did the FDA say it was? And then,
 2 how much does it cost?
 3 DR. HUH: Definitely, it's an acceptable
 4 outcome measure for a clinical trial and a sleep
 5 medication. Actually, wrist-worn actigraphy is an
 6 acceptable outcome for a clinical trial and a sleep
 7 medication.
 8 DR. KOSTEN: I was thinking about it mostly in
 9 terms of the withdrawal phase; that risk outcomes on
 10 the withdrawal phase are a little problematic --
 11 DR. HUH: Right, tough, yes.
 12 DR. KOSTEN: -- and bounce around. But the
 13 sleep profile is a whole lot easier than the usual EEG.
 14 DR. HUH: Yes. We couldn't do that for
 15 somebody in withdrawal, like a whole polysomnography.
 16 It wouldn't happen.
 17 DR. KOSTEN: I saw where you're using it in
 18 withdrawal, and it was showing a pretty big effect.
 19 DR. HUH: Yes. They're not that -- I don't
 20 know, 8 grand, maybe, for one. I'm not sure.
 21 DR. KOSTEN: That's knowledge --
 22 DR. HUH: Yes, I think so; something like

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1 that.

2 DR. KOSTEN: That's my practical question.

3 DR. STRAIN: Kurt?

4 DR. RASMUSSEN: Just to follow up on Kelly's

5 point, it's well known that chronic morphine will

6 increase the orexin system in animals and in man, but

7 also chronic administration of cocaine will also

8 increase the orexin system, the number of

9 orexin-producing neurons. There's a chance that

10 suvorexant and other orexin antagonists could have

11 useful utility and stimulate use disorder as well.

12 DR. STRAIN: Thanks. Patrick?

13 DR. FINAN: I'm wondering if we could talk a

14 little bit about suvorexant dosing and get some -- we

15 don't have to talk about the dosing that is blinded

16 here, but if you talk with sleep clinicians who are

17 prescribing sleep aids, a common refrain is that

18 suvorexant thus far has not been very effective in

19 practice, and that many clinicians will not prescribe

20 it.

21 The culprit that you'll hear is that the FDA

22 has only approved a lower dose, the 20-milligram dose

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1 that is not as effective in treating sleep as the

2 40-milligram dose, which was seen as more effective in

3 earlier trials but also had more adverse events that

4 prevented it from getting approved.

5 So I wanted to see if anybody had thoughts on

6 that, practically speaking.

7 DR. HUH: Just to add to that, one issue is

8 suvorexant has a relatively long half-life, so the

9 higher dosing -- and it has, actually, a pretty safe

10 and mild side effect profile. But one issue is that

11 with that long half-life, there's next-day drowsiness,

12 and that was the issue with the larger dose. Although,

13 it's common across sleep medications, anyways. The

14 safety profile is much greater than that, like

15 benzodiazepines. That would be the competition for a

16 suvorexant level medication.

17 DR. STRAIN: I've prescribed it clinically.

18 When it came out, I was all excited because it was a

19 non-benzo, and it's supposed to have a different

20 mechanism of action and stuff. I think I'd say

21 probably about a quarter to a third of the patients

22 that I've tried it with have responded. It's not been

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1 as robust as -- you know, everybody likes Ambien; at

2 least in my prescribing of it.

3 DR. LEVIN: That's what Roger and I were just

4 saying to each other, quietly.

5 DR. STRAIN: About a quarter to a third.

6 DR. LEVIN: Maybe.

7 MALE VOICE: At best.

8 DR. LEVIN: At best. I use a lot more. I use

9 a lot more trazodone than I do that, in higher doses. I

10 don't know what doses you were saying you needed to go

11 on that slide, but --

12 DR. HUH: Trazodone?

13 DR. LEVIN: Yes.

14 DR. HUH: He started at 75 and went up to

15 150, but I know in different scenarios, we've used up

16 to 300.

17 DR. LEVIN: Yes.

18 DR. STRAIN: Do you have a sense that the

19 limited efficacy is due to perhaps the dosing or do --

20 DR. FINAN: People start at 20 milligrams. I

21 never asked the question, except talk to --

22 DR. STRAIN: Initially when it came out, it

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1 was really hard to get prior auths on it, which was a

2 pain, so that probably discouraged some. And I'll stop

3 on this story, and it's just an anecdote. I've got a

4 guy -- I didn't do this -- he was on 3 milligrams of

5 Klonopin to sleep at night. I started him on it, and

6 he's down to 1 and a half of Klonopin, and intends to

7 keep titrating down; otherwise, a well-functioning guy.

8 DR. KOSTEN: Can I ask one practical question?

9 You said there were 50 percent greater orexin

10 responsive cells --

11 DR. HUH: Um-hmm.

12 DR. KOSTEN: -- in opioid addicts. Does that

13 have a practical impact that orexin might work a whole

14 lot better in opioid addicts?

15 DR. HUH: That's the thought. If increased

16 orexin signaling is ubiquitous in folks with opioid-use

17 disorder, then an antagonist might kind of kill two

18 birds with one stone. It might help you sleep, and it

19 might improve other outcomes as well.

20 DR. KOSTEN: Right now, whenever we do

21 detoxes -- I hate to admit this, but clonidine doesn't

22 work that perfectly, and we typically add a

1 benzodiazepine to it. I'd be happier adding orexin to
 2 it than a benzodiazepine.
 3 DR. STRAIN: Kurt?
 4 DR. RASMUSSEN: So that addresses the dose
 5 question as well. Suvorexant, my understanding is 40
 6 is a much more efficacious dose for sleep, but there's
 7 some daytime sleepiness, and that that's problematic.
 8 However, in this OUD population, where it's clear that
 9 the number of orexin-producing cells is increased by 50
 10 percent, no wonder they can't sleep.
 11 The orexin is a lower drive, first of all, but
 12 to me, it would indicate that a higher dose may be
 13 needed in the OUD patient population. So that dose of
 14 40, with any luck, will be more effective and less
 15 problematic in this patient population.
 16 I'll also point out there are two other
 17 non-selective orexin antagonists in development.
 18 They're in phase 3. These companies are eager to get
 19 these on the market and looking to differentiate them.
 20 We're in discussions with both of them. So there could
 21 be more choices soon for orexin antagonists.
 22 DR. STRAIN: Okay. We've gone over thanks.

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

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

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

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1 this isn't a guided session per se. It's not
2 psychotherapy as such. We're asking people to go in
3 and have their own inner experience.
4 Under these conditions, this just shows the
5 dose and time effects with psilocybin over the course
6 of a 6- session. You can see onset occurs in about
7 30 minutes. Effects peak at 2 or 3 hours, and taper
8 off over the afternoon. By the end of the session day,
9 the volunteers are released into the care of a friend
10 or family member that accompany them home.
11 The qualities of these experiences are varied
12 and substantial. Two of the elements that we think are
13 most interesting and may be related to the therapeutic
14 effects of these drugs are these drugs produce -- and
15 this is post-session ratings of mystical type
16 experiences and psychological insightful experiences.
17 These are dose effects in healthy volunteers.
18 Their quality is particularly of the so-called mystical
19 experience. There's a sense of the interconnectedness
20 of everything. That is felt to be precious. Some
21 people would use sacred. It's also felt to be
22 authentically true. It's more real and more true than

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1 everyday waking consciousness.
2 I think it's the amalgam of those features,
3 this interconnectedness of all things, the preciousness
4 of the experience, and the authority with which that
5 experience comes through that may account for why these
6 experiences turn out to be so memorable, and the
7 memories of these effects endure.
8 This is just post-session, but here's where it
9 becomes interesting. When you follow these people up
10 at 1 month, or 14 months, or anecdotally 10 years
11 later, people are attributing very substantial positive
12 changes in their attitudes, moods, and behavior to that
13 experience.
14 This is 1 month after high-dose sessions.
15 About 80 percent are saying that that experience a
16 month ago was among the five most personally meaningful
17 experiences of their life, comparing that, for
18 instance, to the birth of a first-born child. But 90
19 percent are endorsing increased life satisfaction,
20 positive behavior change, perhaps relevant to substance
21 use.
22 These positive attributions are sustained way

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1 out. We've gone out to 14 months, as I said,
2 anecdotally many years later. Importantly, they're
3 confirmed by the ratings of community observers; that's
4 friends, family members, and colleagues at work. So
5 this is something other than just a narrative that the
6 participant is volunteering. Their closest people
7 among their friends and family endorse changes of the
8 types that they're claiming to have made.
9 Turning to the therapeutic indication, this is
10 a study we did in 2016 similar to the one that was
11 conducted at NYU. In this case, 51 cancer patients, a
12 randomized, double-blind, crossover design, 2 sessions,
13 5 weeks apart, comparing a high dose of psilocybin to a
14 very low dose of psilocybin.
15 This jumps to the primary outcome measure.
16 Along with this, there were mystical type experiences
17 and these attributions of the important piece of these
18 experiences. However, when you look at HAM-D, a gold
19 standard measure of depression -- it's a clinician
20 rated depression measure -- we're looking now at
21 percent of the participants, and this is 5 weeks after
22 the high dose, 92 percent of the participants are

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1 showing clinically significant improvement, as 50
2 percent drop on the HAM-D, and that's sustained out to
3 6 months at almost 80 percent.
4 Here's remission to normal range. For HAM-D
5 scores below 7 are within the normal range, and here we
6 have 60 percent have remitted. At 5 weeks, it's 70
7 percent out of 6 months.
8 This is a unpublished data and won't show up
9 in the public slides yet. It's a randomized delayed
10 treatment. It's a wait-list control treatment,
11 examining the efficacy of 2 psilocybin sessions under
12 these same psychologically supported conditions. This
13 is, again, HAM-D for delayed treatment group. This is
14 prior to receiving psilocybin in the immediate
15 treatment group, and these time points coincide between
16 these two groups, and this is HAM-D again.
17 We're getting these enormous effect sizes,
18 delayed treatment control, so that weakens the design.
19 But these are effects sizes over 2 and a half. At
20 3 months, if you take a look at all participants that
21 were treated, we have about 70 percent clinically
22 significant response and 54 percent remission to normal

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

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

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

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1 use, but something to be aware of that might be a clue
 2 into some ongoing research, exploring the use of these
 3 compounds, to treat potentially migraine and cluster
 4 headaches, some work going on at Yale currently on
 5 those disorders.
 6 Finally, there is a pretty rare phenomenon of
 7 hallucinogen persistent perceptual disorder. It's a
 8 DSM diagnosis, pretty mysterious. A lot of things are
 9 called flashback. This is only a subset of that. This
 10 is not just seeing some perceptual things like the next
 11 day. This is a chronic disturbance to the individual
 12 in the perceptual realm.
 13 The important thing to learn, to note here,
 14 pretty rare even amongst recreational users, but has
 15 never been identified in either the older era from the
 16 '40s through the '70s of classic psychedelic clinical
 17 research or in the modern era. It seems to be an
 18 exclusive product of recreational use. It could be a
 19 result of some type of vulnerability that we're
 20 screening out even though we're not targeting for any
 21 known factor to screen it out, and it could be a result
 22 of polysubstance use, including alcohol, but something

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1 important to keep screening for.
 2 For everything that I've gone over, we know
 3 that there are good methods for squarely mitigating
 4 these risks in clinical research and in potential
 5 medical use through screening, monitoring, and follow
 6 up of the participant. As Roland mentioned, one last
 7 thing is that it does not appear that the classic
 8 psychedelics, the two-way agonists, are drugs of
 9 compulsive drug seeking or addiction. They're
 10 certainly drugs of abuse; that is to say they can be
 11 used in a way that causes harm to the self and others,
 12 but doesn't appear that folks are jonesing for that
 13 next mushroom or LSD fix.
 14 We published over a decade ago our recommended
 15 guidelines for essentially how you conduct this
 16 research safely, taking into account all of those risks
 17 and doing the research safely. Part of that is the
 18 comforting physical and interpersonal environment.
 19 This is kind of addressing the challenging experiences,
 20 the anxiety or the panic, that sometimes occurs. It
 21 occurs about a third of the time at a high dose of
 22 psilocybin that we use, but holding of the hand and

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1 words of reassurance seem to be pretty powerful in
 2 addressing that.
 3 If no one's jonesing for their next psilocybin
 4 fix, why in the world would we expect it, though, to be
 5 able to treat addiction? A couple of threads there.
 6 One is in anthropological literature suggesting stories
 7 of addiction recovery from the sacramental use of these
 8 compounds. Those stories come from peyote use
 9 associated with the Native American church that
 10 contains mescaline, and also the use of Avahuasca.
 11 This South American concoction used ceremonially
 12 contains dimethyltryptamine.
 13 Of course, this is observational. Also, we
 14 know religious involvement is associated with addiction
 15 recovery as well, so by itself might be suggestive but
 16 certainly not conclusive. Another thread of evidence
 17 comes from this older research using LSD to treat
 18 alcoholism. There were a lot of studies. It was
 19 previously considered a mixed bag. Some studies didn't
 20 find an effect, some showed a significant effect, some
 21 showed a trend with a small number of subjects that
 22 wasn't significant.

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1 Several years ago, some Norwegian colleagues
 2 published a meta-analysis of the only six studies that
 3 randomized folks to either LSD or some other comparator
 4 condition. As you can see here, I'm showing the odds
 5 ratio, this side favoring LSD. These are the
 6 individual studies with the error bars. This is the
 7 aggregate meta-analysis effect size across those
 8 studies.
 9 It was a clear significant effect in
 10 aggregate. More impressive is the effect size,
 11 essentially suggesting that there was nearly double the
 12 likelihood that folks were improved in their alcoholism
 13 outcomes at whatever the first follow-up visit was,
 14 suggesting something was there, although the rug was
 15 pulled out before we could follow up as a field on
 16 that.
 17 This category is suggestive of potentially
 18 cross-compound anti-addiction. This is a single study
 19 that was published. In LSD in the treatment of heroin
 20 addiction, there were limitations that were some other
 21 differences besides the drug that were described in the
 22 original study published in '73, but nonetheless found

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1 some promising effects with increased biologically
 2 confirmed long-term success associated with LSD
 3 compared to a controlled condition. I'll say that,
 4 yeah, urine biological confirmation wasn't the norm
 5 back then, so that was an impressive component of that
 6 earlier research.
 7 I just wanted to show you one quote from that
 8 paper, pretty interesting. These were inner city,
 9 Baltimore, heroin-using addicted participants, and they
 10 were asked to compare the drugs. One person said
 11 heroin has a numbing effect on you. It tends to relax
 12 you and somewhat takes you out in a way from your
 13 surroundings and yourself. LSD makes you more aware of
 14 yourself and puts you right into whatever has been
 15 troubling you.
 16 I think that's a pretty good description
 17 anecdotally of what we tend to see in our various
 18 studies, that these drug experiences tend to prompt a
 19 confrontation with issues the person has been
 20 subjectively putting aside.
 21 With this idea of cross-drug, potential
 22 anti-addiction efficacy, we tried our hand at smoking

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

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

16 There were three psilocybin sessions over
 17 8 weeks, starting at a moderate dose, then moving up to
 18 a high dose. We had the ability to adjust those later
 19 doses depending on the initial session response. But
 20 the first psilocybin session was actually scheduled on
 21 a target quit date. This is a big day for people, and
 22 not only are they going to quit smoking, but you're

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

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

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

22 We published a qualitative long-term interview

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

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

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

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

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

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

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

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1 still think more sessions is probably better
 2 clinically, but more for experimental reasons; scaling
 3 back to one session on their target quit date.
 4 The study's in progress, but these are our
 5 current results, so note the different end as we get to
 6 these different lengths of long-term outcomes. But at
 7 12 months, those people, what we're seeing right now is
 8 56 percent are biologically confirmed as 7-day
 9 prevalence, biological abstinence, versus 17 percent in
 10 the nicotine replacement group, interestingly. We'll
 11 see if all of this holds up. It may not. None of it
 12 may hold up. But it seems like the difference between
 13 groups is getting larger as time goes on, and as more
 14 of the nicotine replacement folks are relapsing.
 15 Very quickly, I'll say we studied fMRI pre-
 16 and post-quittings. This is not during the experience.
 17 We are looking here at a number of tasks, and we only
 18 have one analyzed so far with a subset of initial
 19 participants, but we administered the oddball task.
 20 This is a task of cognitive interference. People have
 21 to identify the oddball digit, and identify that digit
 22 with the finger number that corresponds to whatever

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1 that oddball digit is; if there's one 1 and two zeros,
 2 and 1 is the oddball.
 3 Resist the urge to use the finger that's in
 4 the same spatial location. This is kind of like the
 5 Stroop task. You have to override a pre-potent
 6 response, and you get a difference in reaction times,
 7 which index is that interference effect. We're getting
 8 a significant improvement in that measure, dealing with
 9 that interference for psilocybin compared to the people
 10 24 hours after quitting, who have gotten the nicotine
 11 patch treatment.
 12 I don't want to make too much of a story out
 13 of it. This could change. But we are seeing an
 14 associated fMRI response, normalization of the
 15 task-associated response in the right lingual gyrus the
 16 day after. Again, we'll see if that holds up. But
 17 this might be kind of a clue into the more mindfulness
 18 type approach people are anecdotally reporting after
 19 they've quit with psilocybin; so this awareness that
 20 they have quit, less inclined to fall into
 21 automaticity.
 22 Briefly, very similar results to our pilots;

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1 they were published by Michael Bogenschutz, who's with
 2 us here, who conducted this work at the University of
 3 New Mexico. He's now at New York University. In this
 4 study with 10 alcohol-use disorder participants, found
 5 strong reductions in drinking days and heavy drinking
 6 days after a series of psilocybin experiences. He,
 7 like us, is following up his data with, in his case, a
 8 large, I think, 100-person randomized, double-blind
 9 study, so we will see what results are there.
 10 I'll go through this really quick. We've done
 11 a series of studies, again, like the smoking research,
 12 assessing the landscape, getting descriptors of these
 13 reports of people who have largely used for fun on
 14 their own, and they report quitting a drug. We did
 15 some of this work with alcohol, with some structural
 16 equation modeling.
 17 I'll just briefly say it seems like -- we
 18 can't determine causation here, but the model suggests
 19 there may be a causal pathway involving both the
 20 mystical nature and the insightful nature of the
 21 experience, leading into how meaningful the experience
 22 was, and that predicting the change in alcohol-use

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1 severity.
 2 We've published that. We haven't published
 3 this yet. We've done a similar thing with opioids,
 4 cannabis, and cocaine. I'll show you the opioid
 5 component here; 343 people said they quit or reduced
 6 opioids because of a psychedelic experience. These are
 7 all largely user classic psychedelics, largely
 8 psilocybin and LSD, is what people were using, and
 9 found the same model held up with these individuals in
 10 that study.
 11 Just briefly getting into lessons for design
 12 and outcomes, in terms of the acute measures, certainly
 13 continuing to look at these with this trend of the
 14 nature of the experience that they have under
 15 psilocybin, predicting outcomes. We need to keep
 16 looking at that, and probably need to look at an
 17 additional number of measures; so mystical experience.
 18 We have psychometrically developed essentially a bad
 19 trip scale, the challenging experience questionnaire;
 20 weightings of how meaningful the experience is.
 21 Peter Hendricks, who's with us, who's doing
 22 work using psilocybin to treat cocaine-use disorder, he

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

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

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

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

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

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

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

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

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

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1 we're seeing and the long-term effects.

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

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

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

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1 when you're looking at something new. I think the
 2 ultimate answer is going to come from comparative
 3 efficacy studies, open-label studies, and
 4 double-blinded studies. I thought with smoking
 5 cessation, the next step, in terms of what we're doing
 6 now, is open label but a randomized comparative
 7 efficacy study to a known standard.
 8 I think compared to other double-blinded
 9 medication studies, we are looking at something
 10 particularly bizarre with psychedelics in the sense
 11 that we're telling people this can be like this big
 12 experience in your life, including the most frightening
 13 experience, or you could be bored stiff on the couch
 14 all day.
 15 That's probably something you're never
 16 actually going to get if this stuff is rolled out in
 17 actual medical use and we're modeling something that's
 18 kind of a Frankenstein you're never going to see. But
 19 again, we obviously need that, particularly for
 20 medication development and to fully understand what's
 21 going on. So I really think the ultimate answer comes
 22 through the triangulation of these methods.

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1 Then, big questions about the nature of the
 2 placebo. We've done a bunch within our group, and
 3 others have; a true placebo, an active placebo, another
 4 psychoactive compound. You've got to be careful or use
 5 something like ketamine for depression, and you might
 6 have a comparator that shows an efficacy, too.
 7 You probably only want to throw in something
 8 like that if you also have a true placebo or something
 9 else; lower trivial doses of the same compound, the
 10 MAPP group, working with MDMA. I think they've learned
 11 some things there. There can be a danger in assuming
 12 that a low dose is not active because people differ in
 13 their sensitivity to these therapeutic effects. We
 14 have used, in the cancer work Roland showed, a really
 15 trivial dose that was really just controlling for
 16 instructional sets, so we can truthfully tell them
 17 you're going to get some dose of psilocybin.
 18 So there's a lot going on there, a lot of room
 19 for creative thinking in terms of experimental design.
 20 Then obviously, the long-term assessment, like I said,
 21 it may be that that's where these treatments really
 22 shine, and certainly concerns about opioid-use laps.

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1 Even though you always have the potential for
 2 fatal relapse when you're dealing with opioid-use
 3 disorder, one extra concern, above the primary risk of
 4 hurting anyone, is that even if you have something
 5 that's not related at all in reality to psilocybin,
 6 this is such a sensational area, there might be this
 7 extra causal attribution to something that normally
 8 wouldn't be front-page news if it was more boring in
 9 terms of attention.
 10 Medication, some real thought about -- yeah,
 11 as there should be for any study -- about really
 12 minimizing fatal outcomes with a relapse when people
 13 have lost their tolerance. Finally, a lot of thought
 14 around navigating the true believers. I've been doing
 15 this 15 years. Earlier on, I've always done some of
 16 both, but I've spent most of the time trying to
 17 convince people, yeah, there's something really
 18 credible and interesting here that we should invest in.
 19 Now I think I spend most of my time arguing
 20 back to the people thinking it's going to be a panacea
 21 and that there aren't any risks. We really need to be
 22 thoughtful about how we model this stuff going forward

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1 in terms of mainstreaming it. These are sometimes and
 2 often described in mystical, spiritual language that
 3 can mean different things for many people. I've seen a
 4 lot of atheists go through this; they're still
 5 atheists. You can come to these experiences from a
 6 religious framework. It's not necessary.
 7 So we need to really be thoughtful about how
 8 we're framing this for a broad audience and not fall
 9 into -- it's been called a cultigenic effect in the
 10 history of these compounds, that there can be an
 11 inclination for folks to form a religion around these
 12 kind of high-magnitude experiences. There's a lot of
 13 room for thought around how we mainstream these
 14 compounds.
 15 I think that's it. Thank you to a whole lot
 16 of folks for the work that I showed you. I think we
 17 have a few minutes for questions. We have until 3:15.
 18 (Applause.)
 19 DR. JOHNSON: For Roland and I, if there's
 20 time for questions.
 21 DR. STRAIN: Questions on this?
 22 DR. JOHNSON: Michael?

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

10 DR. JOHNSON: Right.

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

19 DR. JOHNSON: Right.

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

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

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

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

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

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

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

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

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

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

1 they apparently expect some return on investment.
2 I would say it's a different treatment model.
3 Folks have jumped out of the psychiatric drug space,
4 and I think there's a recognition this is a potential
5 niche. Maybe more of the opportunities are not along
6 the model of selling the pill every day. I think
7 there's plenty of opportunity for IP, for intellectual
8 property, because there's a whole lot we know about
9 structure and activity of relationships now and the
10 potential for novel compounds here that can improve
11 upon what we're seeing.

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

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

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

1 We're going to turn to vaccines now. Sandy
 2 Comer is going to start. Sandy, the podium is yours.
 3 As you're going up, then Marco Pravetoni will do the
 4 last 10 minutes of this session
 5 Presentation – Sandra Comer
 6 DR. COMER: I'd like to thank Eric for
 7 inviting me here to give this presentation on a project
 8 that we're really excited about, and I'd like to thank
 9 NIDA for funding the bulk of the research so far.
 10 This is our team. It's very much a
 11 collaborative effort. Marco, Paul, and Scott at the
 12 University of Minnesota, were the ones who originally
 13 developed this vaccine concept. Paul was the person
 14 who developed a nicotine vaccine that made it into
 15 phase 3 clinical trials, and Marco has taken over that
 16 program at the University of Minnesota. My team at
 17 Columbia will be conducting the first-in-human studies
 18 of the vaccine, and more recently, we've set up a
 19 collaboration with Clinilabs. It's a contract research
 20 organization who will help run that study.
 21 When I first started talking to Paul about
 22 this concept of a vaccine, my immediate reaction was

1 another is a morphine vaccine. The oxycodone vaccine
 2 targets oxycodone and other substances that are
 3 chemically similar to oxycodone, so hydrocodone and
 4 oxymorphone. The morphine vaccine would target
 5 heroine, 6-acetylmorphine, and morphine.
 6 This is really a multivalent concept here, and
 7 I want to spend a little bit of time talking about
 8 that, because this is really important. The first
 9 vaccine that we're going to be studying is the
 10 oxycodone vaccine. Then, assuming all goes well with
 11 that, we'll look at the morphine vaccine, and the
 12 original concept was that it would be a bivalent
 13 vaccine. So both of the vaccines would exist in one
 14 vial that would be given to patients.
 15 Then over the course of the last few years,
 16 of course, fentanyl became a problem, so Marco has
 17 developed a fentanyl vaccine as well, so this could be
 18 a trivalent vaccine, and it could be a multivalent
 19 vaccine more than just these three, which I think is
 20 really interesting. Whatever new opioid might come to
 21 be abused could be added to this vaccine.
 22 To put it into context a little bit, we're

1 why a vaccine? I mean, we have naltrexone. Wouldn't
 2 it work in kind of the same way? The short answer is
 3 no, actually. Once we started discussing the ins and
 4 outs of what the vaccine would do, it became clear that
 5 there are certain clinical advantages of a vaccine over
 6 something like naltrexone.
 7 There are unique concerns about using a
 8 vaccine that I will talk about today, and then there
 9 are certain regulatory hurdles as well. Hopefully, you
 10 can answer all of these questions in the course of the
 11 talk.
 12 Just to give you a brief description of what
 13 the concept is, a person will initially get vaccinated
 14 and develop antibodies to a target drug. The first one
 15 that we're going to be working with is oxycodone. In a
 16 vaccinated person, if they end up using oxycodone,
 17 these antibodies will bind that substance and prevent
 18 it from getting into the brain. A series of injections
 19 are typically given with vaccines over a series of
 20 months in order to achieve maximal antibody production.
 21 These are the two vaccines that we originally
 22 started working with. One is oxycodone vaccine and

1 kind of conceptualizing it almost like a flu vaccine.
 2 Every year the components of the flu vaccine change,
 3 depending on what strains of the virus might be
 4 prominent that year; so that's kind of the way we're
 5 thinking about this as well.
 6 Just to remind you all to get your flu vaccine
 7 if you haven't done that yet.
 8 (Laughter.)
 9 DR. COMER: Here, I just want to show you some
 10 data briefly from the preclinical labs, Marco's lab.
 11 On the top are serum levels of oxycodone here; on the
 12 bottom are brain levels of oxycodone. The dark bars
 13 are the vaccinated animals and this is the control
 14 animals. When they received this 0.5 milligram per
 15 kilogram IV dose of oxycodone, serum levels go up and
 16 brain levels go down. Remember, I showed you that
 17 figure where the vaccine is supposed to prevent the
 18 drug from -- or the antibodies will bind to the
 19 oxycodone. With a lower dose of oxycodone, the same
 20 thing happens. Serum levels go up, brain levels go
 21 down.
 22 This was a study that I thought was really

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1 interesting, where they gave animals the vaccine, and
 2 then started to train them to self-administer
 3 oxycodone.
 4 These are across several sessions. The
 5 animals that received the active vaccine never acquired
 6 self-administration behavior. This is intravenous
 7 oxycodone. The animal presses the lever in order to
 8 get the drug. The control animals show this typical
 9 pattern of acquisition of oxycodone
 10 self-administration. So here it's preventing the
 11 acquisition of oxycodone self-administration.
 12 Clinically, when I started thinking about
 13 these vaccines, I started to think of where it would
 14 fit in the treatment scheme. The progression of use
 15 goes from no use, to severe opioid use, to treatment,
 16 to relapse, unfortunately, in a lot of patients.
 17 A typical progression of disease could be
 18 recreational use of oral prescription opioids
 19 progressing to daily use. Oftentimes, people switched
 20 to intranasal use of prescription opioids or they start
 21 dabbling into heroin or fentanyl. Then when the
 22 disorder gets really severe, they might start

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1 injecting. I know that people who love oral opioids
 2 also can have severe opioid-use disorder, but I'm just
 3 using this as an example.
 4 Then, a subset of the patients will seek
 5 treatment, and they'll go onto buprenorphine,
 6 methadone, or naltrexone. Where I'm thinking the
 7 vaccine could be useful is in this situation where it
 8 might prevent the progression from recreational use to
 9 daily use. It can be used potentially as a stand-alone
 10 medication. We'll have to see after we run the trial
 11 how robust be effect is.
 12 This is where I think it gets really
 13 interesting. In patients who are maintained on
 14 buprenorphine, methadone, or naltrexone, the vaccine
 15 could be used as an adjunct, actually, because the
 16 vaccine is really targeting a particular chemical
 17 structure. So the buprenorphine, methadone, and
 18 naltrexone have structures that are so different that
 19 it wouldn't interfere with their effects, and Marco has
 20 some data to show that this is the case.
 21 In the patients who have been on
 22 medication-assisted treatment who end up relapsing to

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1 opioid use, the vaccine could be really helpful here
 2 because they might not experience much drug effect, so
 3 it would provide us with an opportunity to reengage
 4 them in treatment, and it could potentially provide a
 5 safety net for overdose at any of these phases. Again,
 6 Marco has some preclinical data to show that this might
 7 be the case.
 8 These are the areas where I think it might be
 9 useful to prevent OUD, to use it as a stand-alone
 10 medication, to use it as an adjunct, to maybe prevent
 11 relapse, and to prevent fatal overdoses.
 12 Here, I like doing this kind of exercise to
 13 think what are the pros and cons of different types of
 14 medication approaches compared to what's existing.
 15 This is agonist maintenance, this is sustained-release
 16 naltrexone, and then here's the vaccine. We know these
 17 two forms of treatment are effective.
 18 For agonists, it's easy to get them on to the
 19 agonist maintenance from heroin. Buprenorphine has
 20 some unique challenges, but it's relatively easy once
 21 you kind of get the hang of it. With naltrexone, you
 22 have to detox patients. That's a hurdle for a lot of

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1 people. With the vaccine, it should be relatively easy
 2 because it should not precipitate withdrawal. This is
 3 something that's a big question mark. I don't know how
 4 we would transition patients onto the vaccine, so
 5 that's something that we need to answer empirically.
 6 The risk of relapse is low if somebody
 7 relapses, and the same with naltrexone. I don't know
 8 if it's true anymore, now, with fentanyl on the scene.
 9 Medication compliance tends to be pretty decent for
 10 both forms of therapy. With agonist maintenance,
 11 patient convenience is poor, especially with methadone.
 12 There's a risk of diversion. Sedation can be an issue.
 13 There's a respiratory depression risk, especially with
 14 methadone during dose titration. There's child safety
 15 risks.
 16 All of those are not the case with naltrexone,
 17 but as someone mentioned earlier today, patients don't
 18 like naltrexone, so that's the biggest hurdle with that
 19 one. With the vaccine, it should also have a lot of
 20 these same advantages as naltrexone has.
 21 I to walk you through some of the interactions
 22 that we've had with the FDA in terms of discussing this

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

7 The FDA response was absolutely not. You
8 cannot do this study in normal, healthy volunteers. So
9 we're like, okay, we'll go back to the drawing board.

10 They really insisted that we study the vaccine first in
11 participants with opioid-use disorder. So in 2018, we
12 wrote a grant, which was funded, thankfully. At a
13 meeting that we had, where members -- so it's CBER, the
14 group that we were working with at the FDA.

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

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1 Their initial concerns -- and I think these
2 are some of the things that are potentially unique with
3 the vaccine approach, is they were worried about the
4 vaccine blocking the effects of endogenous opioids.

5 Marco ran a study to address that in rodents. They
6 also were worried about the vaccine blocking the
7 euphoric effects of opioids without blocking its
8 respiratory depressant effects.

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

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

22 So we were very, very careful about that with

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1 our sustained-release naltrexone studies, and it turns
2 out that they don't do that. That doesn't happen.

3 There were a few people who tried to override the
4 blockade, but the doses that block the reinforcing
5 effects or the euphoric effects of the opioids are also
6 the same doses that block the respiratory depressant
7 effects.

8 So while this is a theoretical concern, we
9 don't think that this is going to be a real clinical
10 concern, but we'll monitor that very carefully as well.

11 Really, what happens is that people are just not
12 willing to spend 100 bucks on heroin to get a very
13 mediocre high. They're governed by laws of economics
14 just like anybody else, and that just doesn't happen.

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

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

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

6 We also will look at preliminary efficacy.

7 The primary endpoint here is what the FDA usually
8 expects to see in these types of studies, so our
9 primary endpoint will be mean peak ratings of drug
10 liking.

11 The inclusion/exclusion criteria for people in
12 this type of study are different than what we normally.
13 This is not different, actually; men and women 18 to 59
14 years. They have to meet criteria for moderate to
15 severe opioid-use disorder and be physically dependent
16 on opioids, but not physically dependent on any other
17 substances of abuse, with the exception of nicotine.

18 They currently will not be seeking treatment for their
19 drug use because we're going to be giving oxycodone and
20 fentanyl, actually, in the lab

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

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

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

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

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

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

4 The between subjects part of it is that we'll
5 look at three different doses of the vaccine. We'll
6 have alum, which is the adjuvant as a control, and then
7 100 and 400 micrograms of the vaccine. We'll do it in
8 ascending order. It will be roughly a 2-to-1 ratio of
9 active versus control.

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

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

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

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

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

22 The oral morphine, we decided to maintain

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

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

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

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

1 the candles at both ends, passing the application back
 2 and forth. It's really, really awesome that Bob and
 3 his group are helping us with this because it's a lot
 4 of work. So we're really grateful for that.
 5 We hope to receive FDA approval sometime early
 6 next year; knock on wood. Hopefully, the pre-IND
 7 meeting was enough to address most of the FDA's
 8 concerns, so we'll see what happens.
 9 We have conditional IRB approval now, and we
 10 hope that final IRB approval will happen sometime at
 11 the end of January maybe, and then we can start
 12 enrolling patients. We hope to finish that by the end
 13 of 2021, and then initiate the morphine KLH study some
 14 time in 2022, assuming all goes well and there are no
 15 issues.
 16 I'd like to thank my colleagues at Columbia
 17 for being great, and helping, and working really hard,
 18 and then I'd like to invite Marco up to show some other
 19 data that are, I think, really, really exciting because
 20 this is Marco's brilliant idea that hopefully will help
 21 us with efficacy issues.
 22 (Applause.)

1 highest antibody levels will also show the greatest
 2 efficacy. Roughly, that accounts for about 30 percent
 3 of the population that has been immunized. So what
 4 will happen if we can actually select patients
 5 a priori?
 6 Here, when you're looking at antibody
 7 responses, even if you have not done analysis, you may
 8 appreciate that antibodies are the endpoint by a
 9 cascade of events that involve the immune system, both
 10 innate and the adaptive response. Prior to
 11 immunization, the naive new repertoire included a
 12 variety of immune subtypes that recognize different
 13 antigens, vaccines, infectious disease, et cetera. In
 14 that mix, there is the possibility that some of these
 15 cells will also recognize opioids or opioid vaccines.
 16 After vaccination, a lot of these entities,
 17 whether they are innate or adaptive immunities -- so
 18 things like B cells/T cells -- are going to be
 19 activated. Lots of events will yield to an antibody
 20 response that may be characterized by IgG subclasses or
 21 by specific molecular pathways that are conducive to
 22 antidrug and antibodies that will then be effective in

1 Presentation - Marco Pravetoni
 2 DR. PRAVETONI: Thank you for the
 3 introduction, Sandy, and thank you for the
 4 brilliant -- we don't know if it works yet, but
 5 hopefully. I thank you to the organizer to give me the
 6 opportunity to speak at this meeting.
 7 Here, where I want to spend a little bit of
 8 time is, essentially, where the preclinical and the
 9 clinical program merge so that we can inform how to go
 10 about this clinical trial. One of the challenges in
 11 this field is being to identify immunological
 12 mechanisms and biomarkers that can predict the vaccine
 13 efficacy to accelerate translation.
 14 From previous data, clinical data on
 15 evaluation in humans for nicotine and cocaine vaccines,
 16 we know a great deal of this. We know that, for
 17 instance, people that are vaccinated, against nicotine
 18 and cocaine, people that show the highest antibody
 19 levels also show vaccine efficacy. Roughly, in various
 20 trials of nicotine and cocaine, that corresponds to
 21 roughly about 30 percent of the subjects.
 22 So the idea here is people that have the

1 reducing either drug distribution to the brain or
 2 behavioral toxicity. The idea here is by digging here
 3 in the weeds, we can actually point out where we can
 4 find biomarkers that are predictive of vaccine efficacy
 5 and whether we can apply that to our system.
 6 Taking a step back here, what did we spent
 7 some time on is looking at various vaccine components.
 8 Each vaccine component is critical for optimization of
 9 this vaccine. As you can appreciate, as you improve
 10 your vaccine formulation, you may improve the vaccine
 11 efficacy. But on the other end, also these components
 12 are interfacing with a new system as soon as you
 13 vaccinate somebody.
 14 This is a general schematic of our oxycodone
 15 vaccine. The molecule on the left is essentially the
 16 backbone of hydrocodone and oxycodone, that can be
 17 modified by various linker and attached to carrier
 18 proteins to actually make so that the new system will
 19 see it. These cells are generally thought to recognize
 20 this portion of the vaccine, so we we'll define them as
 21 Hapten-specific B cells. CD4 T cells are known to bind
 22 to the pertinacious part of the vaccine, so essentially

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

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1 all sort of tissue from human models, primates, and so
 2 forth, and essentially enrich for B cells, they do
 3 recognize the opioid of choice or any antigen for that
 4 method. In a way, you can actually isolate the cells,
 5 the B cells of interest, that won't bind -- in this
 6 case oxycodone -- and then you can analyze by a flow
 7 cytometer or cell sorter. Essentially, you can take a
 8 lot of material and get down to a few cells. Just to
 9 give you a comparison in mice, we're able to look at a
 10 200 microliter of blood and find 5 B cells that
 11 recognizes oxycodone.
 12 Obviously, this is just mouse work, and that's
 13 where we've spent time in the last years. To give you
 14 an example of how this may apply to vaccines, here we
 15 have our oxycodone vaccine. The oxycodone KLH that
 16 Sandy was describing was given to mice, and here on my
 17 right is the individual variability. These are
 18 vaccinated animals versus control. The mean effect is
 19 obviously the vaccine will reduce the amount of drug
 20 that gets to the brain -- that is oxycodone -- but also
 21 you can appreciate there is a lot of individual
 22 variability.

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

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

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1 year. By the technology I mentioned before, we are
 2 able to compare and see if these individuals have a
 3 higher frequency of opioid-specific B cells.
 4 This is an output of what flow cytometry looks
 5 like. Most immunologists get very excited about things
 6 like that; most people don't. This is standard
 7 [indiscernible] cells used in clinical labs to
 8 standardize your blood measures. In the red box, we
 9 have two opioid users, and down here in green, we have
 10 no opioid users. Across, you are to look at the gates
 11 in the flow cytometry, where we look at opioid-specific
 12 B cells.
 13 Story short, we are actually able to find
 14 opioid-specific B cells, and their frequency is higher
 15 in opioid users. That translates into roughly this
 16 type of data. If you don't like looking at a flow
 17 plot, this is just an overall estimate of some
 18 opioid-specific B cells, the number of cells that we
 19 found for amount of blood.
 20 What we found is that people who have been
 21 using opioids for a given time, they show a higher
 22 number of opioid-specific B cells compared to people

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1 that have never used opioids. If you further down this
 2 analysis to look at specific B cell subtypes, results
 3 may come in many flavors, so antibody [indiscernible]
 4 cells, memory cells, et cetera. We show they have
 5 different roles in contributing to vaccine efficacy.
 6 But the bottom line is that we can find these things in
 7 opioid users and not necessarily in naive people, or at
 8 least the frequency's higher in people that use
 9 opioids.
 10 The question here that we're going to try to
 11 answer is that opioid-specific B cells is a valuable
 12 marker that can help us to predict vaccine efficacy.
 13 We are gearing up to the clinical trial, and with the
 14 NIDA funding, we are able to start developing the
 15 technology that we will be able to apply to patients.
 16 As you can appreciate, there are lots of
 17 logistics. Some of the flow cytometry analysis is done
 18 in fresh samples. We collect blood at sites. We ship
 19 it over and process it. There is actually a third lab
 20 on that slide that is also sequencing some of these
 21 B cell receptors, and that is done in Germany. So as
 22 you can appreciate, there are a lot of logistics

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1 involved with the different type of samples. We want
 2 to focus on what is actually doable and also cost
 3 effective that can be implemented in the clinic.
 4 The biomarker, bridging what we learned from
 5 the preclinical studies, for years we've been working
 6 on different types of immunomodulator. Story short, we
 7 found that interleukin 4 would increase or is well
 8 associated with vaccine efficacy.
 9 In this particular study, we co-administered
 10 the OXY-KLH vaccine with a neutralizing antibody of
 11 anti-IL-4. What we found is that we have increased
 12 antibodies and also increased the efficacy in blocking
 13 distribution of oxycodone to the brain. Some of these
 14 modulators are actually in clinical use for other
 15 indications, so there is value in that.
 16 To validate the studies, we looked at animals
 17 that were genetically modified to not express IL-4.
 18 What we found was essentially the same story. IL-4
 19 knockout animals vaccinated with the oxycodone vaccine,
 20 which showed an increase in antibody titers and also
 21 increased efficacy. This particular increase in
 22 efficacy was associated with a shift in IgG subclasses.

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1 IgG comes in many flavors, and some of them have a
 2 different function that contributes to vaccine
 3 efficacy.
 4 We're hoping to bring some of these parameters
 5 into the clinical trial. Specifically, something like
 6 IL-4 can be simply sampled in blood. The idea here is
 7 that IL-4 could be a pharmacological target, a
 8 biomarker, and possibly both.
 9 Looking even closer, we started implementing
 10 new techniques, like trying to look at the molecular
 11 signature of the vaccine. This was obviously done in
 12 the mouse, but some of these approaches can easily be
 13 done in people. This was sequencing of CD4-T cells,
 14 and we looked at animals that were either vaccinated
 15 with control, with OXY-KLH, or with OXY-KLH and the
 16 anti-IL-4 modulators.
 17 Without going into details, you may appreciate
 18 this cluster of activities that are associated with
 19 vaccine efficacy. Obviously, if you bring this to a
 20 clinical trial, we will need some bioinformatic person
 21 to deconvolute the information so that you can actually
 22 correlate individual signatures through actual vaccine

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1 outcome. This is just a thought, and this is something
 2 that could be done as has been done for other vaccines
 3 against HIV, malaria, and so forth.
 4 Finally, I tried to convey this idea that
 5 preclinical data supports the use of biomarkers. What we
 6 learned about these vaccines in the past few years,
 7 from my lab but also other labs in the field, we can
 8 bring that and possibly improve vaccine design, or
 9 routine [indiscernible] like a design, or the vaccine,
 10 possibly preparing it for something like a phase 2 so
 11 that we can stratify patients.
 12 One of the easiest biomarkers is sex. We've
 13 seen that female mice and rats have greater responses
 14 to vaccines, so that's something to keep in account.
 15 Frequency of hapten-specific B cells, as I just
 16 mentioned, by flow cytometry, we can analyze that, and
 17 that's doable. We can look at IgG subclasses; pretty
 18 much anybody can do that, and we see the value in that.
 19 Also, there are other things that may be more
 20 on the genetic side. We've seen, in our studies or
 21 others, that toll-like receptors may be involved or
 22 uninvolved [indiscernible] the responses to vaccines.

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1 So humans have well-characterized polymorphisms for
 2 things like TLR. So those are things that we can look
 3 and maybe help us to better understand the data.
 4 Finally, and I just mentioned, interleukin 4
 5 and other cytokines might be something that can be
 6 sampled in blood. Of course, if you do approaches like
 7 sequencing, you can come up with other unknown targets.
 8 For that, I thank the people in my lab.
 9 Obviously, we have this wonderful collaboration with
 10 Sandy. I'm not that clinical person, so she's the
 11 right person to move this stuff forward. Then, as you
 12 can imagine, we have lots of people at different
 13 institutions, and then of course we have NIDA to thank
 14 for the generous awards that are supporting this
 15 research. Thank you very much.
 16 (Applause.)
 17 DR. STRAIN: We have a few minutes before we
 18 open it up for a more general discussion, if there are
 19 questions for Marco or Sandy.
 20 DR. KOSTEN: A couple of things.
 21 DR. STRAIN: Tom Kosten?
 22 DR. KOSTEN: We found out in our early cocaine

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1 studies that some of what's happened is there are
 2 people who have cocaine antibodies before you ever
 3 vaccinate them, then there are a couple of other groups
 4 that have the same thing.
 5 I guess the one question that I might wonder
 6 about is when you're finding your B cells that are
 7 already activated before you vaccinated them in any
 8 way, they may do just the opposite of what you think;
 9 that is, they're in fact identifying people -- well, in
 10 this case, they're mice -- who are not going to respond
 11 to your vaccine.
 12 That's in essence what we found with the human
 13 studies. They already had these cells activated, and
 14 they were making very low affinity antibodies, and the
 15 high affinity antibody-producing B cells had presumably
 16 already been eliminated, which is a way that you get
 17 immune tolerance.
 18 So the first question I had was, do you have
 19 any idea whether those cells are making high-affinity
 20 IgG reads [indiscernible], let's say, rather than
 21 making a bunch of IgM or some of the other classes of
 22 that low affinity.

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1 The second question, we found the same thing
 2 with the genetic polymorphisms, and that was using
 3 toll-like receptor adjuvants. I think adjuvants are
 4 going to be critical. The alum just isn't good enough.
 5 We found that if people have the TLR4 polymorphism that
 6 led to dysfunctional TLR4 receptors -- they weren't
 7 totally gone but they were dysfunctional -- you in fact
 8 got an augmented response to the vaccine when you gave
 9 a TLR4 agonist as your adjuvant, which was the opposite
 10 of what we thought until we thought about it some more,
 11 and then realized what you were probably looking at was
 12 when you have a poorly functioning receptor in terms of
 13 its G-protein coupling, and then that whole sequence
 14 that follows, you get more of those receptors.
 15 If you finally stimulate them with an excess
 16 amount of your toll-like receptor antigen, then you do
 17 in fact produce much more things.
 18 Related to that, I think probably what you're
 19 going to find with the interleukins is it's the
 20 toll-like receptors that drive those interleukins and
 21 why you produce more or less of that. So you might
 22 want to think more about those toll-like receptors.

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1 They're clearly critical for vaccinology.
 2 Now they're looking at 2 -- I guess, let's
 3 see, 4, 5, 9, 13, 6 and 7. The big guys in vaccines
 4 are doing a bunch of that. But it's terrific to see
 5 what you're doing, and I think that it will be
 6 interesting if it turns out the opposite of what you
 7 might expect. But maybe you've got some data on that.
 8 DR. PRAVETONI: Yes, I pretty much agree on
 9 all your questions. They were very good points.
 10 Starting from the last, what we've seen, and other
 11 people have seen, is that there are, as you pointed
 12 out, different TLR agonists. So depending on
 13 experience and depending on which vaccine formulation.
 14 Some may work better than others. For example, for us,
 15 TLR9 works much better with oxycodone vaccine, while
 16 TLR4s, they don't work at all, to the extent that if we
 17 give the vaccine to a TLR4 [indiscernible] animal, you
 18 don't really see a good response.
 19 As far as the other questions, I agree with
 20 you that preexisting antibodies may interfere with
 21 vaccine efficacy. We didn't find preexisting
 22 antibodies; we found preexisting B cells, which may

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1 have a bunch of other crap mixed in with their heroin,
 2 or their fentanyl, or whatever they're using. So it
 3 will be quite exciting to see how this turns out with
 4 white blood cells from people.
 5 DR. STRAIN: Other questions?
 6 DR. WEISS: I may have missed this, but how
 7 long does the antibody last for? Similar to the
 8 Vivitrol question, if somebody had some sort of major
 9 accident where they needed opioids, if they were
 10 getting the multivalent vaccine that hit a lot of the
 11 commonly used opioids, is this something you can
 12 overshoot? How do you deal with that situation?
 13 DR. PRAVETONI: Well, I can answer on the
 14 preclinical, and then Sandy can answer on the clinical.
 15 As far as vaccine antibodies, vaccine antibodies
 16 [indiscernible], we find antibodies up to 6 months in
 17 animals, so we cannot project that. Also based upon
 18 what groups, including Dr. Kosten here, we foresee
 19 doing essentially most immunizations every year with a
 20 vaccine like that. So depending on variability,
 21 antibodies may last from 6 months to 1 year.
 22 As far as selectivity and interference with

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1 have a different implication.
 2 Also, one of the things to point out is each
 3 drug is slightly different, so perhaps if you have
 4 something like cocaine, that may be -- I don't know. I
 5 guess if it's bought on the street, that means illegal
 6 mixture and it's containing excipients. Those
 7 excipients may work just like a carrier. Therefore, if
 8 you have optimized cocaine, loosely optimized, not
 9 covering the bar, you may have [indiscernible] and so
 10 forth.
 11 In terms of something like oxycodone, it may
 12 not be the same, so until we actually test it, we can't
 13 really see. But even if there is a negative
 14 correlation between [indiscernible] specific B cells
 15 and response, but if you have no correlation, you can
 16 still stratify patients, either by move them out or
 17 hold them in, I guess.
 18 I don't know if I've answered all your
 19 questions.
 20 DR. KOSTEN: Yes. Other than the
 21 people -- just like cocaine, there's a bunch of other
 22 crap mixed in. Most of the drug abusers on the street

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1 other drugs, these particular antibodies, they are very
 2 selective, so we made sure that did not prevent action
 3 of, things like methadone, naltrexone, naloxone, and so
 4 forth. As far as protections, he pointed out Vivitrol,
 5 and Vivitrol is like 1 month. If antibodies can offer
 6 protection for 6 months, that has implication for
 7 overdose.
 8 Then to your point, Vivitrol, which as an
 9 opioid antagonist blocks pretty much everything,
 10 including endogenous opioids, these things, they're
 11 very selective. So even if you have a multivalent, you
 12 can still [indiscernible] some by their opioids, and
 13 maybe use in a clinical setting.
 14 Also, antibodies can be surmounted
 15 [indiscernible], not easily, but can be surmounted
 16 [indiscernible]. Unless you do an actual comparison
 17 where you have extended-release naltrexone versus a
 18 vaccine, and see how much drug you need to surmount, it
 19 would be kind of hard to tell. But I would say
 20 selectivity, that would be the benefit of the vaccine.
 21 DR. COMER: I completely agree with that.
 22 Roger, thanks for that question because that

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1 was asked of us a lot when we were doing the sustained
 2 release naltrexone. With this vaccine approach, in
 3 some ways, it's easier to address that concern for the
 4 reasons that Marco gave.

5 With naltrexone, it blocks all mu agonists, so
 6 you'd have to switch to a non-opioid or something that
 7 might have higher efficacy like buprenorphine, and you
 8 hope to override the blockade with naltrexone. With
 9 this, you could use methadone. You could use
 10 buprenorphine. If somebody needed pain, you could use
 11 anything that was off target. Then as a second step,
 12 as Marco said, the antibodies ultimately would be
 13 saturated, so there would be a dose of the agonist that
 14 would be able to provide pain relief.

15 Group Discussion and Q&A

16 DR. STRAIN: Thank you.

17 We're on the home stretch. The afternoon
 18 sometimes can get slow. For the last 25 or 30 minutes,
 19 I wanted to open this up for questions and discussions
 20 of any talks that have come up today, especially this
 21 afternoon's talks. We're going to go back through in a
 22 systematic way tomorrow, each of the topics that we've

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1 heard about this afternoon.

2 I wonder if people have questions. You've
 3 been not just digesting the snacks but also the content
 4 that you've been hearing and have something that comes
 5 out of that.

6 Roger?

7 DR. WEISS: I have a question about the
 8 psychedelic presentation. I find the data very
 9 compelling, but I worry a lot about what if this thing
 10 became commercially available. I think if somebody
 11 were going to be treated at Johns Hopkins by this
 12 group, that's very different, with two people holding
 13 your hand for 8 hours that have done this for hundreds
 14 of patients versus Joe Dokes [ph] saying, "Here, take
 15 this."

16 This seems like a don't try this at home sort
 17 of operation. In the hands of probably the world's
 18 experts in this, it seems like a very exciting sort of
 19 thing. How that would get rolled out is a big question
 20 for me.

21 DR. KOSTEN: I can say something --

22 DR. STRAIN: Did you want to make a comment,

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1 Bob, about that?

2 DR. DWORKIN: Well, I was thinking the same
 3 thing. I think perhaps the example of what Roger is
 4 talking about is the ketamine infusion center a mile
 5 away from my house, where people, is my understanding,
 6 go in and get ketamine, and they go out. There's no
 7 preparation, there's no set and setting, and there's no
 8 follow-up. That seems, to me, a concern. How do you
 9 build set and setting into something that's
 10 commercially available? Is that a REMS program?

11 DR. JOHNSON: You read my mind. I think this
 12 is one of the very perfect examples. This is exactly
 13 what REMS is for. We've already included -- in our
 14 recent abuse liability paper of psilocybin that I
 15 mentioned, we made some recommendations about its
 16 potential medical approval and development, and said a
 17 strong REMS would be very much called for,
 18 including -- this is not take two and call me in the
 19 morning. This is like outpatient surgery. This is
 20 like an endoscopy. So it's mandated, much like this
 21 Spravato, esketamine use; not like the wild west of
 22 off-label ketamine use.

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1 So yeah, the requirement for preparation, the
 2 requirement for screening essentially models what we
 3 and our colleagues in the field are doing now. I think
 4 REMS is going to be absolutely critical, and we're
 5 going to be strong advocates for a strong REMS.

6 DR. STRAIN: Roland, do you want to comment as
 7 well?

8 DR. GRIFFITHS: Yes. Just to reiterate, the
 9 set and setting conditions are going to be critical.
 10 FDA, the companies that are developing this, the
 11 academic researchers are all very sensitive to this
 12 issue. I'm imagining, should it ever reach approval,
 13 it would be done so under conditions in which perhaps
 14 there was a central pharmacy dispensing drug to a
 15 clinic with clinical providers that are well trained in
 16 this, but that all needs to get worked out through the
 17 regulatory structure.

18 DR. STRAIN: In the back?

19 MR. BARROW: Rob Barrow. I work for Usona
 20 Institute, one of the commercial IND sponsors of
 21 psilocybin for major depressive disorder. We've spent
 22 a lot of time thinking about this, and I know that our

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1 colleagues at FDA have spent a lot of time thinking
 2 about this.
 3 I think one of the challenges for the REMS is
 4 that there are bounds on REMS that are legislated by
 5 Congress. The delivery of medical care can veer
 6 outside of a REMS. So while we very much endorse the
 7 idea of a strong REMS, we also think that there is a
 8 intrinsic need for the delivery of the care side of
 9 things, for medical professionals to build an
 10 infrastructure around this that would enable them to be
 11 trained and support delivery.
 12 We are working on models of how this would be
 13 funded, ultimately; how is someone getting a session of
 14 psilocybin going to be able to afford or get
 15 reimbursement for an 8-hour session. If it's two
 16 people, hours of preparation, hours of integration.
 17 That's a complex issue, which we're spending a lot of
 18 time thinking about.
 19 I think it's going to require both guidance
 20 from FDA and input on a REMS as tight as we're allowed
 21 to make it, but also practitioners stepping up and
 22 state level organizations stepping up to really drive

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1 home the importance of this and actually delivering the
 2 care.
 3 DR. STRAIN: If I could comment on that, I
 4 think it's extremely dangerous to count on
 5 practitioners to step up and do it, frankly. I mean,
 6 all the people in this room will step up and be
 7 responsible. The problems are the Lance Goodmans of
 8 the world, who was an anesthesiologist in Delaware who
 9 had big billboards saying, "Come get subcutaneous
 10 naltrexone for cash on the barrelhead." It's only
 11 going to take a handful of people like that.
 12 I think, though, one possibility would be to
 13 say, okay, this can only occur in particular settings
 14 that have, say, the Joint Commission or CARF
 15 accreditation to do this. I think that's the way to
 16 get it forward so that you don't have the IV ketamine
 17 guy down the road from Bob, because, otherwise, there's
 18 going to be somebody who's going to say, "Oh yeah.
 19 I've got it. I asked the person, hey --"
 20 FEMALE VOICE: Are you ready?
 21 DR. STRAIN: "-- are you ready?"
 22 (Laughter.)

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1 DR. STRAIN: There's a document to read about
 2 this. We'll send you a document. We've got a couch,
 3 just like Roland.
 4 (Laughter.)
 5 DR. STRAIN: Frances?
 6 DR. LEVIN: I would think it's like in the
 7 setting the way methadone is, that you have
 8 regulations. You get certification. You'd be audited.
 9 If you had that kind of level, at least initially, I
 10 think --
 11 DR. STRAIN: Well, that's the Joint
 12 Commission --
 13 DR. LEVIN: Right.
 14 DR. STRAIN: -- or CARF. Tom?
 15 DR. KOSTEN: If you don't mind changing the
 16 topic a little bit about the -- the problem we have in
 17 opiates right now is getting people on naltrexone, and
 18 we've now had several studies to demonstrate once you
 19 do that, they in fact look like they do -- maybe even
 20 better than buprenorphine.
 21 I don't know how. I guess they got my number
 22 from Herb Kleber. But I can't tell you the number of

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1 people that call me about ibogaine and that I should be
 2 giving ibogaine to opioid addicts. And if I did that,
 3 they would go through detox with -- they would just
 4 hallucinate it away, and it would all disappear.
 5 Has anybody tried any of this to really
 6 markedly attenuate opiate withdrawal syndrome? Is that
 7 possible? Is that something -- I'm sorry. I don't
 8 mean to look at you and put you on the spot.
 9 DR. GRIFFITHS: Are you asking about ibogaine?
 10 DR. KOSTEN: No, no. I'm asking about real
 11 drugs, and ibogaine, as far as I know, rots your brain;
 12 maybe more ibogaine doesn't. But it's the concept
 13 that's here, which is you have something that might
 14 work for what is a real problem for us right now.
 15 We've got a wonderful blocker, but getting onto it has
 16 not been so easy.
 17 DR. GRIFFITHS: That's certainly been one of
 18 the clinical targets that we've considered in talking
 19 about opiates. As Matt outlined, there are many
 20 different ways to go, but that's a very attractive one,
 21 and it also --
 22 DR. STRAIN: I'm sorry. I didn't hear Tom's

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1 question. What clinical target?
 2 DR. KOSTEN: Opiate withdrawal.
 3 DR. STRAIN: Withdrawal.
 4 DR. GRIFFITHS: And going on to naltrexone
 5 would have the advantage of protecting people from
 6 overdose, which is very attractive. There are a whole
 7 bunch of different ways to go; very interesting ones.
 8 DR. KOSTEN: I think of that one as something
 9 that you can get your answer in a 10-day trial. It's a
 10 fast one. If it works, it works, but it's like
 11 clonidine or lofexidine.
 12 DR. GRIFFITHS: And the answer is whether or
 13 not they go on naltrexone?
 14 DR. KOSTEN: Yeah. That's the outcome. You
 15 don't need to show that naltrexone works. There's
 16 plenty of data that works.
 17 DR. STRAIN: Kurt, did you have a question?
 18 DR. RASMUSSEN: I love out-of-the-box
 19 thinking, but it sounds like to me opioid withdrawal on
 20 a hallucinogen is a recipe for a bad trip.
 21 (Laughter.)
 22 DR. KOSTEN: What you figure out, you'll miss.

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1 DR. STRAIN: I would propose that we actually
 2 can get people off opioids. The problem is not getting
 3 people off opioids; it's getting people to stay off
 4 opioids. Because if we had a way to get people off
 5 opioids and they would stay off it for 10 years, we
 6 would basically put everybody in the hospital for a
 7 week, get them off, if we can do that. Then if they
 8 could stay off for 10 years, we'd be great. The
 9 problem is that people relapse.
 10 So I would propose -- and I think the three of
 11 us have discussed this, and we've talked about
 12 everything else, I think -- the model should be what
 13 happens if you can take somebody and get them off
 14 opioid, and give them a psilocybin session; can you
 15 decrease the risk of relapse? That would be a game
 16 changer.
 17 DR. JOHNSON: That's, in fact, the direction
 18 that we're interested in. In fact, this whole idea
 19 that ibogaine does something special -- first of all,
 20 there's virtually no human research on that. There's
 21 very compelling non-human research with the
 22 normalization of the [indiscernible] response that's

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1 probably mediating the reductions and drug
 2 self-administration.
 3 We don't know that this isn't going on with
 4 psilocybin and the other classic psychedelics; number
 5 one. Then number two -- this is my general ibogaine
 6 kind of answer; number two is exactly like Eric said.
 7 The action is all in the long-term response. If it
 8 takes putting people asleep for a few weeks or sending
 9 them to Club Med, it's easy. There are ways to get
 10 people off. But then also, you name the drug, and
 11 there are so many people that relapse long after the
 12 withdrawal has passed.
 13 It strikes me that if we're on to something,
 14 the real power in these is really a fundamental change
 15 in the positive reinforcing potential of the drug of
 16 abuse, and the craving, if you will, the long-term, and
 17 the rewriting of the narrative surrounding that drug
 18 that can have an effect long term, after the
 19 withdrawal. But it's all an empirical question.
 20 DR. STRAIN: Let me just --
 21 DR. KOSTEN: No. You can't talk. You're only
 22 the moderator.

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1 DR. STRAIN: I'm the moderator, but I'm going
 2 to jump in.
 3 Let me just make a quick economic point.
 4 Methadone treatment is probably something on the order
 5 of \$45,000 a year. I remember having a conversation
 6 with Johns Hopkins' healthcare insurance provider years
 7 ago and saying, "Oh, it will run about \$40,000 a year,"
 8 and they said, "Oh, that's not bad. And then at the
 9 end of the year they're cured?" And I said, "No. Then
 10 it's another \$45,000 the next year."
 11 (Laughter.)
 12 DR. STRAIN: And they go, "Well, how many
 13 years does that have to go on?" And I said, "Well, in
 14 some cases, it's 20-30 years." And they said, "Oh,
 15 that's not a sustainable economic model for us."
 16 If you could say we've got a high probability
 17 of 5 years but they don't have to be in methadone
 18 treatment, you will have the methadone treatment
 19 community eating you alive because it's such a threat
 20 to them, because you can do it for much less than
 21 20[000] or \$25,000.
 22 Tom, what were you going to --

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1 DR. KOSTEN: Just to follow up, how long after
2 they're opioid free would this treatment be thought
3 as -- after 5 days of acute detox? Do you have to be a
4 month until you're really off it? Do you have any
5 parameters with that? I guess I didn't quite
6 understand that from the presentations.
7 DR. STRAIN: They haven't done the study yet;
8 they don't know. They're still designing the study.
9 DR. KOSTEN: Oh, so you're still figuring that
10 one out. No wonder I couldn't figure it out.
11 (Laughter.)
12 DR. KOSTEN: You don't know.
13 DR. STRAIN: Sandy?
14 DR. COMER: I wonder if, Matt and Roland, you
15 can talk a little bit more about the potential abuse
16 liability of psilocybin. I come from a generation
17 where people were using mushrooms every weekend to get
18 high, so I'm surprised that you're seeing so little of
19 it. Did you have to be really selective in the
20 participant population that you included in your
21 trials, or what?
22 DR. GRIFFITHS: No. Let's see. In terms of

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1 abuse liability, again to reiterate what both Matt and
2 I said, NIDA doesn't consider these to be drugs of
3 addiction. They don't produce at least compulsive,
4 repeated self-administration.
5 Do people use them intermittently of the type
6 you say? I'm sure there are subgroups that do. Were
7 we selective in picking people? No, most of the people
8 who came into our studies -- except for a couple of
9 studies that used psychedelic experienced people who
10 were interested in psychedelics. But most people did
11 not have histories of use, or if they did, it was just
12 intermittently.
13 Under those conditions, when you expose
14 someone to a high dose of psychedelic, this is really a
15 challenging experience. For most of those people,
16 they're not about to seek it out again. If they were
17 going to do it again, they would want to do it under
18 highly supportive conditions.
19 I think the kind of situation you're talking
20 about, people using mushrooms on weekends, you're
21 talking about relatively low doses, and then in a
22 social context, that's going to be supportive of that,

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1 but this model looks very different from that.
2 I don't imagine, that the doses that we
3 administer, that you'd have many people running back to
4 seek it out again. If they're interested in
5 re-exposure to psilocybin, they can look up on the
6 internet how to grow mushrooms and do it themselves.
7 Psilocybin mushrooms are almost freely available,
8 although they're illegal.
9 Matt, do you have anything further?
10 DR. JOHNSON: If this is approved as a
11 treatment and the numbers increase, you're going to
12 get -- if you expose 2 million people to this, you're
13 going to get people that never used before, and then
14 they do use every once in awhile. We haven't seen it
15 so far. I think that's got to be part of the
16 landscape.
17 The typical response is, so many times -- and
18 some people are just so compelling when they say
19 it -- "Holy cow! People do this for fun? You've got
20 to be kidding me." They just can't imagine it and part
21 of that I think is the really substantial dose.
22 We so often get the feedback -- and I'm sure

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1 Michael, and Peter, and Randy can speak to this, too,
2 from their experience -- that folks will say, "I can't
3 imagine having done this without the preparation. I
4 would have been completely lost, and it would have been
5 dangerous."
6 Part of that is our whole framing, to really
7 encourage that, the importance of this framework. I
8 think it's largely been successful. But in the grand
9 scheme of things, I think it's likely there's going to
10 be some of that.
11 Fortunately, we know it's a drug that even if
12 they do get into extra medical use, it's not going to
13 be a daily use habit, and probably not going to be a
14 whole lot of disordered use, and hopefully it's kept to
15 a minimum. But in the risk-benefit ratio, if you're
16 looking at getting them off, if it's effective -- a big
17 if for opioid-use disorder -- yeah, it still might be a
18 positive intervention.
19 DR. COMER: Do you think it would be like an
20 unintended consequence of what you're doing? You're
21 publishing your data on these really high doses of
22 psilocybin. Somebody who has used mushrooms before,

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1 they may say, "Oh wow. Maybe if I take 10 mushrooms,
2 I'll be able to stop smoking, I'll be able to feel less
3 depressed," and do it on their own. I don't know. I'm
4 a worry wart.
5 DR. GRIFFITHS: No, we worry about it, too.
6 And the cultural narrative around this now seems to be
7 so skewed positively, and it's an issue and concern.
8 We have these state level decriminalization and
9 legalization initiatives for psilocybin and other
10 compounds. I don't know how to manage that, frankly.
11 I don't think diversion of chemically synthesized
12 psilocybin is going to be an issue at all. But they're
13 very powerful change agents, and unless we want to keep
14 it a secret from the culture and the world, that
15 information is going to be out there.
16 DR. STRAIN: We've got others. We've got
17 Peter, then Tanya, and then Roger. Peter?
18 DR. HENDRICKS: I'll just add to that a little
19 bit. We're about half-way done with a pilot trial of
20 psilocybin facilitated treatment for cocaine
21 dependence. We do ask our participants if they'd be
22 willing to participate in a medication session like

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1 this again, and almost universally the response is I'd
2 rather not, or no, "but I might consider it if at some
3 point in the future I felt like maybe I really needed
4 it, and of course only under very similar conditions."
5 Many people have reported that it feels like a
6 lot of work. It's not especially pleasant, which is
7 interesting because these mystical experiences can be
8 very positive and experienced as a very positive event,
9 but at the same time not the kind of experience that
10 people wish to repeat. We had one participant liken it
11 to running a marathon. They might say it was
12 meaningful to me, and I'm glad I did it, but it's just
13 not something I'd want to do on a regular basis.
14 DR. STRAIN: Interesting. Tanya?
15 DR. RAMEY: I have some small concerns. It
16 seems to me that the discussion that we are having is
17 around superficial things, such as, for example, like,
18 oh, there are good changes; people have changed. We
19 don't know how they have changed, how their lives have
20 changed; not based on self-report, but, really, based
21 on real data, functionally, what changed in their
22 lives.

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1 Then again, I don't hear the discretion about
2 cognitive changes, which are common to, actually, not
3 only opioid users, but to other addicts. It's far
4 above and beyond just executive functioning, and it
5 affects the high levels of cognition. Apparently,
6 that's what is changing, but you need to name that.
7 What are those mystical experiences?
8 It's kind of a overarching feature of an
9 addict, is they change in the higher level of -- they
10 start to become conscientious. The first thing, when
11 you deal with an addict, he or she changes -- changes
12 goes to zero, practically. Maybe there is something on
13 that level, and maybe it's not a mystical experience,
14 that we call mystical experience, but what is it?
15 A window opens up into the self-perception.
16 Everybody who's dealing with addicts, they know that
17 their self-understanding, based on even psychometric
18 scales, is impaired, so that's what you're repairing,
19 practically. And whether it's mystical experience, or
20 how, it translates to a higher level of consciousness.
21 Conscientiousness is a very important trait, and if
22 you're having all those long-term positive

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1 consequences, maybe that's where you need to focus.
2 DR. GRIFFITHS: There are just so many
3 questions to be asked about the nature of these
4 experiences. We're just scratching the surface. In
5 Matt's presentation, he went through a number of the
6 mechanistic possibilities.
7 You're absolutely right. Under the conditions
8 in which we administer it, the appearance is that it
9 skews very positively, and certainly people are
10 reporting these positive changes in moods, attitudes,
11 and behavior. Nonetheless, I think we should be
12 extraordinarily sensitive to downside risks and adverse
13 effects, and this all needs to get worked out in
14 research over time.
15 DR. STRAIN: Roger, then Kit. I'm going to
16 interject myself.
17 Let me just, Tanya, say when we've had these
18 internal discussions about the opioid study, for
19 example, I said, well, what we want to see is we want
20 to see people stop using illicit opioids. That's what
21 we really want.
22 If we've got an opioid user who says, "Well,

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1 I'm still using, but I've had one of the top five most
 2 powerful experiences I've had in my life," that's good,
 3 but at the end of the day, I want him to stop using.
 4 In that vein, what I'd come back to is the
 5 pilot study of smoking cessation because if you can get
 6 smokers who have failed 2 quit attempts -- wasn't that
 7 the pilot study, failed 2 quit attempts?
 8 DR. JOHNSON: They all to have tried, yeah,
 9 multiple times; right.
 10 DR. STRAIN: Multiple times, at least two.
 11 And you've got 50-60 percent cessation at 6 months,
 12 that's a game changer. Chantix, which is our best, did
 13 something like 20 percent, so my head explodes when I
 14 think about that because that's a behavior change, not
 15 to denigrate having a truly wonderful experience.
 16 Roger, then Kit.
 17 DR. WEISS: I want to change the subject to
 18 cannabis.
 19 DR. STRAIN: Yes!
 20 (Laughter.)
 21 DR. WEISS: Trying to study medical cannabis
 22 is so difficult because there are hundreds of thousands

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1 of pre-/post-studies going on every day with people
 2 using all kinds of things on their own to treat
 3 whatever it is they're trying to treat; whether it's
 4 CBD that they buy at the gas station, or whether it's
 5 cannabis.
 6 I think of medical cannabis sometimes like if
 7 someone said we have medical food; well, what kind of
 8 food? Because it could be anything. The problem is
 9 the tortoise and the hare, that these natural
 10 experiments are going on a mile a minute and research
 11 moves at this glacial pace.
 12 There's this study recently, a European study,
 13 that talked about adolescent cannabis use and its
 14 negative effects during adulthood. It said people with
 15 high THC content did the worst, defined as greater than
 16 10 percent, when average now is 16 percent.
 17 So by the time something is done and is
 18 published, it's so far behind the time, that it becomes
 19 irrelevant. I just don't know how we deal with that.
 20 If there was some opportunity for some big data
 21 solution, that would be great, but we can't get access
 22 to any of the data.

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1 DR. STRAIN: Let's see. Ryan, did you want to
 2 respond to that? Did you have any thoughts?
 3 DR. VANDREY: I don't really have a response
 4 to that; I agree. It's a big issue because cannabis is
 5 not cannabis, is not cannabis. We're using one
 6 umbrella term for something that describes a massive
 7 array of products that have different effects,
 8 different pharmacologies, and different time courses.
 9 There's so much variability.
 10 The term "cannabis" doesn't mean anything
 11 anymore. It's not useful from a scientific
 12 perspective, so we have to drill down and talk about
 13 it, about a THC product, a CBD product, a CBG product,
 14 and we have to talk about it with respect to
 15 formulation and route of administration.
 16 DR. STRAIN: Kit?
 17 DR. BONSON: These cognitive questions are
 18 really fascinating, especially when we're dealing with
 19 the psychedelics. But those are really intellectual
 20 questions; they're academic questions. And hopefully,
 21 if there is continued interest in psychedelics, it's
 22 something that NIDA would want to -- but let me finish.

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1 This is not a regulatory question. For
 2 regulatory purposes, we don't need to know what the
 3 mechanism of action is. This was like a shock to me
 4 when I first started working at FDA because you didn't
 5 need to -- like it was good; we kind of wanted to know,
 6 but maybe we didn't know.
 7 All we need to know is that it's safe and that
 8 it's effective. And if we can show those two
 9 things -- all of these other things are fascinating,
 10 and they lead to other directions for new research, but
 11 for the particular product that we're talking about,
 12 it's not a regulatory question. I just wanted to make
 13 that distinction.
 14 DR. RAMEY: For example, there would be an
 15 endpoint that is related to change in social cognition,
 16 not an executive function because cognition is not like
 17 a car. Executive function, there's something beyond
 18 executive function, which is really important in
 19 addiction.
 20 For example, there are measures on
 21 psychometric scales, which has a social cognition, that
 22 could be very important for psilocybin because it seems

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1 to me that there's something there that changes, like
 2 what he's described as a positive change in life, and
 3 that's what it is.
 4 DR. BONSON: Right, but in the end, we're
 5 going to be asking does it tell somebody get off this
 6 drug. That's the bottom line.
 7 DR. STRAIN: Let me let Dr. Dworkin have the
 8 last word.
 9 DR. DWORKIN: It's not interesting enough to
 10 be the last word. It's a question for --
 11 DR. STRAIN: Then step up your game, Bob.
 12 (Laughter.)
 13 DR. DWORKIN: It's a question for Ryan.
 14 In Canada, of course, Sativex is approved for
 15 neuropathic pain associated with multiple sclerosis. I
 16 was just wondering, given that we know exactly what
 17 Sativex is, is there any anecdotal experience, among
 18 Canadian psychiatrists, I suppose, and
 19 addictionologist, with using Sativex for OUD? Because
 20 we know what it is.
 21 DR. VANDREY: I'm not aware of anybody using
 22 Sativex to treat opioid-use disorder. Part of the

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1 issue, too -- and you're not seeing any off-label
 2 prescribing of Epidiolex here in the U.S. because it's
 3 prohibitively expensive, and insurance isn't covering
 4 it for anything, except for Dravet or Lennox-Gastaut.
 5 So we have a problem there of how do you get
 6 it out there making a fit? But that approach where you
 7 have a defined product, it's manufactured GMP, you know
 8 the dose, and it's going to be the same every time is
 9 really what we want, and I think we're going to start
 10 to see more of that emerge.
 11 But again, it's picking. Well, do you pick
 12 Epidiolex, do you pick Sativex, or do you pick some
 13 other thing? Do you pick Charlotte's web? What do you
 14 pick, and how do you do it, and what makes the most
 15 sense?
 16 I think we need to, again, come back and look
 17 both at preclinical data and look at these
 18 observational studies, and not epidemiological
 19 observational studies but longitudinal observational
 20 studies, where you look at changes within the same
 21 individual.
 22 We're a part of a research program that's

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1 doing that. Stacey Gruber is doing it. Mark Ware is
 2 doing it. There's a group in Arkansas doing these
 3 similar kinds of longitudinal natural history type
 4 studies, where we can gather data on, well what happens
 5 to people using cannabinoids for any different reason?
 6 Then we can pick people with pain or
 7 opioid-use disorder; what are they using, how are they
 8 using it, and how often, and try to glean some
 9 information from them to then try to say, "Well, let's
 10 pull this into the lab and then go to the clinic from
 11 there." But we need some sense of where in the array
 12 of products to start, I guess. Then it becomes dose
 13 finding, and then efficacy.
 14 DR. STRAIN: Thanks. That was alright.
 15 (Laughter.)
 16 Adjournment
 17 DR. STRAIN: We've gone over a little bit, but
 18 there's a sense of some of the discussion we may be
 19 starting to get into tomorrow.
 20 Thank you to our speakers throughout the day
 21 today. Thanks to all of you for your participation.
 22 Dinner will be from 7:00 to 9:00 on the first floor.

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1 If you were here last night for dinner, I think it's in
 2 that same space back there. Otherwise, we'll see you
 3 at breakfast tomorrow morning, as well. Thanks,
 4 everybody, and have a good evening.
 5 (Whereupon, at 4:37 p.m., the meeting was
 6 adjourned.)
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