

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

November 22, 2019

*A Matter of Record
(301) 890-4188*

Page 1

1 ACTTION

2

3

4

5 BEYOND THE MU OPIOID SYSTEM FOR

6 TREATING OUD (B-MOST-O)

7

8

9

10

11

12 Friday, November 22, 2019

13 8:37 a.m. to 1:01 p.m.

14

15

16 W Hotel

17 Washington, DC

18

19

20

21

22

Page 2

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Recap Day 1: Review of Goals for Day 2	
4	Eric Strain, MD	3
5	Needs in the field of assessing the	
6	following specific domains when studying	
7	non-mu agents for the treatment of	
8	OUD: designs, outcomes, risks, benefits	
9	Group Discussion	
10	Cannabinoid-Related Compounds	6
11	Sleep Agents	53
12	Psychedelics	88
13	Vaccines	127
14	General discussion, including agents not	163
15	specifically considered, consensus and	
16	next steps	
17	Adjournment	196
18		
19		
20		
21		
22		

Page 3

1 P R O C E E D I N G S

2 (8:37 a.m.)

3 Recap of Day 1 – Eric Strain

4 DR. STRAIN: Welcome to day 2, or day 1.5,

5 of the meeting. I really have very little to say

6 in terms of introductory comments. Dennis and

7 Bob -- I checked in -- and they're both giving

8 thumbs up to day 1, but didn't have anything of

9 substance that they wanted to convey for today.

10 I just want to take a moment to make sure

11 that we're on the same page in terms of what we're

12 trying to accomplish today. We're going to go

13 through each category of the 4 categories that we

14 heard presentations on yesterday and talk about the

15 potential design issues of trials in that

16 particular category; the outcome measures that

17 might either exist or need to be created to study a

18 compound in that category; the risks and what kind

19 of risk assessments we might need to be

20 considering, especially if they're different from

21 what we've used in the past; and likewise, the

22 benefit assessments that we might want to be

Page 4

1 looking at for those.

2 I want to be sure to say thank you to all of

3 our presenters yesterday for really helping to set

4 the stage for today's discussion. I took copious

5 notes, and, really, a lot of thoughtful points were

6 raised.

7 I want to return at lunch time to at least

8 spend a little time thinking about a step back from

9 this and what we might want to see happen as next

10 steps. So in the back of your head, be thinking

11 about are there studies that need to be done, or

12 papers that need to be written, or meta-analyses,

13 or data mining that needs to occur going forward.

14 Any questions about any of that; any

15 thoughts, points?

16 DR. KOSTEN: To follow up on yesterday, when

17 will the slides and things like that actually

18 be -- transcript, I understand that takes a while,

19 but are the slides going to be available like

20 tomorrow?

21 DR. STRAIN: Not tomorrow, no. Dr. Dworkin

22 is --

Page 5

1 DR. TURK: Two things. One is that those
 2 people who presented, you need to make sure there's
 3 nothing in your slides you don't want to be in
 4 there. So you have the first right to remove any
 5 of those things. Then it could be a month until it
 6 actually gets up on the website. However, if you
 7 wanted to talk to one of your colleagues about
 8 getting access to their slides, and they're
 9 willing, they could provide them to you. But it
 10 takes us at least a month to get them mounted on
 11 the ACTION website.

12 DR. STRAIN: Yes, that was my sense of it.
 13 And I think the transcript takes even longer, to be
 14 honest.

15 DR. KOSTEN: Then if we wanted to use any of
 16 these slides to educate the rest of the world,
 17 what's the procedure for that?

18 DR. STRAIN: I would contact the presenter;
 19 go to the presenter and make sure that they're
 20 comfortable with that.

21 DR. KOSTEN: I was going to steal all of
 22 Kyle's slides, for example. I'd never want to do

Page 6

1 that myself.

2 DR. STRAIN: Kyle is flattered.
 3 (Laughter.)

4 DR. STRAIN: Any other general questions?
 5 (No response.)

6 Group Discussion - Cannabinoids

7 DR. STRAIN: If not, we're going to start
 8 with cannabinoids, cannabinoids and related
 9 compounds. This is a chance for us to think about
 10 what kinds of design trials, outcomes, benefits,
 11 and risks that we need to be thinking about. As
 12 I've thought about cannabinoids for the treatment
 13 of opioid-use disorder, there are two things that
 14 come to mind, just to frame it; and I'll come back
 15 to each category to give this thought.

16 It seems to me they're somewhat unique
 17 because cannabinoid compounds could be layered into
 18 existing medication treatments like methadone or
 19 buprenorphine if there was some efficacy, depending
 20 upon what the outcome is; or they could be proposed
 21 as having unique characteristics that could be
 22 stand-alone medications for opioid-use disorder.

Page 7

1 I think as you're making comments, you may
 2 want to think about am I saying, the design of the
 3 study, this is a study that we'd need to be
 4 thinking about adding into a medication-assisted
 5 treatment.

6 Ryan, did you have any preliminary thoughts
 7 that you would want to convey, given you've thought
 8 a lot about this?

9 DR. VANDREY: I don't think so. I think I
 10 said everything I needed to say yesterday.
 11 (Laughter.)

12 DR. STRAIN: Well, for the group as well,
 13 what do you think would be a good design for a
 14 trial of a cannabinoids to see if it could help
 15 opioid-use disorder in patients with or without
 16 maintenance on, say, methadone or buprenorphine?

17 DR. VANDREY: To add to that, I think one of
 18 my big questions coming into this -- because,
 19 again, coming into this meeting, I always thought
 20 the cannabinoids for treating opioid-use disorder
 21 was a bad idea.

22 DR. STRAIN: Okay.

Page 8

1 DR. VANDREY: So I guess the question to the
 2 opioid-use disorder experts in the room is how do
 3 you think cannabinoids could help? What would be
 4 the most interesting research questions, and where
 5 do you think there's clinical promise? Then that
 6 might help inform discussion about design issues
 7 and measurements.

8 DR. LEVIN: I don't remember if you
 9 mentioned it yesterday. I don't think you did;
 10 maybe you did that. At Columbia, we did a study in
 11 which we gave dronabinol as an idea to help with
 12 withdrawal. I mean, it's not -- all the other
 13 products of marijuana. It was found to help with
 14 withdrawal.

15 But the problem with the study was that
 16 after they left, the induction and the retention in
 17 treatment was no different. But part of it was a
 18 lot of these patients are using marijuana, and what
 19 they found as a secondary outcome was the patients
 20 that were on marijuana actually stayed more; that
 21 there's some signal of some sort -- if you use too
 22 much or too little, it wasn't helpful, but if you

Page 9

1 used a certain amount, it actually kept people in
 2 treatment more, which was an interesting finding.
 3 But the dronabinol didn't help because the
 4 dronabinol they were still using -- it wasn't
 5 exclusionary for them to be able to use marijuana
 6 once they left the inpatient program.
 7 People have noticed this clinically, that
 8 some marijuana isn't the worst, even though
 9 somebody who does cannabis -- it's sort of an
 10 interesting signal that may be there.
 11 DR. WINCHELL: I guess my question is why
 12 are we asking the question that way; how do we
 13 design trials with cannabis for whatever? Are we
 14 saying that cannabis is somehow different than any
 15 drug X, which could be administered once a day, or
 16 throughout the day, or at different doses? How is
 17 cannabis or is cannabis really different than any
 18 other drug X that we might look at?
 19 We see this stuff all the time, and people
 20 propose all kinds of interesting designs, and it's
 21 not about any particular class of drugs
 22 necessarily. So is there something unique about

Page 10

1 cannabis compared to anything else, is really my
 2 question.
 3 DR. STRAIN: Sandy?
 4 DR. COMER: My question is similar,
 5 actually. I was just curious to hear Ryan say that
 6 you were opposed to the idea initially, and I was
 7 just wondering why. As Frances said, we've had
 8 some pretty interesting findings with cannabis. I
 9 can understand smoked marijuana being a problem for
 10 all kinds of reasons, but --
 11 DR. VANDREY: It's not that I'm opposed to
 12 the issue. It's just I think more that I've never
 13 thought of -- I guess from the lens of all of the
 14 dozens of health problems that people think
 15 cannabis is good for, I would put opioid-use
 16 disorder toward the bottom in terms of list of
 17 priorities just because there are effective
 18 treatments. You've got methadone and you've got
 19 buprenorphine. It just seems to me that cannabis
 20 would be kind of a low signal there.
 21 Now, that being said, if you do see
 22 withdrawal attenuation and you have a case where

Page 11

1 somebody does not want to go on methadone or
 2 buprenorphine, could it be helpful? Sure, maybe.
 3 But again, I think, in my mind, I'd want to see
 4 comparative efficacy data. How well does
 5 dronabinol or smoked cannabis attenuate withdrawal
 6 compared to lofexidine, compared to some other non
 7 opioid medication?
 8 So I think that might be where we start, and
 9 then if you see something there, then you can start
 10 getting excited and start thinking about, okay,
 11 well, what's the right dosing and what's the right
 12 regimen, and then we could consider that.
 13 DR. COMER: I think two areas that are of
 14 potential interest are for the withdrawal; really,
 15 not so much detox but for transition to Vivitrol,
 16 for example. Lofexidine is a great medication for
 17 treating withdrawal, but it has issues with blood
 18 pressure and all that kind of stuff.
 19 Dronabinol also has issues that are
 20 different, but its abuse liability is pretty low,
 21 and it has certain advantages. So I think in that
 22 clinical scenario, it would be useful. As Frances

Page 12

1 said, even though we do have buprenorphine, and
 2 methadone, and naltrexone, the relapse rates are
 3 pretty high long term. So if we can prevent
 4 relapse, then that's a really great place to use
 5 it.
 6 MALE VOICE: I think making the distinction
 7 between cannabis versus cannabinoid product, we're
 8 sort of interchanging them, but Ryan mentioned
 9 one -- I think there are cannabinoids that we could
 10 look at it without it having to be smoke marijuana.
 11 DR. JOHNSON: Getting back to Eric's
 12 question, I wanted to get it in there. I think the
 13 most interesting target would be -- and there are a
 14 number of interesting targets -- looking at pain
 15 patients and looking at opioid sparing effect, like
 16 dose-related affects: everything bad that comes
 17 with opioids, the less potential for addiction,
 18 moving into illicit use, fatal overdose. These are
 19 all dose-related effects. Everything we know about
 20 the cannabinoid system suggests that there's
 21 something there, like there's good rationale for
 22 this.

Page 13

1 Experimental work in patient populations, in
 2 pain populations, on top of opioid use, do people
 3 use less opioids, that's something I'd like to see
 4 more work on.
 5 DR. BOGENSCHUTZ: We've talked about it
 6 several times, but the cannabis is not a thing and
 7 there are a lot of things inside of it. It's going
 8 to depend strongly on which cannabinoids we're
 9 talking about. For example, CBD, we don't know
 10 exactly what it does, but in animal models, it's
 11 not just like something you would take as a quasi
 12 replacement or dampening it. It's something that
 13 may have persisting effects on reward systems and
 14 drug-seeking behavior.
 15 So it might not be something that you would
 16 be taking as a maintenance or as a substitution to
 17 blunt withdrawal symptoms. It might be something
 18 that you would take in the context of an inpatient
 19 treatment for some period of time or persistently,
 20 but we just don't know. But it's not
 21 necessarily -- it could be very different models
 22 because of its mechanisms, which might be quite

Page 14

1 different.
 2 DR. STRAIN: Kit?
 3 DR. BONSON: Remember, though, FDA does
 4 welcome botanical applications. So if you wanted
 5 to study cannabis as cannabis, that is a
 6 possibility. You don't need to necessarily have an
 7 isolated cannabinoid, But there needs to be a
 8 specific cultivar, and it needs to be all grown
 9 similarly. There are standards that one has, but
 10 it isn't that you can't do cannabis as botanical
 11 potentially, or any other botanical.
 12 DR. STRAIN: So it's kind of interesting.
 13 As I'm hearing the comments, a couple of minutes
 14 ago, I was thinking, well, maybe the first question
 15 is should there actually be research done on this
 16 topic, the use of either marijuana or a cannabinoid
 17 of some sort for the treatment of opioid use
 18 disorder, be it withdrawal; be it pain sparing; be
 19 it maintenance in lieu of methadone; be it an
 20 add-on to methadone to help anxiety, or depression,
 21 or sleep, or some ancillary symptom.
 22 I think that might go back to maybe the real

Page 15

1 question is, is the first step to ask patients what
 2 they think about using cannabis in some way, or a
 3 cannabinoids --
 4 DR. McCRAE-CLARK: Well, we know.
 5 (Laughter.)
 6 DR. STRAIN: What's that?
 7 DR. McCRAE-CLARK: I think we know that, and
 8 given the fact that there is such interest, it's
 9 sort of --
 10 DR. STRAIN: For opioid-use disorder, you
 11 think that --
 12 DR. McCRAE-CLARK: I think there is.
 13 DR. STRAIN: But for what purpose? I guess
 14 that's --
 15 DR. McCRAE-CLARK: I think if you look at
 16 the press, it's all over the place. I think people
 17 are saying --
 18 DR. STRAIN: Aimee is speaking, by the way.
 19 DR. McCRAE-CLARK: -- the need for opioids
 20 reduces the risk of overdose. There's so much out
 21 in the press about it, that I think that given that
 22 public perception, there does need to probably be

Page 16

1 some good, well-designed trials so that we can
 2 actually get some answers.
 3 DR. STRAIN: Dennis?
 4 DR. TURK: As an outsider to this topic, I
 5 just want to sit back. And what I've been hearing
 6 is there are different types of agents, chemical
 7 components of different cannabinoids, so that
 8 potentially has to be split apart. There are
 9 different populations that you're thinking of;
 10 problems that you're thinking of using them for.
 11 For example, we've mentioned for a chronic
 12 pain patient, that might be quite different what
 13 you're looking for than to reduce withdrawal in an
 14 opioid-use disorder patient. I almost could see a
 15 table in which you say all the potential uses and
 16 all the relevant outcomes, because the outcomes are
 17 going to be different. For the chronic pain
 18 patient, the opioid sparing criteria might be
 19 important. For the opioid-use disorder patient, it
 20 might be relapse. There's a lot of variation.
 21 So I think the issues are, one, what's the
 22 population; what's the issue or the question that

Page 17

1 you're trying to think about using this for; what's
 2 the appropriate agent you're thinking of evaluating
 3 for that purpose; and what's the appropriate
 4 outcome for that? It seems to me those are going
 5 to be how you're going to do it. There's not going
 6 to be one simple -- there's one design for any
 7 cannabinoids study. It's going to vary depending
 8 upon the purpose of what you're trying to use this
 9 for.

10 I think that's what you're going to have to
 11 think through, is what's unique about the outcomes
 12 for these different populations, and then what
 13 would be the outcomes that you'd want to consider
 14 in using them? Is it an acute use? Is it a
 15 chronic use to reduce symptoms of withdrawal? So
 16 it's very short term. Is it to try to be used in
 17 combination with one of the other drugs that are
 18 used for opioid-use disorder?

19 So you've got a range of questions, and I
 20 think you've got to be careful because I think if
 21 the discussion starts flipping around from these,
 22 we're going to be constantly getting confused with

Page 18

1 what we're talking about. So I think you're going
 2 to have to narrow -- so pick the one that you want
 3 to talk about.

4 Let's assume it's to reduce withdrawal. In
 5 that kind of study, what would you want to do?
 6 What would be the outcomes that you would want to
 7 consider? Is there a particular cannabinoid
 8 agent -- whatever, a mechanisms, a
 9 component -- that you specifically think would be
 10 relevant for that?

11 Then you go on to the next, and you'd have a
 12 whole sequence of these things. Maybe some, we are
 13 fine with the measures that we have, and maybe for
 14 other purposes, we don't have good measures. That
 15 will come up, I'm sure, later when we talk about
 16 some of the other conditions, as well as
 17 cannabinoids.

18 DR. JOHNSON: I wanted to get in there
 19 because it sounds like I might be in the
 20 minority --

21 DR. STRAIN: This is Matt Johnson.

22 DR. JOHNSON: -- but I think we're ready for

Page 19

1 experimental work, clinical experimental work in
 2 this area. I don't think we need to do a whole
 3 lot -- I mean, there's research going forward on
 4 all these angles, including what's happening
 5 naturalistically, but I think we know enough.
 6 There's a lot of interest, and I would say probably
 7 the biggest is as a substitution therapy.

8 Like anything else, the field is going to
 9 have to take some educated guesses, but I don't
 10 think we need to wait years to do more work to jump
 11 into experimental clinical research, looking at
 12 cannabinoids as substitution treatments in
 13 opioid-use disorder.

14 It's kind of crazy we don't have anything in
 15 that realm, randomized designs, in a clinical
 16 population outside of the lab to really look at
 17 this. I don't think we need to wait. I think we
 18 need to do all of these types of research. We make
 19 some best guess about what the product would be,
 20 but I think there are different routes of
 21 administration and different strains. There's THC
 22 and CBD, but we might be overstating.

Page 20

1 Most of the cannabis, unless it's divorced
 2 of all THC, it's a bit analogous to different
 3 benzodiazepines and anxiolytic sleeping agents.
 4 I'm more struck by more commonalities than
 5 differences. So we make a best guess, and we start
 6 doing some experimental work.

7 DR. SHURTLEFF: Can I just comment?

8 DR. STRAIN: Sure. David, then Els, then
 9 Frances.

10 DR. SHURTLEFF: I agree with Dr. Turk's
 11 analysis. I think it's also marrying the specifics
 12 of the cannabis with a specific condition. For
 13 example, there's a lot of work done with, for
 14 example, Sativex, the GW compound, showing that it
 15 can be effective for treatment of chronic pain. We
 16 know that 50 to 80 percent of patients on methadone
 17 or buprenorphine have issues of chronic pain, so I
 18 could imagine a trial where you combine, say, a
 19 Sativex product, getting very concrete, with
 20 individuals on methadone or buprenorphine.

21 Similarly, I think CBD may have some
 22 benefits for controlling anxiety. I think Yasmin

Page 21

1 Hurd just reported a paper showing changes in
 2 craving for opioids. And I think CBD for managing,
 3 for example, those kinds of conditions, anxiety,
 4 craving, could be another kind of approach. So I
 5 think you're right in breaking down the components
 6 of the OUD and marrying those components with
 7 specific elements of the cannabis plant that we
 8 know have shown some efficacy.
 9 I would promote using the more
 10 pharmaceutical grade, the GW compounds, the
 11 FDA-approved compounds, just because I think in the
 12 long run, standardizing dose administration makes
 13 more sense than a smoke product that has so many
 14 variations. We know there's 110 cannabinoids, 120
 15 terpenes, within the cannabis plant itself.
 16 That's a lot of variation. And depending on
 17 how it's grown, and the season, or whatever else
 18 might be involved in the agriculture around that, I
 19 think going with these, either whether it's
 20 EMA-approved or FDA-approved compounds seems to
 21 make more sense to me.
 22 DR. STRAIN: Thank you. Els?

Page 22

1 DR. HOUTSMULLER: This is a situation where
 2 there is widespread use by, as we've discussed,
 3 different populations for likely different
 4 purposes, so I think this is exactly the situation
 5 where it is really important to talk to patients
 6 because we know that different people use this for
 7 different purposes, but we don't know exactly who
 8 uses it for what.
 9 I think that talking to patient advocacy
 10 groups, or just talking to people who are active in
 11 the field -- I'm not suggesting that you just pull
 12 a patient out of a practice and say, "So what do
 13 you think we should do?" But there are ways to do
 14 this, where you can get very valuable information.
 15 For example, people who have become
 16 dependent on opioids because of pain, but don't
 17 have a history of a lot of drug abuse, but have
 18 been taken off those opioids because that's what
 19 has been happening fairly recently, and then have
 20 gone to street drugs, et cetera, talking to those
 21 people specifically about what they may be using
 22 marijuana for will give you very different answers

Page 23

1 than talking to people who have a 30-year history
 2 of just using all kinds of drugs, et cetera.
 3 So before you make those decisions, I think
 4 it's really helpful to get that input, so that for
 5 each of these, you can then incorporate that
 6 information into the design; what is the question
 7 you're actually asking for that population.
 8 DR. STRAIN: Frances, Tom, and then David.
 9 DR. LEVIN: It's interesting, because I
 10 think that because we've had these effective
 11 treatments like buprenorphine or methadone, the
 12 idea is that anybody can be on these drugs, and
 13 they're going to do well. And the reality is that
 14 we're finding that if you have a lot of psychiatric
 15 comorbidity, if you have a lot of impulsivity, if
 16 you have not the right social situation in your
 17 life, these drugs don't work as well, and you wind
 18 up dropping out of treatment.
 19 So I think that this has been a thing for
 20 the field, and I've been a very strong proponent
 21 like with cocaine. I don't think we're going to
 22 find a single medication for cocaine users. We're

Page 24

1 going to have to have different medications based
 2 on either different phenotypes, or endotypes, or
 3 whatever you want to say.
 4 What prompted me to ask to say something is
 5 that when you mentioned the idea about substitution
 6 therapy, I think the reason why most of us who see
 7 these patients are thinking as an adjunct, whether
 8 it's for withdrawal, getting people inducted, or
 9 after keeping them and retaining them in
 10 treatment -- because I think a lot of these
 11 patients have an underlying anxiety either caused
 12 by protracted withdrawal or an underlying anxiety
 13 disorder -- is I think we're afraid of thinking of
 14 marijuana, good or bad, because it hasn't been
 15 studied as a stand-alone substitution therapy
 16 because of the high risk of overdose.
 17 What we know is that methadone, and
 18 buprenorphine, and Vivitrol, particularly
 19 methadone, reduces greatly the risk of overdose.
 20 So the idea that you could use a substitution of a
 21 cannabis product, the fear that I would have as a
 22 clinician is, gosh, I've given them a cannabis

Page 25

1 product, and they overdosed, and you feel protected
 2 more.
 3 So that's why I think the thinking is more
 4 towards an adjunct treatment rather than a
 5 replacement therapy, like using it like we do
 6 methadone or whatever else. So that would be why I
 7 would say be afraid to use it alone.
 8 DR. JOHNSON: And I would agree with all
 9 that, the idea like taking people who have
 10 failed --
 11 DR. STRAIN: I'm sorry. Matt?
 12 DR. JOHNSON: -- institution therapy, those
 13 folks.
 14 DR. STRAIN: I'm going to try to keep
 15 people -- Tom, David, then Dustin.
 16 DR. JOHNSON: How about I do this? Does
 17 that help you?
 18 DR. STRAIN: Yes, that's fine as well.
 19 Tom?
 20 DR. KOSTEN: One of the groups that's not
 21 been well represented at this meeting is the
 22 pharmaceutical industry; at least it doesn't seem

Page 26

1 like it. They did a tremendous amount of work with
 2 cannabinoids and making artificial versions.
 3 Now, we think of them mostly as dangerous
 4 substances, that people are coming in with K2 and
 5 all these other bizarre combinations of making
 6 these -- there are hundreds of these compounds, and
 7 most all are full agonists as opposed to partial
 8 agonists like THC. And there has been found that
 9 there are toxicities, but they were all developed
 10 with the commercial idea that they would decrease
 11 tolerance to opiates, so therefore give them
 12 together with opiates as a way to markedly reduce
 13 the amount of opiates you need and how much over
 14 time.
 15 They were not tested out in terms of using
 16 them for what about a detox, or what about a
 17 transition off of opiates? So contacting some of
 18 these companies -- I mean, they've got
 19 pharmaceutical grade substances that are much more
 20 simple to manufacture, unfortunately, which is why
 21 they're manufactured in Mexico all the time now, or
 22 in China. They're highly potent, and you have a

Page 27

1 great specificity to them, which you don't have
 2 with these natural biologics. We're talking about
 3 THC as if it just hits the CD1. It doesn't. It's
 4 all over the place.
 5 So it just seems a dialogue about this
 6 without having the benefit of all of that
 7 knowledge -- the knowledge is admittedly 40 years
 8 old now, but it's there, and patents could be
 9 developed on that.
 10 Commercial development of this is the other
 11 thing I think about. Right now, it's all stuff
 12 that, in fact, the only regulation around it is
 13 from the Federal Trade Commission to see if you're
 14 lying about what it might be, but otherwise,
 15 nothing about its production. Somehow it seems
 16 like the FDA needs to be able to get in here and
 17 regulate some of the junk that's out there.
 18 That's a little bit off the -- as I said, I
 19 think we're missing a major piece of what's in this
 20 dialogue.
 21 DR. STRAIN: Thanks. David?
 22 DR. SHURTLEFF: Yeah. Just to follow up on

Page 28

1 a couple of comments, we're running this natural
 2 experiment now; 33 states have legalized marijuana
 3 for medical use, and there's a lot of
 4 epidemiological data showing why patients are
 5 taking the cannabis. From what I've read, the
 6 predominant reason is for pain management.
 7 The other comment is before we get into
 8 these comorbidities related to OUD, I think
 9 studying the conditions in and of themselves, we
 10 know CBD, there have been some studies to suggest,
 11 for example, CBD may have effects on social
 12 anxiety, for example, but those studies are
 13 relatively weak.
 14 I think where we could go is first let's
 15 step back and study the individual conditions with
 16 the cannabinoids before we try to think about how
 17 to combine that with OUD. I realize there's a need
 18 to do that, but it may be worth stepping back and
 19 studying these disorders independently.
 20 Then the other thing related to Tom's
 21 comment, I agree that cannabis is a natural
 22 product, it's messy, but I think, actually, CBD,

Page 29

1 that may be the benefit. It's hitting multiple
 2 targets, as many drugs of abuse do. They may
 3 provide some medical benefit.
 4 The final comment, we're not studying the
 5 minor cannabinoids. There's so much more in the
 6 cannabis plant that we just don't know much about,
 7 that I think having industry, or government,
 8 or -- certainly we at NCCIH are trying to do more
 9 in studying the terpenes and the minor
 10 cannabinoids, that may show some clinical benefit
 11 for a variety of disorders. We're focusing on
 12 pain, but I could imagine setting those more
 13 broadly for other indications.
 14 DR. STRAIN: Thank you. Dustin, then Matt.
 15 DR. LEE: Yes, I'm just going to add into
 16 what's just been discussed right now. I just
 17 wanted to bring in consideration of the reality of
 18 the therapeutic cannabis marketplace and what are
 19 the chances that that whole systems is going to
 20 change. As you said, we don't have a lot of
 21 pharmaceutical representatives. You can say we
 22 also don't have dispensary representatives here,

Page 30

1 because that's really where medical cannabis is
 2 being practiced right now.
 3 So it's great to do this research, and I
 4 think it's absolutely needed. But we also have to
 5 take really proper care of how this research gets
 6 marketed and displayed because whatever we put out
 7 there, it's going to be a different product than
 8 what, in reality, people are going to use in most
 9 states in this country, where I think the reality
 10 is it's not going to be pharmaceutical grade
 11 cannabinoids.
 12 DR. STRAIN: Matt, did you have a comment?
 13 DR. JOHNSON: I didn't.
 14 DR. STRAIN: Oh, Mike?
 15 DR. BOGENSCHUTZ: Michael Bogenschutz. It's
 16 just interesting watching this conversation kind of
 17 go on two parallel tracks. One is about cannabis
 18 or maybe THC, a very well characterized risk and
 19 effect profile, and the harm reduction approaches
 20 that we're comfortable with, and ready to do
 21 pragmatic trials with, it sounds like.
 22 Then the other is all these other

Page 31

1 cannabinoids we know, really, very little about,
 2 even CBD. Just the example of that, it's in your
 3 coffee if you want to buy it out on the street
 4 probably, probably only about a milligram. Many
 5 people think of it as this very benign substance,
 6 and in a lot of ways it is, but it's got a lot of
 7 very complicated pharmacokinetic interactions,
 8 particularly with opioids.
 9 So the point being there's a need for a lot
 10 of really basic dose-response, and safety, and drug
 11 interaction studies with any of these new
 12 compounds, including CBD, which is not that new.
 13 DR. STRAIN: I cut you off before, Matt.
 14 Did you have a comment that you wanted to make?
 15 DR. JOHNSON: I'll say a little more about
 16 what I've said before. Again, I think we need to
 17 be moving on all tracks. Scientists have this sort
 18 of propensity that it's a self-control issue, that
 19 maybe 20 years from now, we'll have all of the
 20 background information to go forward; yet, every
 21 year goes by without more effective treatments.
 22 Then we're talking about a number of things like

Page 32

1 chronic pain and OUD, but for these different
 2 things, there's an opportunity cost. I think we
 3 know enough to step in with experimental clinical
 4 research for a number of these questions, and we
 5 need to look at both products.
 6 There's the Sativex on the market, extremely
 7 well characterized. Maybe that company's not
 8 interested in the use of that product, but if it's
 9 on the market -- doing experimental research with
 10 these things and modeling what's happening in the
 11 whatever, the wild west, legalized states. But we
 12 need experimental clinical research, like
 13 yesterday, and we can take some best guesses.
 14 Like Dustin said, this stuff is happening,
 15 and it's absent any experimental evidence, largely.
 16 So we just need to not wait until we have all of
 17 this -- there's always going to be more to learn.
 18 That's my major point.
 19 DR. STRAIN: Sandy?
 20 DR. COMER: I just want to bring maybe the
 21 discussion back to the purpose of this meeting,
 22 which is to talk about methodology.

Page 33

1 DR. STRAIN: Thanks.
2 DR. COMER: Well, not to be snarky or
3 anything, but there are all these regulatory and
4 practical issues in working with cannabinoids, and
5 I think Ryan did a really good job yesterday of
6 identifying most of those. But if we want to talk
7 about, okay, what would a clinical trial look like
8 for a cannabinoid as an adjunct to
9 medication-assisted treatment, I completely agree
10 with Frances that I can't even imagine taking a
11 patient with opioid-use disorder, and then just
12 putting them on a cannabinoid as a stand-alone
13 medication just because the risk is too high.
14 What if we just, as an exercise, think about
15 what a design of a trial would look like.
16 Immediately it comes to mind that in medications
17 development, NIDA wants to develop a product. So
18 immediately I'm thinking, well, buprenorphine would
19 be a good platform to use as maintenance
20 medication. But then how would you add a
21 cannabinoid onto that as a single -- I don't know
22 if it's feasible to add a cannabinoid onto

Page 34

1 buprenorphine strip.
2 So then my next thought was, okay, methadone
3 might be easier. So if we had methadone, and then
4 added a cannabinoid into that as a single kind of
5 product, then we would talk about doing the
6 drug-drug interaction studies. We would talk about
7 what doses of methadone and the cannabinoid would
8 make sense; what kind of safety questions are we
9 raising here, and how would we design that kind of
10 study.
11 DR. STRAIN: Our goal, just to be clear, is
12 not to actually design the study today, obviously,
13 but to lay out the parameters of what we want to
14 do.
15 Now, Bob Dworkin's name card is up,
16 which --
17 DR. HOUTSMULLER: I'm not Bob.
18 DR. STRAIN: That's alright. Did you have a
19 comment you wanted to make, Els?
20 DR. HOUTSMULLER: I do have a comment, and I
21 don't have my --
22 DR. STRAIN: Well, okay, and then we'll go

Page 35

1 over to this side.
2 DR. HOUTSMULLER: -- oh, here it is.
3 MALE VOICE: Yes, you do.
4 DR. HOUTSMULLER: Thank you so much.
5 I'm Els.
6 DR. STRAIN: It was a little eerie to see
7 Bob's name without Bob.
8 DR. HOUTSMULLER: He also got to be you
9 yesterday.
10 DR. STRAIN: What's that?
11 DR. HOUTSMULLER: He got to be you
12 yesterday.
13 DR. STRAIN: Yeah.
14 DR. HOUTSMULLER: I did have a comment.
15 When I heard -- and I'm not really an expert on the
16 research in this area, so I'm listening to what
17 people are saying. And when I hear Matt talk about
18 we need to actually look at these and perhaps
19 compare them, then my comment was going to be, if
20 this is a field where it would be appropriate to
21 compare, for example, different -- to compare
22 either adding some cannabinoid, or just a marijuana

Page 36

1 that people can buy from a dispensary, with not
2 adding that or with adding something else.
3 Then I was going to put a plug in for PCORI
4 and say you should really start thinking about a
5 real-world effectiveness study, and do a large
6 study where you have some control over what people
7 take, and you add some standard -- I mean, not to
8 just, well, go buy your marijuana, but something
9 from dispensaries, et cetera, and you compare that
10 to a whole group that doesn't get that. But then
11 when I heard Sandy talk more about efficacy and
12 safety, I don't know that it's ready for that.
13 So I'm not making any comment about that. I
14 was just thinking, oh, maybe it isn't there yet.
15 If there is widespread use and people are using
16 this, different populations are using this, in
17 addition to a maintenance treatment, then it sounds
18 like that would be ready for a comparative
19 effectiveness study, and a real-world setting,
20 where you're not looking in the lab at isolated
21 parts of marijuana, but looking at something that
22 is available.

Page 37

1 DR. JOHNSON: And I wanted to say something
 2 on --
 3 DR. STRAIN: Celia?
 4 DR. JOHNSON: -- oh, go ahead.
 5 DR. WINCHELL: You've got to wait, Matt, if
 6 I may.
 7 DR. JOHNSON: Oh, yeah; go ahead.
 8 DR. WINCHELL: I'm very interested in what
 9 Dr. Comer and Dr. Levin both said about being
 10 loathe to imagine a non-mu treatment as a stand
 11 alone because that's a very important point. We
 12 certainly have a number of non-mu treatments that
 13 have been proposed to treat addictions of various
 14 kinds. And OUD being the sexy topic of the day,
 15 where the money is, people bring new molecular
 16 entities, all kinds of different molecular
 17 pathways, different targets, and they are
 18 interested in studying these in patients with
 19 opioid-use disorder.
 20 Sometimes the sponsors are a little fuzzy
 21 about what aspect of the disorder would be amenable
 22 to treatment by their molecule. "Oh, it could

Page 38

1 probably treat withdrawal, but it probably would be
 2 good for relapse prevention," and, "Yeah, we think
 3 it'd be a maintenance drug, and also opioid sparing
 4 in pain patients."
 5 So first of all, we get them to break those
 6 into little parts because you can only study one
 7 thing at a time. But I'm very interested in this
 8 idea that, perhaps, maintenance treatment or
 9 relapse prevention would not be an appropriate use
 10 for a non-mu agent. Would it be acceptable in
 11 patients who are not interested in agonist
 12 maintenance? Would it be acceptable in patients
 13 who are not candidates or they're, I don't know,
 14 airline pilots or something?
 15 I'd like to hear more about that because,
 16 the key of why we wanted to talk about study
 17 design, populations, endpoints, and so forth, and
 18 different kind of risk-benefit evaluations for
 19 non-mu, and I'm just wondering if everybody feels
 20 the same way.
 21 DR. JOHNSON: That was exactly what I was
 22 going to say. There are folks that would not be

Page 39

1 interested in being on methadone or bup and that
 2 would. I think it's a pretty good guess there's a
 3 chunk of folks that say, yes, cannabis; they would
 4 be open for that.
 5 I completely agree with the ethical concerns
 6 about putting people on cannabinoids who are
 7 candidates for mu agonist or partial agonist
 8 treatment, so keeping that in mind and looking at
 9 people for whatever reason it hasn't worked for
 10 them or they're not interested in that; that would
 11 be of interest.
 12 DR. STRAIN: David, then Ryan.
 13 DR. WINCHELL: And I'd love to hear Frances'
 14 answer to this question.
 15 DR. STRAIN: David, Ryan, and then Frances.
 16 DR. SHURTLEFF: Just coming from NIH, NCCIH,
 17 from a federal research organization, I'm sort of
 18 in the middle. I sympathize with Matt's issues,
 19 and I somewhat agree that we're playing catch-up
 20 here with the science and the public use, and we
 21 need to move as quickly as possible. Of course, we
 22 have some regulations around how we can study

Page 40

1 marijuana, per se, given the current federal
 2 regulations, but I think there are some creative
 3 solutions and ways of moving forward.
 4 Certainly, just highlighting some of the
 5 work of Kent Hutchinson, looking at what's going on
 6 in Colorado where he's doing observational studies
 7 but applying very rigorous outcome measures to
 8 that. He can't randomly assign people, but he can
 9 look to see how people are using this product and
 10 what the outcomes are from the use of that product
 11 in a very rigorous way.
 12 I think that's one approach where you
 13 probably have people who are addicted to opioids,
 14 who are using marijuana in some way, and then
 15 overlaying some sort of rigorous outcome measures
 16 on that natural occurrence is a way to give you
 17 more insight into why and how these products are
 18 being used, number one.
 19 The second thing is, as NCCIH, we're very
 20 interested in doing clinical research with
 21 cannabinoids or cannabis. I can't speak for NIDA,
 22 and I can't speak for other institutes at the NIH,

Page 41

1 but for our center, we are very much moving ahead
2 with doing clinical research.
3 We're primarily interested in minor
4 cannabinoids, and particularly CBD, just because
5 THC has so many potential issues with abuse
6 liability and other potential -- it's not the best
7 profile in terms of abuse liability and safety.
8 But that's not to say that there can't be some
9 minimum dose combined with some other cannabinoids;
10 we can get into the weeds on that.
11 But I think the point is, Matt's urgency
12 about moving forward with some clinical research, I
13 think we are open to that, as NCCIH, to go into the
14 clinical realm. We're doing that already. We just
15 spent over \$3 million on projects looking at minor
16 cannabinoids. At least two of them were with human
17 subjects. We're about to award a third project
18 this year, looking at CBD and THC for the
19 management of neuropathic pain.
20 So there are opportunities at the federal
21 level to move the clinical research forward, I
22 guess is my point. There's also a wealth of

Page 42

1 information to learn from what's actually going on
2 in the real world, using rigorous approaches,
3 scientific approaches. I think Kent Hutchinson has
4 a good model for doing that.
5 DR. STRAIN: Thank you. We've got Ryan,
6 Frances, and Tanya.
7 DR. VANDREY: I just want to come back and
8 comment on themes that I'm hearing. The way I've
9 tried to think about an approach of how you go
10 about testing some of the things that you're
11 hearing from the industry and some of the things
12 that you're hearing from patients, I think in the
13 cannabis world, there's so much noise about how
14 it's amazing and great for everything.
15 What I try to do when we develop studies and
16 design things, I think there's enough
17 information -- I agree with Matt -- that we can
18 come up with some questions. It's important, if we
19 think that this is a good idea, to listen to what
20 patients are saying and don't listen to what the
21 cannabis industry is saying. But where we step in
22 is we design a study that's appropriate to answer

Page 43

1 or address the issue that they say.
2 Essentially, if the cannabis industry says
3 that cannabis is great for opioid withdrawal, then
4 you design the study for that. I think that that's
5 where we can have credibility not only in the
6 decision making, but also we're addressing a key
7 clinically relevant outcome. So we're saying,
8 alright, they're using it for this right now
9 anyway; let's find out if that's a good idea or
10 not.
11 So you're essentially calling them on what
12 their claim is, so good or bad, the outcome becomes
13 important.
14 The other thing that kind of gets lost in
15 this a little bit is that as you're doing this, we
16 can get really wrapped up in the idea of product
17 development, the use of Sativex versus cannabis,
18 and things like that. The reality right now in the
19 product that gets evaluated is that, for most
20 people in the U.S., they have access to cannabis.
21 So even if you develop a nice, clean
22 pharmaceutical, there's not a good business case

Page 44

1 for doing that right now because that costs a ton
2 of money, who's going foot the bill, and then
3 what's the likelihood that that's going to then be
4 the product that people are using? So while we
5 really want to put this nice package together and
6 have Sativex or Epidiolex be our product, if that's
7 available, that's good, but to also recognize that
8 there might be cases where that wouldn't be
9 adopted.
10 So I think we want to kind of have that
11 going in and think carefully about that, how
12 important is it going to be that we have a really
13 well-defined, specified dose, combination
14 opioid-cannabinoid product versus you give people
15 their bup or their methadone, and let them use
16 cannabis on top of it, and maybe there's some
17 flexibility in what kind of product, what route,
18 and what cannabinoid they're using.
19 Then, the other thing that I think we need
20 to be very careful about and not lose sight of is
21 that we don't want pilots taking THC. We have to
22 be very careful about people with psychiatric

Page 45

1 comorbidities. And long-term use of THC we know is
 2 generally pretty bad for people with anxiety, and
 3 depression, and PTSD, and psychosis; so making sure
 4 that we're carefully thinking about which
 5 cannabinoid for which population.
 6 DR. STRAIN: Thank you. Frances, Tanya, and
 7 then Kenzie.
 8 DR. LEVIN: I was just going to comment on
 9 the issue of preference because I think that often
 10 changes frequently with patients over time. I
 11 think the vast majority of people with opiate-use
 12 disorder, as we know, aren't taking any
 13 medication -- I don't say medication-assisted
 14 treatments anymore -- medications for opiate-use
 15 disorder.
 16 Part of that is not because of preference;
 17 it's because of reimbursement, doctors not being
 18 available, doctors not prescribing enough; there
 19 are a whole bunch of reasons why. But I think that
 20 if you could define a group that truly doesn't want
 21 a standard opiate-use disorder treatment, and I
 22 think that's a big question, then I think the idea

Page 46

1 of having an alternative is good.
 2 There was an interesting paper in the
 3 American Journal Psychiatry in which they, no
 4 surprise, found that if you gave a person with PTSD
 5 an option of either psychotherapy or medication,
 6 they were retained in treatment a lot better if
 7 they were first given what they wanted. Often
 8 clinical trials aren't designed that way, and
 9 that's a whole -- I just was listening to Roger
 10 yesterday talking about a clinical trial in which
 11 people are going to get choice in the CTN.
 12 So I think this issue of choice is often not
 13 looked at as clinical trialists, and I think is a
 14 very important one. So I agree with you, but I
 15 think if you could define a group that you know had
 16 all available access to medication treatments, and
 17 were given enough psychoeducation about it and
 18 still refused it -- there's a big difference
 19 between an antagonist and an agonist, so if they
 20 say they don't want an agonist, there's an
 21 antagonist available.
 22 But if you look at the other side, which I

Page 47

1 think, from my perspective as a clinician, is the
 2 first route to go, of can you enhance retention, as
 3 we all quote, 50 percent or more of patients at
 4 6 months aren't on an opiate treatment after
 5 they've been put on it. If you look at pharmacy
 6 data, like prescription data -- Morgan did a
 7 study -- it's like 80-90 percent. In a clinical
 8 trial, we all quote 50-60 percent, but in the real
 9 world, people are dropping out left and right at
 10 much higher rates because of all of the issues
 11 surrounding it.
 12 So to me, if we could find something that
 13 would work on the high dropout because once the
 14 patients stop, the risk of overdose goes way up.
 15 To me, that would be my perspective, and my
 16 opinion, the first thing to look at is keeping
 17 people on medications as a first step.
 18 Adam's study was sort of a naturalistic. He
 19 didn't go into that study really thinking about,
 20 oh, these people are all going to be using
 21 marijuana, but they all continued using marijuana,
 22 and the people on marijuana were retained in

Page 48

1 treatment. The gold standard is just keep people
 2 coming through the door and keeping them in
 3 treatment first. So I think that we have a lot to
 4 do even on that side, even before going to the
 5 preference side.
 6 DR. STRAIN: Thank you. We are closing in.
 7 We've just got a couple more minutes before we
 8 shift gears. I've got left Tanya, Kenzie, and then
 9 Sandy will get the last word on this one.
 10 DR. RAMEY: I just wanted to comment on what
 11 we could glean from a pharmaceutical industry. The
 12 pharmaceutical industry worked a lot in this area,
 13 but what's interesting is their efforts were in
 14 anti-cannabinoids. They were trying to decrease an
 15 appetite. If you could look at whatever's
 16 published, at least you need to be interested in
 17 that to see where they have failed because this
 18 field is littered with negatives.
 19 Where they failed, it was kind of we'll show
 20 you the way from the other side. There were safety
 21 concerns. For example, those safety concerns were
 22 around, that people who were receiving

1 anti-cannabinoids, they were getting depression and
 2 they were suicidal.
 3 So once the signal emerges, it's all kind of
 4 halted, stopped, those programs. It shows you with
 5 the cannabinoids, where to move, in which
 6 direction, and what is the reason, and why the
 7 retention is better, for example; why they would
 8 work in withdrawal, and this is why, because of
 9 this effective component that would hold them.
 10 So again, it's important to research the
 11 failed programs in the pharmaceutical industry.
 12 They're an absolutely different area, but where
 13 neuropsychiatric side effects are very key to the
 14 health program.
 15 DR. STRAIN: Thank you. Kenzie?
 16 DR. PRESTON: You mentioned natural history
 17 studies, and we've done some of those. We analyzed
 18 data from people who were in treatment for opioid
 19 and cocaine dependence, and what we found is the
 20 people who used marijuana did no better or no worse
 21 on the opioid outcome measures and no better or
 22 worse on the cocaine outcome measures. What they

1 you.
 2 DR. SHURTLEFF: You said that you didn't see
 3 any difference with opioid symptoms, but I'm
 4 wondering about some of the issues you just
 5 mentioned, anxiety and pain. Were those part of
 6 your natural history studies?
 7 DR. PRESTON: Unfortunately, we don't take
 8 chronic pain patients and we don't take people with
 9 other major psychiatric symptoms.
 10 DR. SHURTLEFF: There might be some benefit
 11 for more observational studies in those types of
 12 patients.
 13 DR. PRESTON: I think there probably is a
 14 lot of data out there that could be mined to look
 15 for those kinds of effects.
 16 DR. STRAIN: Sandy?
 17 DR. COMER: I just wanted to follow up on
 18 Celia and Matt's comment about, well, what about
 19 patients who don't want to be on medication-
 20 assisted treatment and they want to be on a
 21 cannabinoid? I appreciate Kenzie's work because I
 22 think that really is apropos to what we're talking

1 did have was they were more likely to meet criteria
 2 for marijuana-use disorder.
 3 (Laughter.)
 4 DR. PRESTON: Also, we looked at opiate
 5 withdrawal, and we did a lagged analysis. We
 6 looked at symptoms of withdrawal and marijuana use
 7 or marijuana use followed by opioid withdrawal
 8 symptoms. Again, we saw no effect of marijuana use
 9 and opiate symptoms.
 10 That's a natural history study. I don't
 11 think it's the final word, but what I would think
 12 might be useful is to take those effects that we
 13 have demonstrated efficacy for cannabis, perhaps
 14 pain, perhaps anxiety, and if we have patients who
 15 have those problems, then we could do a trial in
 16 our patients for those indications, which may
 17 actually help the opioid-use disorder symptoms.
 18 DR. SHURTLEFF: Can I just quickly ask, did
 19 you measure generalized anxiety disorder, or those
 20 measures that you think might be helpful, were
 21 those part of your natural history?
 22 DR. PRESTON: I'm sorry. I couldn't hear

1 about.
 2 Setting aside marijuana, because it has very
 3 complicated issues, I was thinking, after you made
 4 your comment, what kind of trial design would be
 5 okay in somebody who wants to take a cannabinoid
 6 and doesn't want to take anything else?
 7 I think the only way that it would be okay
 8 to do that would require very different kinds of
 9 thinking about trial design. I was just assuming
 10 that if we want to study a cannabinoid medication,
 11 we'd have to detox somebody first because you don't
 12 want that background against which to measure the
 13 effects of your medication. But that's where it
 14 gets really dangerous because you're making
 15 somebody non- tolerant, and the risk of relapse and
 16 overdose is really high.
 17 So if you had patients who were physically
 18 dependent on opioids, and gave them a cannabinoid
 19 versus placebo, and then measured their ongoing
 20 opioid use, anxiety, depression, that kind of
 21 thing, then that might be acceptable. But then it
 22 becomes a question of what is your primary

Page 53

1 endpoint? Is it retention? Is it reduced use?
2 What is it?
3 That's where it gets a little fuzzy in my
4 mind. We talked yesterday about the need or the
5 desire to reduce opioid use because that's where
6 the problematic behaviors come in. Then if
7 somebody does reduce their use, does that mean that
8 it's going to put them at higher risk of overdosing
9 in that situation? So that's a risk factor that we
10 have to think about in that kind of trial design.
11 So it's an interesting exercise in terms of
12 what kind of study would we do, and what would be
13 the safest for the patient? What kind of endpoints
14 do we need to think about?
15 Group Discussion – Sleep Agents
16 DR. STRAIN: Well, thank you, to all of you
17 for your thoughts on that; a lot to consider, a lot
18 of questions, and obviously no answers yet. But
19 I'm very appreciative of hearing the interest in
20 seeing this kind of work be done, either in a
21 naturalistic way or in a systematic way from NIH's
22 perspective. The FDA is struggling with this as

Page 54

1 well.
2 We're in the midst of a grand social
3 experiment in this country, which confounds
4 everything because if somebody says, "Well, gee, I
5 think I'm in the placebo condition [indiscernible],
6 so I'm going to go down to this dispensary and get
7 a joint," you're back at square one. But that
8 doesn't mean that we can't figure out ways to do
9 this, and studies, to try to discern if there's a
10 signal there.
11 This is an exercise in your ability to have
12 cognitive flexibility because now we're going to
13 shift gears, and for the next 40 minutes, we're
14 going to talk about sleep agents. I don't mean to
15 put people on the spot. I sort of put Ryan on the
16 spot at the beginning of cannabinoids. Andrew, I'm
17 going to put you on the spot with this one. Matt,
18 you're going to be on for the psychedelics, and
19 then we'll take a break, and then Sandy for the
20 vaccines.
21 Just to see if you have opening thoughts
22 about this, especially, I think it's useful we've

Page 55

1 had that conversation about cannabis because now
2 we're sort of in that groove, where we're saying,
3 okay, we see some of the parameters. Obviously,
4 sleep agents are very different. We've got
5 pharmaceutical grade things. We can do dosing
6 correctly. We don't have local dispensaries that
7 are selling Ambien, if you can get an Ambien card
8 from somebody, so it's a different set of cultural
9 and social stipulations.
10 I'll turn this over to you, Andrew, in a
11 moment.
12 We also know that sleep complaints are an
13 issue that patients report who are in methadone and
14 buprenorphine treatment, and there's a long history
15 of data saying that people continue to report sleep
16 problems even after they've stabilized in other
17 ways in treatment, and we could be doing better
18 with these, probably, symptoms that they're
19 reporting.
20 So with those kind of opening thoughts,
21 Andrew, did you have anything you wanted to say
22 about this as you kind of digested yesterday's

Page 56

1 presentation?
2 DR. HUH: Thanks, Eric.
3 I kind of think about this in two ways.
4 Sleep, a big enough problem where it becomes the
5 primary target of clinical trials for opioid-use
6 disorders. Sleep disturbance is bad enough in this
7 population that that alone is the outcome, and then
8 the relative value of sleep agents or behavioral
9 interventions to treat sleep disturbance as an
10 adjunct therapy to other medication-assisted
11 treatments, or MOUDs, whichever you prefer.
12 Also, I'd add a third discussion point,
13 which is including sleep as a secondary outcome in
14 clinical trials regardless if sleep is the actual
15 focus of that trial. I'm interested to hear
16 thoughts from the rest of the group on this and any
17 ideas that you might have.
18 (No response.)
19 DR. HUH: Not everybody at once.
20 DR. STRAIN: Your voice was soporific.
21 Frances?
22 DR. LEVIN: I don't know the opiate

Page 57

1 literature as well, but at least the marijuana
 2 literature, we've shown repeatedly that improving
 3 sleep isn't necessarily linked with improving
 4 self-administration.
 5 It's certainly a complaint we hear about a
 6 lot, and I think it is driving why people are using
 7 opiates or going back to opiates. I think it's a
 8 mediator, so maybe it's not necessarily in and of
 9 itself the issue, but more that if you treat
 10 it -- in the lab with marijuana, we haven't seen
 11 it, but maybe in a clinical setting that, yeah, if
 12 people are trying to come off of opiates and you're
 13 giving them Vivitrol, for example, and they're
 14 still having sleep problems, they may say the hell
 15 with it, I'm not going to take the next shot, or
 16 maybe the buprenorphine isn't helping enough with
 17 that.
 18 So I think it may serve as an important
 19 mediator that we should be addressing, perhaps.
 20 Again, I don't think it is a stand alone, as a
 21 thing, but I think it's an important factor just as
 22 other ones are. Not treating psychiatric

Page 58

1 comorbidity people, don't stay in treatment and
 2 don't do well. There's a whole variety of factors,
 3 and sleep being one of them, that may be
 4 influencing how well we maintain people in
 5 treatment. They complain a lot about it, so to not
 6 address it I think is not helping. You'd have
 7 happier patients if they're sleeping well.
 8 DR. STRAIN: Sandy?
 9 DR. COMER: This kind of raises a question
 10 in my mind of -- well it's a consequence of the
 11 paper that Nora wrote, with the FDA, talking about
 12 different endpoints that we can consider. I was
 13 really excited to read that because I thought,
 14 "Okay, this is great." It's a way to kind of
 15 rethink the way we would do the research to study
 16 medications.
 17 So the question is, should we treat some of
 18 these symptoms that the patients identified during
 19 that meeting at NIDA, or FDA -- I don't remember
 20 where it was --
 21 DR. LEVIN: FDA.
 22 DR. COMER: -- as symptoms that we can

Page 59

1 target as stand-alone symptoms, or do they have to
 2 be tied to opioid-use disorder and improving
 3 treatment there? Because those are two very
 4 different kinds of approaches.
 5 I actually asked Nora that when she was at
 6 Columbia giving a lecture, and she said the latter;
 7 that it has to be tied to reductions in use. But
 8 then I was thinking, and I said this to her. I was
 9 like, "Why is that?" We have a whole aisle full of
 10 medications in the pharmacy that treats symptoms of
 11 a cold. You're not treating the underlying
 12 disorder, but you're treating the symptoms, and
 13 that's really helpful for patients.
 14 So can we think about a sleep medication as
 15 a medication for treating opioid-induced sleep
 16 problems and craving -- craving is the same kind of
 17 issue -- or do we have to tie it necessarily to
 18 actually reducing opioid use?
 19 DR. KLEYKAMP: I'll go first. Annie
 20 Kleykamp with ACTTION, University of Rochester. We
 21 just wrote a scoping review -- and Andrew was at
 22 that meeting -- on craving and opioid-use disorder,

Page 60

1 struggling with these questions, and then we
 2 published a commentary on the idea. I think where
 3 we arrived with craving and the way I've been
 4 thinking of sleep is, of course, it's important
 5 tied to behavior -- we want to reduce -- but
 6 quality of life and the experience was equally
 7 important.
 8 So we're making the argument that pushing
 9 forward research on craving is important for both
 10 of those reasons. I think it was well received. I
 11 haven't gotten a lot of feedback, but I know at our
 12 meeting -- so just to add that to it.
 13 I also wanted to add, while I have the
 14 microphone, I'm tasked with pooling together some
 15 ideas for a paper for this meeting. I have to
 16 say -- and this may change by lunch -- hearing
 17 everyone yesterday, the sleep topic seems the most
 18 clean so far, for me, if we were to focus our
 19 paper -- I'm just throwing this out there as we
 20 think -- on one type of drug class, which we don't
 21 have to.
 22 As we talk during these next 30 minutes, I

Page 61

1 just feel like there are discrete buckets. There
 2 are new technology measures that are more clear. I
 3 don't know if anyone agrees with that, but
 4 listening to Ryan with cannabinoids, the
 5 psilocybins, everything is very interesting, but
 6 I'm not sure we're there yet to actually write a
 7 recommendation paper. That's two separate things I
 8 wanted to throw out.
 9 DR. STRAIN: Thank you. Celia, and then
 10 Kenzie.
 11 DR. WINCHELL: I think I might have some
 12 insight into what Dr. Volkow was aiming at. It's
 13 perfectly fine to study a drug to treat the
 14 symptom. People are suffering, and you have a drug
 15 that can relieve that symptom; that's great. The
 16 issue is whether you could support a marketing
 17 claim that a drug was an effective treatment for
 18 opioid-use disorder by demonstrating an effect on a
 19 symptom.
 20 So if I could parse that for you a little
 21 bit, obviously, people with opioid-use disorders
 22 have many other concomitant complaints that we

Page 62

1 could probably help them with. If you demonstrate
 2 that helping the people with those problems also
 3 translates to some effect on their opioid-use
 4 disorder itself, then those endpoints could support
 5 a marketing claim for opioid-use disorder.
 6 You don't have to make a marketing claim for
 7 opioid-use disorder for everything in the world
 8 that you're going to treat OUD patients with. I
 9 think that's what the distinction was.
 10 DR. COMER: Can I respond to that?
 11 DR. STRAIN: Sure, if Kenzie -- okay.
 12 DR. COMER: I'm sorry; just a direct
 13 response. So the question, then, is -- I
 14 understand the labeling question, and it's a really
 15 important one at the FDA. But if you had a
 16 labeling claim for this medication is effective in
 17 reducing craving in patients with opioid-use
 18 disorder, is that not -- or would it have to be
 19 broader, this reduces craving in general?
 20 DR. WINCHELL: Craving's a special case.
 21 I'll just put it that way. Craving is the best, is
 22 a special case. But if you were to say insomnia,

Page 63

1 belly ache --
 2 DR. HUHN: Which direction is -- so you
 3 could have an indication for craving?
 4 DR. WINCHELL: No. Craving is a very
 5 complicated thing that we are not here to talk
 6 about today.
 7 (Laughter.)
 8 DR. STRAIN: They're a whole other meeting.
 9 Let me see, I've got Celia, Kenzie, Peter,
 10 and then Naomi.
 11 DR. PRESTON: I just wanted to second what
 12 Annie said about the new techniques for measuring
 13 sleep effects. We've been adding measures of sleep
 14 to our research, and one of the interesting things
 15 we found is that the night after opioid use, sleep
 16 is worse compared to other nights. That wasn't
 17 true for cocaine use, kind of surprisingly.
 18 So I think better understanding the
 19 relationship between sleep and drug use is really
 20 important. That's separate from the withdrawal. I
 21 think that's a different category of sleep
 22 problems. But I think it would help us focus

Page 64

1 better on how we should deal with a problem.
 2 DR. STRAIN: Thank you. Peter?
 3 DR. HENDRICKS: I'm still pretty interested
 4 in pain, and I'm thinking about the conversation
 5 that I had with Patrick Finan yesterday. As
 6 somewhat of an outsider with regard to opioid-use
 7 disorder, it's a little curious to me that pain
 8 isn't more of a focus, considering that is sort of
 9 the primary indication when it's prescribed, but I
 10 understand the idea that perhaps pain may not
 11 really apply to everyone.
 12 Nevertheless, I think there's emerging
 13 literature suggesting that for many addictive
 14 substances, there is this reciprocal relationship
 15 wherein pain can be a reason for use, but use can
 16 also make pain worse. I'm sure that's the case
 17 with opioids. Then with regard to sleep, there
 18 seems to be something of a reciprocal relationship
 19 there as well, where the pain can worsen the sleep,
 20 and the poor sleep can make the pain worse.
 21 So it seems like there's an opportunity to
 22 do something interesting there to determine if

Page 65

1 improving sleep can improve pain, and thereby
2 improve sleep, and have an effect on the opiate use
3 in a mechanistic sort of way. I think that in many
4 ways dovetails on Matt's comment, too. It seems
5 like pain should be, perhaps, more of a focus than
6 it is.

7 DR. STRAIN: I've got Naomi, Matt, and then
8 Kit.

9 DR. LOWY: To address some part of your
10 question, I think that there are two ways to look
11 at an aspect of a disease like sleep. I think that
12 FDA certainly entertains aspects of disease as far
13 as a drug target, but clearly the second way to do
14 it is to get a broad indication, and then, either
15 with the initial application or subsequently, to
16 look at specific aspects of the disease.

17 An example of that -- and we have someone
18 from Psychiatry Products here -- is the
19 vortioxetine. That's approved for major
20 depression, and that label now has some specific
21 wording on improvement in processing speed. That's
22 included in the label. It's not under the

Page 66

1 indications section, but certainly that information
2 is available to patients or prescribers, so I think
3 that's a route.

4 I think in order to get that information in
5 a label, either as wording or a specific
6 indication, you need to show that the aspect of the
7 disease is an important aspect of the disease, and
8 that the change that's seen in the clinical trial
9 was actually clinically meaningful. You may see
10 some improvement in sleep or processing speed, but
11 is that actually clinically meaningful? And that's
12 where I think the input from patients would be
13 useful.

14 DR. STRAIN: Thank you. Matt, and then Kit,
15 and Andrew.

16 DR. JOHNSON: I just wanted to raise a topic
17 that I don't think has come up, a general concern
18 about the use of these medications in a chronic
19 fashion. This might be as much as a comment on any
20 population, but it could be worse -- who
21 knows? -- in those with opioid-use disorder. Not
22 only the impairment, like residual impairment, but

Page 67

1 perhaps even more concerning, it looks like a
2 pretty convincing increase in dementia, with people
3 on these compounds for years.

4 I was actually going to ask Andrew whether
5 this is a concern with the orexin antagonist. It
6 looks like the orexin system releases
7 acetylcholine, and presumably these are
8 anticholinergic effects of these various kinds of
9 SSRIs, as well as traditional sleep medications,
10 benzos and Z compounds, that might be tied to that
11 dementia increase.

12 Perhaps this is -- and we don't really know
13 yet because it's a new thing. This concern that
14 there's a -- it might be a real problem that we're
15 giving these drugs to people chronically rather
16 than pushing sleep hygiene. Whatever we know about
17 the real concerns about chronically putting people
18 on these agents, that could be even heightened for
19 people with substance-use disorders, like opioids.

20 DR. STRAIN: Thank you. Kit, and then
21 Andrew, and then Ryan.

22 DR. BONSON: It's certainly the position of

Page 68

1 the federal government, FDA, NIH, that opioid use
2 is dangerous and should be actively discouraged. I
3 know that that's certainly the position of a lot of
4 researchers as well. But when we start talking
5 about symptom reduction, I keep hearing a lot of
6 what the harm reduction community wants to talk
7 about, which is that opioid use maybe could
8 continue, but without all of the harmful effects;
9 and isn't that really what we're concerned about?

10 So it's kind of an interesting conundrum for
11 me to listen to this because, of course, I'm with
12 the federal government, so I have a position that
13 I'm going to espouse. But I can't help but hear
14 some of these things. When we talk about sleep
15 improvement, is that helping somebody go to work
16 every day, and yet they come home and they use?
17 What do we do with that?

18 DR. STRAIN: Andrew?

19 DR. HUHNS: Yes, that's a good point. I do
20 wonder -- and this also comes back to some stuff
21 Sandy brought up. It's a question at the core of
22 what we're talking about for treatment outcomes.

Page 69

1 Anything for a medication indication change has to
 2 be tied to reduced opioid use or elimination of
 3 illicit opioid use, but I don't think that captures
 4 the full experience of somebody in recovery from
 5 opioid-use disorder; that there's a lot of
 6 dysfunction and issues with cognition and emotion
 7 that are also important to the life experience of
 8 the patient, and it's mostly being ignored right
 9 now in lieu of elimination, or at least reduction,
 10 of illicit opioid use.

11 Then to Matt's point about the long-term
 12 effects of suvorexant, I have no idea about that
 13 because it's only been on the market for a few
 14 years. There's no report on that. A lot of the
 15 long-term stuff that I'm aware of is in relation to
 16 benzodiazepines or Z drugs, which are benzo-like
 17 drugs, and would agree that there are issues in
 18 prescribing those kinds of medications long term.

19 So I think, especially for people with
 20 substance-use disorders, where you don't want them
 21 to be dependent on multiple things, it might make
 22 sense to use a medication intervention for sleep

Page 70

1 for a period of time, and then also study how to
 2 transition people into cognitive behavioral therapy
 3 for insomnia or some type of other strategy to
 4 manage them long term.

5 DR. STRAIN: Ryan, then Brian.

6 DR. VANDREY: Just to kind of follow up on
 7 that piece. we've ran a clinical trial of Ambien in
 8 the treatment of cannabis-use disorder recently,
 9 and Dustin's going to get that paper out any day
 10 now.

11 (Laughter.)

12 DR. VANDREY: But what we've found there is
 13 that qualitatively, we got greater abstinence in
 14 the people that got the
 15 drug, and they had improved sleep during the
 16 initial abstinence period. And that seemed to be
 17 important for folks. But ultimately, what ended up
 18 happening is after we gave them the Ambien for 10
 19 weeks, when we tapered them off, lo and behold, the
 20 sleep problems came back.

21 So it's exactly what you're talking about,
 22 is there needs to be a treatment of the underlying

Page 71

1 sleep disorder, and a medication band-aid for
 2 2 weeks or for 10 weeks is not going to make that
 3 go away. In talking with Michael Smith and other
 4 sleep folks, it's a challenge to get them to do
 5 CBT-I while they're taking meds because the meds
 6 are taking care of the sleep problem. So figuring
 7 out that transition is one of the biggest
 8 challenges.

9 In the cannabis world, the
 10 abstinence-induced insomnia is a really big deal,
 11 and in talking with the opioid folks, it's a big
 12 deal there, too. So my sense is that sleep
 13 problems probably proceed a lot of the problematic
 14 drug use. So that's a key thing that needs to be
 15 addressed in all of this. Long-term medication use
 16 in the sleep treatment community is typically not
 17 endorsed because you have long-term issues and
 18 problems with it.

19 DR. STRAIN: Brian?

20 DR. KILUK: This is in response to some of
 21 the comments about harm reduction and thinking
 22 about clinically meaningful outcomes. Part of this

Page 72

1 is maybe asking the question in the opposite
 2 direction. One way is to think, well, we assume
 3 that if we reduce a person's opioid use, that their
 4 sleep will improve, their cognitive function will
 5 improve, and that hasn't necessarily borne out yet.
 6 But I think this is more asking it in the other
 7 way. Well, what if we improve sleep and improve
 8 cognitive function or some other aspect of it; will
 9 that then reduce opioid use?

10 So rather than asking it in one direction,
 11 asking it in the other, and I think that's kind of
 12 part of it. So maybe it's the chicken or the egg;
 13 which one comes first? I think they're still both
 14 valuable questions that are unanswered right now.

15 DR. STRAIN: Thank you.

16 I will tell you the story I had of a patient
 17 who came to me many years ago, before -- well,
 18 there's a pause. He wanted medicine to help him to
 19 sleep. He was not a drug user. I said, "Well,
 20 tell me your sleep patterns." And it turns out
 21 that he would sit in bed watching TV, eating green
 22 peppers, and drinking a 2-liter bottle of

Page 73

1 Coca-Cola.
 2 (Laughter.)
 3 DR. STRAIN: And I said, "Before we try a
 4 medicine, let's try a couple of other things." But
 5 I was a miracle worker, and he got the TV out of
 6 the room, stopped eating green peppers, and
 7 drinking Coca-Cola, a 2-liter bottle, in bed. So
 8 there's something to be said for those non-
 9 chronologic [inaudible - mic fades].
 10 DR. LEVIN: I think as a clinician, to
 11 respond to those complaints, it's often the way you
 12 bridge a relationship with the patient.
 13 DR. STRAIN: Sure.
 14 DR. LEVIN: So I think that that's part of
 15 it as well. I think that when you have somebody
 16 who comes in with an opiate-use disorder, if their
 17 major complaint is asleep, and you can address that
 18 but you're still trying to work in the treatment,
 19 whether it's psychotherapy or medication
 20 treatments, then I think it could be very helpful.
 21 Again, I'm a little skeptical about going
 22 after sleep as the prime thing with an opiate-use

Page 74

1 disorder, but I think that having it be in
 2 conjunction or something as a way to bridge into
 3 getting people either to stay in treatment or get
 4 into treatment, I think is very valuable.
 5 DR. STRAIN: Well, and for somebody who
 6 persistently reports that they feel depressed,
 7 their abstaining from opiate use --
 8 DR. LEVIN: Would be enough.
 9 DR. STRAIN: -- we would probably institute
 10 a trial of an antidepressant in them. But we are
 11 in this funny situation where somebody who may be
 12 abstaining from opiates and persistently reporting
 13 sleep disturbance, we're much more hesitant, I
 14 think, about diving into prescribing something for
 15 sleep.
 16 DR. LEVIN: I was really interested in what
 17 you talked about with sleep apnea, how much of that
 18 is pre- the opiate-use disorder versus caused by
 19 the opiate-use disorder, because there are
 20 certainly mechanical treatments for that, I guess.
 21 Is it central sleep or is it peripheral that
 22 drives the sleep apnea?

Page 75

1 DR. HUHN: It's the combination, but there
 2 are studies linking chronic opioid use to central
 3 sleep apnea, which brings up -- and there's some
 4 research in methadone-maintained patients also,
 5 clearly, because you're maintained on an agonist
 6 long term, that that might -- it's hard to say
 7 bring on the onset of apnea because probably nobody
 8 was testing for apnea before they got on methadone,
 9 but it's an issue in those patients.
 10 I think there's data that's just come out or
 11 will come out soon that methadone and buprenorphine
 12 maintained patients, their sleep hygiene is -- or
 13 their sense of sleep hygiene -- their sleep, in
 14 general, is not as not as good as the general
 15 population, on average.
 16 DR. STRAIN: It seems to me that there's
 17 interest in the topic because it is something that
 18 we do know the patients report as an issue, those
 19 who are in opiate maintenance treatment. There are
 20 some attractive features to diving into it. There
 21 is the conundrum that Ryan raised about if you
 22 treat somebody with a medicine, their willingness

Page 76

1 to engage in CBT-I, for example, may decrease, but
 2 that's a testable question.
 3 What?
 4 DR. LEVIN: It's true with depression. When
 5 you try to get people to go to cognitive behavioral
 6 therapy and they're on meds, they don't go.
 7 DR. STRAIN: Right. And it's also something
 8 that you could test, you could look at short term.
 9 DR. VANDREY: And because CBT-I takes a
 10 while, in the context of a drug-use disorder, it
 11 may be very reasonable to use a medication for a
 12 short term to initiate abstinence; get people going
 13 in the right direction, and then you work on the
 14 sleep piece.
 15 DR. STRAIN: Go ahead.
 16 DR. TOURE: I'm from the Division of
 17 Psychiatry Products. My name is Juliette. To kind
 18 of piggyback on Naomi's point, if you were looking
 19 into a sleep indication, generally, I mean -- I
 20 have a lot of questions since I'm not as familiar
 21 with the substance-use space.
 22 We're drafting a guidance related to drug

Page 77

1 development and insomnia, and there are some
 2 important points that I think are worth sharing.
 3 We would want to have a trial to have both
 4 objective and subjective measures. When you take a
 5 subjective complaint of insomnia, and total sleep
 6 time, and things like that, it's important to have
 7 an objective measure, like the PSG would be the
 8 gold standard, and then to complement that with a
 9 subjective measure. And that can come in a number
 10 of different ways that hasn't yet been
 11 standardized.
 12 So I think those are important things to
 13 think about. I think another thing that we want to
 14 understand, since a lot of times, when somebody
 15 gets started on a drug for insomnia, they usually
 16 end up taking it for a long time. So we'd want the
 17 clinical trial to reflect safety and efficacy over
 18 time.
 19 Then another consideration, in yesterday's
 20 presentation, you did a really good job talking
 21 about the various instruments now being used to
 22 measure sleep beyond just PSG, because it is very

Page 78

1 impractical sometimes. I think there's a lot of
 2 room to try to standardize how we interpret that
 3 data, so that's something that we would definitely
 4 also be interested in.
 5 DR. STRAIN: Thank you. Oh, keep going if
 6 you want.
 7 DR. TOURE: The guidance, we don't have a
 8 date in which we will have it published. It's
 9 certainly a work in progress. We're nearing the
 10 end, at least from an agency's standpoint, but
 11 certainly when it's time for the public comment
 12 period, we'll welcome the comments that you have.
 13 DR. STRAIN: Thank you. David, and then
 14 Celia?
 15 DR. SHURTLEFF: I just wanted to echo a
 16 comment made about non-pharmacologic approaches. I
 17 think granted there, the gold standard, for
 18 example, in BSR [ph] is an 8-week program with lots
 19 of practice built in, patient commitment. A
 20 program developed by Eric Garland to look at pain
 21 and opioid-use disorder is a similar program.
 22 There's some data that suggests that modest

Page 79

1 training -- for example, work by Yang, et al
 2 suggests that even 5 hours of training can reduce
 3 smoking and can reduce the number of cigarette
 4 smokes per day. Work done with clinical
 5 administered pain suggests that as little as
 6 2 hours of meditation training can reduce the
 7 intensity of the pain sensation.
 8 So I think there's an opportunity here in
 9 the non-pharmacologic space. I know that's not the
 10 focus of this meeting, but I think there are
 11 ways -- if you get the camel's nose under the tent,
 12 with some modest training in these
 13 non-pharmacologic approaches, that may be
 14 acceptable to patients with opiate-use disorder to
 15 get them started, so that when you're able to wean
 16 them off medication, maybe you can then move
 17 towards a more complete training as they progress
 18 through their treatment.
 19 So it's just a way of saying that there's a
 20 lot of work that could be done with short-term
 21 training with meditative and other kinds of
 22 behavioral approaches.

Page 80

1 DR. STRAIN: Thank you. Celia?
 2 DR. WINCHELL: I just wanted to make sure I
 3 understood the consensus, and it's [inaudible - mic
 4 not positioned]. Sleep disturbances are a concern
 5 for patients with opioid-use disorder, and that
 6 improving sleep could be a goal in and of itself
 7 just to make the patient --
 8 DR. STRAIN: Can you move your mic closer?
 9 DR. WINCHELL: -- sure -- just so the
 10 patient's more comfortable. But there also could
 11 be ways in which improving sleep could improve
 12 opioid-use disorder related outcomes; like they
 13 could remain longer in treatment.
 14 My question is, people come to us and they
 15 say we have heard that this symptom is a problem
 16 for people with opioid-use disorder and contributes
 17 to relapse. We'd like to study our drug because we
 18 think it could fix this problem. We generally say
 19 to them, you need to select for people with opioid-
 20 use disorder who have that problem, and they're
 21 always surprised to hear that.
 22 So I want to make sure that you would agree

Page 81

1 that sleep drugs would be appropriately studied in
 2 opioid-use disorder patients who complain of sleep
 3 disturbances.
 4 DR. STRAIN: Kenzie, Andrew, and Tom.
 5 DR. PRESTON: Actually, what I was going to
 6 talk about were objective measures versus
 7 subjective measures. What we're finding in our
 8 population is that for our participants, sleep is
 9 worse objectively than it is what they talk about.
 10 So there may be, in fact, undiagnosed sleep
 11 problems, that if they lead to long-term cognitive
 12 problems or whatever, we may want to think about
 13 it. I think that would, again, second my
 14 suggestion that we do more research with objective
 15 measures of sleep in our patient population.
 16 DR. STRAIN: Interesting. Andrew?
 17 DR. HUH: I agree with that. I mostly
 18 agree that -- at least this is the trial I have
 19 that's outpatient. We have criteria around you do
 20 have to be complaining of sleep disturbance to be
 21 on a sleep medication.
 22 The scenario where I don't think that's true

Page 82

1 is an opioid withdrawal study because, at least in
 2 my experience, people going through acute opioid
 3 withdrawal across the board have poor sleep.
 4 DR. BONSON: So it's prophylactic.
 5 DR. HUH: Yeah. So in that case, in the
 6 opioid withdrawal study we have, we're not
 7 accepting people who complain of sleep disturbance
 8 coming into it because they aren't in withdrawal
 9 yet. They're out, actually.
 10 DR. STRAIN: Tom?
 11 DR. KOSTEN: Great minds think alike. Thank
 12 you very much for your comment.
 13 (Laughter.)
 14 DR. HUH: If I could, going back to
 15 Kenzie's point about using more objective measures
 16 of sleep, I do kind of wonder from other people in
 17 the group as well about the growing use of wearable
 18 technologies in our clinical trials. Some of these
 19 wearable technologies are so easy to apply. Even
 20 if the study wasn't focused on sleep, per se, there
 21 are watches and rings that can measure heart rate
 22 activity throughout the day and night, and there's

Page 83

1 a lot more data we could be collecting about not
 2 just sleep, but stress and general health in our
 3 trials.
 4 So I wonder what other people think about
 5 incorporating those.
 6 DR. TOURE: FDA's perspective, I think we
 7 want to understand, I think, some of the coding.,
 8 so we welcome data to help us understand what are
 9 the coding rules that help
 10 us understand the sleep patterns?
 11 A lot of times, we all have some sort of
 12 actigraphy on our phones, or watches, or whatever.
 13 And we could just be lying down reading a book, but
 14 it might be thinking that we're sleeping. So we
 15 just need to make sure that the data reflects
 16 sleep.
 17 DR. STRAIN: Again, a quick story. I'm
 18 sorry. I wear a Fitbit, as does my daughter, and
 19 we've discovered that, actually -- does anybody
 20 else have a Fitbit here? Anybody?
 21 Have you discovered this? Folding laundry
 22 actually gives you lots of steps?

Page 84

1 (Laughter.)
 2 DR. STRAIN: My daughter now actually will
 3 go down and fold the laundry if she needs to get a
 4 few more, a couple hundred steps.
 5 (Laughter.)
 6 DR. STRAIN: Because it's like, who knows?
 7 So the programming, obviously, has got a little
 8 glitch, but Google will fix that now that they own
 9 it.
 10 DR. TOURE: Yes. We need to figure out how
 11 to marry the AI --
 12 DR. STRAIN: Yeah.
 13 DR. TOURE: -- with our results.
 14 DR. STRAIN: If we could just hold on fixing
 15 that for maybe another year or two, that would help
 16 on the home front.
 17 Tom, and then Annie.
 18 DR. KOSTEN: Just a question about the
 19 sleep, particularly during withdrawal, that when we
 20 give people clonidine, or we give them lofexidine,
 21 they don't seem to recognize, necessarily, that
 22 they're falling asleep during the daytime all the

Page 85

1 time.

2 So are you doing these sleep measures

3 24 hours a day?

4 DR. HUHN: The actigraphy we do, and we also

5 have them self-report daytime sleepiness.

6 DR. KOSTEN: No, I was thinking of that

7 device that you --

8 DR. HUHN: That's not 24 hours; that's just

9 when they go to bed. I think there might be a

10 battery issue with that.

11 DR. KLEYKAMP: I wanted to add a couple of

12 things about the technology development, and I'm

13 sure you have more here to say. When I was at

14 BPRU, we published an Ambien study. I did this

15 with Miriam Mintzer, healthy volunteers. We

16 brought them on the Ambien and maintained them for

17 a month. My focus was cognitive performance, sort

18 of an interest of mine.

19 So speaking to Matt, you have the concerns

20 of long-term maintenance, but then you have the

21 benefit of -- and we all relate to this when we

22 sleep well and maybe write better the next day, and

Page 86

1 speak more coherently at something like

2 this -- having, say, more executive function on

3 board; then for treatment or behavioral

4 interventions, it's something to look at. If we

5 were to write something up, I'd want to prompt that

6 in the discussion.

7 But also a personal use; I'm sort of

8 obsessed with my own sleep. I have an Apple 4, and

9 the technology -- I had a Fitbit for a while, so

10 the app I use now -- and I don't know if you're

11 familiar with it -- it's quite sensitive to my

12 sleep, and it bases it on heart rate, and movement,

13 and light, and I know the newest Apple watch is

14 even more advanced.

15 So I say that because I think things are

16 going very quickly with this sleep technology, and

17 I'm certain you all would support that. I feel

18 like in the next year, it could be really small

19 devices that people could use to get pretty precise

20 findings.

21 DR. STRAIN: I think we're just about up to

22 the time for the break, and I know at least some of

Page 87

1 us need to make sure we check out of the hotel.

2 Any final thoughts? Tom, is yours up there?

3 I thought there was a residual.

4 DR. KOSTEN: Yes, that one of the things

5 that maybe we should think about is we were doing a

6 study in geriatric patients, where we gave them a

7 gift of a Fitbit like thing, and ours was the cheap

8 kind we got from China that only cost like 15

9 bucks, but it worked reasonably well.

10 But a number of them were getting opiates

11 for various kinds of pain. We just got some of the

12 weirdest -- they don't recognize when they're

13 falling asleep. I know I fall asleep during these

14 meetings, and other people recognize it, but I

15 don't.

16 (Laughter.)

17 DR. STRAIN: Yes, we have been.

18 (Laughter.)

19 DR. KOSTEN: As I was thinking about this,

20 24 hours a day, opiates put you to sleep during the

21 day, I think. If you just think about sleep

22 disruptions during the night, I'm afraid you're

Page 88

1 missing a whole bunch of stuff that's going on.

2 DR. STRAIN: No, that's a great point.

3 Well, thanks. We have about a 15-minute

4 break. We do have some snacks. After the break,

5 what we'll do is we'll do 45 minutes on

6 psychedelics and then 45 minutes on vaccines.

7 Lunch, actually, we're going to have sandwiches

8 available back where we had breakfast. But what

9 we're going to ask is that you go down and grab

10 your sandwich, bring it back here, and we'll do a

11 wrap up, kind of big picture thing, around like

12 12:15, start around 12:10 or 12:15. But in the

13 meantime, let's go ahead and take a break. Thanks.

14 (Whereupon, at 10:14 a.m., a recess was

15 taken.)

16 Group Discussion - Psychedelics

17 DR. STRAIN: I got distracted with the

18 conversations. Others will be hopefully wondering

19 again, but I am trying to keep us somewhat on

20 track.

21 We are now going to talk about psychedelics.

22 As I mentioned before, a similar sort of

Page 89

1 conversation. I think there are a lot of similar
 2 aspects in terms of themes that will probably come
 3 up as we talk about this, but it will be certainly
 4 useful to go through it.
 5 Matt, I wonder if you had any opening
 6 thoughts that you wanted to convey. Again, I don't
 7 mean to put people on the spot, but just because
 8 you're the expert and presented yesterday.
 9 DR. JOHNSON: It sounds like there's a lot
 10 of interest, which is reinforcing and exciting. I
 11 think the major issues, we just need a lot more
 12 work in this area. There's been a strong trend of
 13 more folks jumping into this research with
 14 psychedelics, so I hope that continues.
 15 There are a million questions. We need to
 16 be completely data driven. We need to consistently
 17 be mindful of the risks and safety factors at play
 18 in the research. Yes, we need more research.
 19 DR. STRAIN: Good. Thanks.
 20 (Laughter.)
 21 DR. TURK: You're supposed to say more and
 22 better research.

Page 90

1 DR. JOHNSON: Yeah, right.
 2 DR. STRAIN: More and better research.
 3 DR. BONSON: You're supposed to say, "Please
 4 fund us."
 5 DR. JOHNSON: Yeah, that's the real -- what
 6 I said was code for that.
 7 DR. STRAIN: There's a streamer going below
 8 his table saying, "Need funding. Please fund us."
 9 DR. JOHNSON: Money, please.
 10 DR. STRAIN: This is open for discussion.
 11 Yes, Celia?
 12 DR. WINCHELL: I wanted to circle back to
 13 some of the discussion yesterday. A lot of people
 14 seem to agree that if a psychedelic or psilocybin
 15 like product were to be marketed as a
 16 pharmaceutical, your ideal situation would be that
 17 there would be some type of FDA enforced REMS that
 18 would limit the context of use to specific
 19 providers and settings.
 20 What I wanted to ask you to expand on was
 21 how we would articulate what the risks were for use
 22 outside of those settings because we have to

Page 91

1 articulate, when we require a REMS, the elements to
 2 assure safe use, the serious risks that would
 3 happen if somebody did it wrong.
 4 Sometimes I hear people kind of talking out
 5 of both sides of their mouths, like, really,
 6 psychedelics are fine, but also if you want to use
 7 them therapeutically, you have to be super, super
 8 careful. So we are going to need your help in
 9 articulating these risks in a way that would
 10 support the type of groups that you envision.
 11 DR. STRAIN: Michael, and then Matt, and
 12 then Kit.
 13 DR. BOGENSCHUTZ: I wanted to circle back to
 14 the issue that came up in when we were talking
 15 about cannabinoids, that Sandy, and Frances, and
 16 others articulated, about the fact that it's
 17 potentially life threatening for people not to be
 18 on a mu agonist or antagonist. I think the same
 19 issue comes up with the psychedelics, unless they
 20 turn out to be really miraculously effective, which
 21 we are not counting on at this point.
 22 There's really three ways of dealing with

Page 92

1 that. One is that you administer the psychedelic
 2 at a moment in treatment when the person is
 3 detoxified, and then you don't have to worry about
 4 the drug-drug interactions. You can do that with
 5 psychedelics, unlike most other drugs, because it's
 6 an episodic treatment. You do it in a day, then
 7 they can be on whatever their preferred medication
 8 is.
 9 The second is to do it concurrent with their
 10 treatment with Vivitrol or a partial agonist. We
 11 need to know a lot more about drug- drug
 12 interactions in both directions, how having the
 13 opioid on board might affect the experience and the
 14 acute effect, and the persisting effect.
 15 Then the third, which I think is maybe even
 16 more dicey than with cannabis, is the idea of
 17 finding a population who really is adamantly
 18 refusing the first-line treatments, and then
 19 feeling okay about that. But I can't get there,
 20 especially with these drugs, such as psilocybin,
 21 where there's so much hype about expectations about
 22 how it's going to work.

Page 93

1 It's hard to imagine not overtly or covertly
 2 creating the impression of why don't you try this
 3 cool new thing instead. Ethically, I think that
 4 the big problem. Post-detox, pre-Vivitrol is one
 5 idea that I've been developing. Randy Brown, who
 6 was here yesterday, is working on co-administration
 7 with buprenorphine, and Hopkins has been working on
 8 designs, too.

9 I think, practically speaking, we need to
 10 find a way to integrate it into treatments that we
 11 already know work and save lives.

12 DR. STRAIN: Thanks. Matt, Kit, and then
 13 Rob.

14 DR. JOHNSON: Regarding the risks in the
 15 wild, so to speak, speaking out of both sides of
 16 the mouth, it's tough. We just have to
 17 consistently describe the nuances. It's difficult.

18 I'd refer people to a recent paper that
 19 Peter, and Jack Henningfield, and Roland and myself
 20 published, really, revealing everything we know
 21 about the abuse liability, risks, and harms of
 22 psilocybin, in particular.

Page 94

1 It's true that there are some promising
 2 preliminary findings that we should follow up on.
 3 It's also true that in the realm of illicit use,
 4 the harms consistent of that drug class,
 5 consistently rank towards the bottom. And it's
 6 true that there are harms, but compulsive drug
 7 seeking doesn't appear to be one of them. But it's
 8 also true that people appear to be psychiatrically
 9 harmed. That's probably interacting with
 10 vulnerability. It's true that there are accidents,
 11 sometimes fatal.

12 So all of these things can be true at the
 13 same time, so I think we have to just be completely
 14 data driven. I never give a talk to any audience
 15 without spending some time, typically at the
 16 beginning, about what we know about the real risks
 17 and what we do to address those.

18 I beg every time I talk to a journalist, and
 19 it's largely successful. It's like, "Please say
 20 we're not encouraging use. Please mention that
 21 there are risks, and that the way we're doing it
 22 addresses what we know about the risks." So I

Page 95

1 think that's all you can do.

2 DR. STRAIN: Kit, Rob, and then Eric, and
 3 then David.

4 DR. BONSON: I think I'm going to respond to
 5 Matt, actually, first before I get to the other
 6 comment. I think what's unique about the history
 7 of psychedelics is that the community that was
 8 using them was very invested in making sure that
 9 people didn't have a bad time. So the concept of
 10 set and setting came out of the community, the
 11 people who are using these drugs. It didn't come
 12 out of the researchers who were doing it,
 13 necessarily; it was already in place.

14 So there are also ways that -- the community
 15 kind of took care of itself in large part, so that
 16 when there were disturbances that people were
 17 getting to, they kind of were -- they're like
 18 manuals back from the '60s, where it helps you
 19 understand how to help your friend who's having a
 20 bad trip. So the reason that people may not have
 21 been showing up in emergency rooms could be because
 22 that community, unique among any other drug-using

Page 96

1 community, was invested in that perspective.
 2 That's kind of an odd thing about this category of
 3 drugs.

4 The thing I really wanted to say, though,
 5 Celia, I wonder if you can speak more about what is
 6 possible in terms of REMS because we, obviously, at
 7 FDA do not regulate the practice of medicine, and
 8 yet there are things that can go into a REMS that
 9 sort of sounds like regulating practice under the
 10 name of safety.

11 So I wonder if you can elaborate on that.
 12 And then, there was a question posed to me
 13 yesterday about there may be a really great REMS
 14 for the originator drug, but what happens when a
 15 competitor comes out after a number of years? How
 16 much of that is maintained or could they change it?

17 Could you speak to some of those
 18 possibilities? I'm not sure about the law as well
 19 as you are.

20 DR. WINCHELL: I can when Eric --

21 DR. STRAIN: Why don't we break out of the
 22 sequence? Yes, I'll take that prerogative.

Page 97

1 Celia, if you want to respond to that? And
2 then we'll go to Ron, Peter, maybe me, and David.
3 I don't know. I may step out of the role of
4 moderator.
5 DR. WINCHELL: REMS are not really my area
6 of expertise, but I have some experience with them.
7 I would say that the closest parallel in my
8 personal experience to what you're sort of
9 describing for the ideal situation for
10 psychedelic-assisted treatment would be the
11 probuphine story.
12 Probuphine is an implantable buprenorphine
13 that has to be put in place through a surgical
14 procedure. Our surgery colleagues, with a lot of
15 experience in the implantable contraceptive field,
16 identified a number of extremely concerning adverse
17 events that had been associated with these types of
18 drugs: migration out of the arm into the lung;
19 embolism; nerve damage; all kinds of bad stuff that
20 had been happening with these types of products,
21 despite the fact that these drugs are administered
22 by people who are trained as surgeons.

Page 98

1 So under the probuphine REMS, we created a
2 requirement that the drug could only be inserted by
3 people who had been trained to do that insertion
4 and removal.
5 You kind of have to lock down the pathway to
6 make sure that the drug only gets into the hands of
7 the people who are appropriate to use it. You can
8 certify facilities. Only specific facilities are
9 allowed to administer the drug. Only specific
10 pharmacies are allowed to dispense the drug or at
11 least specific individuals. You can create these
12 systems, and they have to be closed distribution.
13 But there's pharmacy certification, or practitioner
14 certification, or institutional certification. All
15 of these are possible.
16 What happens after the drug goes generic,
17 the generic drugs are actually marketed under
18 comparable REMS. They're supposed to all cooperate
19 on one, but we've given some waivers to that
20 requirement when necessary.
21 Does that help?
22 DR. BONSON: Could you argue that some of

Page 99

1 these REMS for generic were anticompetitive?
2 DR. WINCHELL: That has been an issue, is
3 that people had been using these REMS to block
4 competition, but that's been addressed, I believe.
5 DR. BONSON: Can you explain how?
6 DR. WINCHELL: Well, certainly in one case,
7 we authorized the creation of a separate but equal
8 REMS for the generic products and other products
9 because the innovator wouldn't play ball. But for
10 the most part, I think that people have managed to
11 get those REMS working.
12 DR. STRAIN: Thank you. Let's go back to
13 Rob, Peter, and David.
14 MR. BARROW: Building off the comments that
15 were just made, one of the challenges that we
16 certainly see -- and Usona's primary program being
17 for the treatment of major depressive disorder with
18 psilocybin. But one of the biggest challenges we
19 see is there are over 17 million people with
20 depression. Then if we talk about use disorders,
21 and all of the studies of the Hopkins folks and
22 others, and Michael have done, the potential

Page 100

1 patient population that could have access to
2 psilocybin, for instance, upon approval, is
3 astronomical. Even if you just look at the folks
4 who are taking antidepressants who might be
5 eligible, it's more like 30 million people.
6 So we very much embrace and endorse the idea
7 that this needs to be rolled out in tightly a
8 controlled, secure way. A very well-informed,
9 controlled REMS is going to be a critical component
10 of that. As I alluded to yesterday, I think it's
11 going to require a multipronged approach, both from
12 FDA and from practitioners, and delivery, and
13 training to really prepare the system to roll this
14 out, if it ultimately gets approved.
15 I think the challenge we face is how do you
16 offer a new medication for these major problems,
17 and tightly control it, but scale it in a way that
18 more than a hundred people can get it? It doesn't
19 quite make sense to say we're going to treat these
20 major public health issues, but the delivery has to
21 be so tightly controlled that it's going to be
22 virtually impossible to scale.

Page 101

1 The comment I think Kit and I were talking
 2 yesterday about, or just exploring, I was asking
 3 these general questions. Where is that done,
 4 because the work we do under our IND and
 5 Hopkins -- those are our INDs -- and all of us are
 6 in agreement, there's a clear need for significant
 7 provider involvement, including doctoral level,
 8 psychotherapists, effectively, who are in the room
 9 during a dosing session, who are involved prior to
 10 administration of a psychedelic, and then have
 11 follow-up visits.

12 The healthcare system doesn't seem
 13 particularly great at handling delivering therapy.
 14 If we're going to have an impact on these large
 15 populations, how do we do it if it requires
 16 50 person-hours per treatment? These are some of
 17 the biggest questions I think we faced if,
 18 ultimately, psychedelics are successful at
 19 obtaining approval. It needs everyone's greatest
 20 minds thinking on this. It's not going to happen
 21 in isolation.

22 DR. STRAIN: I will conveniently not answer

Page 102

1 all those questions, but go on. And it will be
 2 Peter, and David, then Michael, I think, and then
 3 Matt.

4 DR. HENDRICKS: I just wanted to provide a
 5 little backdrop, too, because the psychedelics are
 6 really quite unique. Some medical historians and
 7 others have argued that they might be the very
 8 first psychoactive substances that humans ever
 9 used, and there's, I think, some convincing
 10 archeological, anthropological evidence indicating
 11 that humans have used these substances, or I should
 12 say these psilocybin [indiscernible] mushrooms,
 13 many thousands of years ago in a very highly
 14 ritualized context. So there seem to be some
 15 awareness, from what we can gather, that they
 16 needed to be handled with extreme caution and care.

17 In the same way that we know folks are out
 18 there in the natural environment using cannabis, it
 19 appears as if folks are out there in the natural
 20 environment using psychedelics. Some of the
 21 research would indicate, at the population level,
 22 there seems to be evidence of benefit. We're

Page 103

1 careful in implying causation. But of course, like
 2 anything, there are certainly risks.

3 So what we are offered in this really unique
 4 position of almost, always having to be very clear
 5 that we're not advocating for use -- and not only
 6 our interviews with media but in our publications
 7 in some cases. I'm not sure that many other people
 8 are in that sort of position, where they have to be
 9 very clear about that.

10 We know that for many thousands of years,
 11 humans have used these substances, it appears, in a
 12 therapeutic manner, and that continues to take
 13 place in some indigenous older traditions. In the
 14 case of Avahuasca and peyote in the Native American
 15 church, and now we know that there are some
 16 decriminalization initiatives in Denver and
 17 Oakland; perhaps you've heard of these.

18 Though many of us who work in the world of
 19 addiction aren't fond of the idea of
 20 criminalization of drugs, in general, we do have
 21 some concerns about these initiatives and what
 22 might happen as a result.

Page 104

1 That said, I do think there are
 2 opportunities to evaluate what's happening in the
 3 real world and to get a better sense of risks from
 4 that perspective as well. It seems, no matter what
 5 happens on the drug development side, that people
 6 are going to continue to use these substances for
 7 therapeutic intent, and that's something we have to
 8 keep in mind.

9 DR. STRAIN: Thank you. David, Michael,
 10 Matt, Tanya, and Roger.

11 DR. SHURTLEFF: Just a couple of points.
 12 Here we go again, Right? We're following the
 13 cannabinoid, the cannabis story here, where Oakland
 14 and Denver have decriminalized these hallucinogens.
 15 That is both a risk and an opportunity to get some
 16 observational data about what's happening in the
 17 real world.

18 I will say, speaking for NCCIH, this is an
 19 area we're interested in pursuing for various
 20 conditions. We're primarily interested in chronic
 21 pain, intractable chronic pain, but of course
 22 others would be of interest.

Page 105

1 But I think, harking back to the comments
 2 about the feasibility or practicality of using this
 3 therapeutically, the time and intensive nature of
 4 this approach with the psychotherapy and the
 5 pharmacology may make it a limited availability to
 6 many patients because of the labor force.
 7 We're dealing with that with
 8 non-pharmacologic approaches. We know that some of
 9 them work quite well for pain, but we don't have
 10 the labor force to implement this kind of approach
 11 broadly. I think that's going to be a limiting
 12 factor, potentially, for these psychedelics and
 13 treatment. I imagine they would be third tier or
 14 something like that, but maybe that's a comment,
 15 that someone could comment on that.
 16 I think, too, I can't overstate, as we see
 17 with CBD now, as somebody mentioned, it's in your
 18 coffee. I would hate to see us go back to the
 19 '60s, where it's become popularized to a point
 20 where it's misused again, and we're back where we
 21 started several decades ago because we're back to
 22 the future now. I think in the '50s, there was

Page 106

1 productive research and general consensus that
 2 there was some benefit for these, and then of
 3 course the '60s, the counter-culture changed all
 4 that. I'd hate to see us go back there again.
 5 Then just a final thought, I don't know if
 6 there are any lessons learned from the roll out of
 7 ketamine for treatment of depression, but I'm
 8 wondering if that's sort of a model that might be
 9 thought about as we move forward with this
 10 approach.
 11 DR. STRAIN: Thank you. Michael, Matt,
 12 Tanya, Roger, and Rob.
 13 DR. BOGENSCHUTZ: I wanted to just kind of
 14 broaden the scope of the discussion for a moment.
 15 We've really focused on primarily psilocybin and
 16 getting to clinical applications in opioid-use
 17 disorder, which is important and kind of the most
 18 immediately, clinically relevant question, and one
 19 that we're all interested in.
 20 But classic psychedelics broadly
 21 are -- they've been neglected for, really, 50 years
 22 now. The amount of research that's been done

Page 107

1 compared to any other class of drugs is vanishingly
 2 small, and obviously it's growing astronomically
 3 now. The basic animal studies that have been done
 4 for all other pharmacology treatments that we're
 5 developing for addiction for the most part haven't
 6 been done.
 7 Earlier this year, the first
 8 self-administration study for LSD and alcohol was
 9 published. The effect was there, but those studies
 10 haven't been done. We're focusing on psilocybin,
 11 but, obviously, there are hundreds of other
 12 compounds, and some of them may have unique
 13 attributes, which would make them as good or better
 14 targets for drug development.
 15 Another set of compounds are the
 16 non-psychedelic psychedelics, or structural analogs
 17 that don't have the pronounced psychoactive
 18 effects. For example, 18-MC is a ibogaine analog
 19 that appears to be safe, relatively
 20 non-psychoactive, and very effective in animal
 21 models of addiction. BOL-148, brom LSD, is another
 22 drug that hasn't been studied in terms of

Page 108

1 addiction, but may be effective for headache, and
 2 is being developed there.
 3 The fourth, which may not be what we're
 4 going to pursue here, is non-psychedelic doses of
 5 psychedelics, micro doses, which have become
 6 fashionable, but there's absolutely no real
 7 evidence about use of that. So there are a lot of
 8 different directions, as we're earlier in the
 9 pipeline of drug development, I think we should be
 10 exploring.
 11 DR. STRAIN: Thank you. Matt, Tanya, Roger,
 12 Rob, and Kit. I'm going to start just saying who
 13 isn't on the list.
 14 (Laughter.)
 15 DR. JOHNSON: We're all shooting for -- have
 16 very, very similar goals, but still active
 17 discussion of how to get there. I sort of argue
 18 that having a requirement of a doctoral level
 19 clinician in the room is in the realm of overreach
 20 that might keep this out of folks -- there might be
 21 overregulation that makes it too expensive.
 22 So I think along the ideas of -- there are

Page 109

1 areas of medicine and in clinical psychology where
 2 you don't need to be -- you could be a graduate
 3 student in psychology and reporting to a licensed
 4 therapist, but not everyone who's doing therapy
 5 needs to have -- there needs to be someone with
 6 those credentials overseeing the process. I think
 7 of nurse practitioners and physicians' assistants
 8 and that there is someone with the fuller
 9 credentialing above them.

10 I kind of think about it this way. Not
 11 everyone in the operating room needs to be a
 12 surgeon; but relatively minor detail. There are a
 13 lot of these. That's just one example of many
 14 parameters that we need to work out.

15 Ketamine lessons, that came up. I think,
 16 gosh, one of the big things is really watching the
 17 off-label use of ketamine. Relatively speaking,
 18 the REMS with esketamine is real keeping on the
 19 track, and it's a world of difference compared to
 20 what's happening off label than esketamine.

21 That said, it would also be very interesting
 22 to see ketamine treated -- and there are just some

Page 110

1 straight up experiments to wrap around this -- as a
 2 medication, facilitated psychotherapy like a
 3 psychedelic. Who knows whether we could get those
 4 antidepressant effects to last longer.

5 Just to reinforce what Michael said about
 6 the really interesting prospect of these
 7 non-psychedelic psychedelics, there are a number of
 8 scaffolds that can be built, and we're learning so
 9 much about structure activity relationships and
 10 biased agonism. David Olson at UC Davis has some
 11 really interesting data on multiple mechanisms for
 12 neuroplasticity in the cortex that he's seeing with
 13 non-psychedelic analogs.

14 So this might be in the same category of do
 15 you get with 18-MC or noribogaine the normalization
 16 of dopamine in the mesolimbic? So it could be
 17 there's this [inaudible - mic fades] or kind of
 18 directly biological mechanisms that are at play
 19 with the psychedelics. We should be pursuing all
 20 of these threads.

21 My best guess is that the long-term effects
 22 that we're seeing, and our correlational data

Page 111

1 across the field, suggests that there is something
 2 about the subjective experience that is
 3 causing -- perhaps that's the
 4 suggestion -- long-term effects, and people learn
 5 something. This is more in the realm of learning,
 6 what you would normally get from a psychotherapy,
 7 so the experience is probably important for those
 8 long-term outcomes.

9 But it may be that in the first several
 10 days, it's called an afterglow, this more kind of
 11 direct biological effect, where you have this
 12 increased neuroplasticity, or whatever mechanism,
 13 and you could get that perhaps without the
 14 psychedelic effect. And maybe you have models
 15 where you get one, the other, and perhaps you get
 16 the best from both.

17 Anyway, a million directions, and you need
 18 data for all of it.

19 DR. STRAIN: Thank you. Tanya?

20 DR. RAMEY: I just wanted to make a
 21 suggestion. As we are entering this route of
 22 research, it's really important to pay attention to

Page 112

1 deep phenotyping. There are batteries, deep
 2 phenotyping batteries, that they developed at
 3 NIAAA, and also NIDA is developing expanded deep
 4 phenotyping battery, which includes all levels of
 5 cognition, not only executive.

6 So there will be interception, and there
 7 will be measures of social cognition. For
 8 psychedelics, it's really very important because
 9 that's where the action occurs. That will be
 10 really important to see what's happening with the
 11 interception, how it changes, and how social
 12 cognitions change, and not only like executive; we
 13 need to have a full spectrum.

14 So this battery is like a short term.
 15 They're composed to be tolerable. In terms of
 16 feasibility, they take less than 2 hours, and
 17 they're all on iPads. So you might want to
 18 consider that because you need to have that full
 19 picture of who is entering and what the changes
 20 are.

21 The other thing is a follow-up to what Celia
 22 was saying. They need to know the risks. With

Page 113

1 these types of drugs, there could be risks that
2 would appear down the road, and not only a bad trip
3 but also other risks.
4 DR. STRAIN: Thank you. Roger, Rob, and
5 Kit.
6 DR. WEISS: My question is a different type
7 of question, which has to do with the mechanics of
8 doing the research, which is the idea of a placebo
9 control. It's my understanding that you try to
10 talk people into believing that if nothing's going
11 on, that that's a possibility. They could be
12 bored.
13 What I don't understand is [inaudible - mic
14 fades] -- with the active drug, it's like you can't
15 possibly believe that you might have gotten a
16 placebo, and I would think that for most people, it
17 would be really hard to believe -- it'd be very
18 tough to blind it, is what I'm saying. I just
19 wonder what your experience is with that.
20 DR. JOHNSON: Should I answer that?
21 DR. STRAIN: Yes, Matt. Go ahead and answer
22 that, and then we'll go back to Rob.

Page 114

1 DR. JOHNSON: We have done a number of
2 things and things are happening currently. In the
3 first study Roland published, he used a really high
4 dose of methylphenidate in people with no
5 psychedelic history and collected data. Even the
6 lead therapist in those sessions, who had conducted
7 hundreds of psychedelic therapy sessions back in
8 the '60s, was fooled; I think it was something like
9 a quarter of the time in terms of not guessing
10 correctly.
11 So there are things you can do. Currently,
12 both Michael and Peter are running studies with
13 diphenhydramine, a high dose as an active placebo.
14 There's the use of lower doses of the drug. I
15 thought in the smoking cessation work, the next
16 step, in terms of really convincing me in terms of
17 whether it's going forward, after the open-label
18 was comparative efficacy, so keep randomization and
19 don't worry about the blinding yet; that's for the
20 next step.
21 We have evidence in healthy normals that
22 there's a real pharmacology; it's not just all

Page 115

1 placebo effect. I think the ultimate answer comes
2 through a triangulation. And there are things that
3 can be done -- nothing's perfect -- to address this
4 blinding question.
5 DR. STRAIN: Thank you. Rob, and then Kit.
6 MR. BARROW: I think Kit probably has
7 comments, too.
8 DR. BONSON: Go ahead. I've got a number of
9 things to talk about now.
10 MR. BARROW: Not to turn it all back to the
11 delivery side of things, I think FDA has been very
12 clear in thinking about methodological aspects of
13 it. Even where there are challenges such as
14 blinding, there may not be one perfect answer, and
15 it may be different by indication that you're
16 studying based on the effects of a comparator.
17 I think one of the things for this group in
18 particular, I think the model of esketamine got
19 brought up, and that's particularly interesting.
20 The REMS for esketamine mandates that you're under
21 observation for 2 hours, which there's a clear risk
22 identified, so there's a clear need for a REMS.

Page 116

1 I think what the field would probably
2 benefit from is a testing of the bounds of this set
3 and setting and heavy therapists -- we call them
4 facilitator involvement -- to understand whether it
5 is a risk or not. And I'm by no means advocating
6 one way or the other, but just that it's a question
7 that needs to be empirically tested; not
8 necessarily for us to try to do away with some
9 component of that, because in an ideal world, I
10 think all of us would say anyone with depression,
11 it'd be great to have heavy therapy as an adjunct
12 in any of these conditions.
13 However, thinking about scalability and
14 thinking about potential use, it would be
15 interesting to see groups like Hopkins test the
16 bounds of this and see can psilocybin administered
17 safely and effectively with a rolled-back kind of
18 model of facilitation or guiding that in the real
19 world may be more scalable. It may not be the gold
20 standard, but it may be still safe.
21 DR. STRAIN: Thanks. Kit?
22 DR. BONSON: I have a bunch of things here.

Page 117

1 In the question of placebo versus blinding, I would
 2 argue that most psychoactive drugs that we
 3 administer, you can tell whether they're on them or
 4 not. There are always going to be the adverse
 5 events that people don't like: SSRIs, sexual
 6 dysfunction, TCAs, being unable to urinate
 7 properly. There are all kinds of things that are
 8 possible and can go on.

9 Blinding is less of a concern to me as a
 10 regulator because what I want to know is does this
 11 actually show efficacy? There are all kinds of
 12 strategies. You can do low dose versus high dose,
 13 but if both of them are the same or neither of them
 14 work, then you've done a study, and you have no
 15 idea against placebo what's going on. So I would
 16 still, personally, advocate for placebo, but there
 17 are lots of different strategies that FDA will
 18 allow and consider.

19 About obscure psychedelics that people are
 20 interested in doing, great, but the thing is,
 21 there's a whole lot of work that needs to happen
 22 before they can ever get into a person. There's a

Page 118

1 lot of toxicology that has to be done. There are
 2 only a limited number of psychedelics with an
 3 extensive clinical history back 50 odd years ago,
 4 where we felt like it was safe enough that it could
 5 go into a person in an IND, but that doesn't
 6 obviate the need for having to do all those tox
 7 studies later on. There's just a whole lot more
 8 work for drugs that we're not familiar with yet.

9 The other thing I want to address is the
 10 history of why the psychedelics went away. There's
 11 this mythology -- and numerous people in this room
 12 have heard me say this before, and I did a whole
 13 paper on this -- that it went away because of the
 14 mean old '60s.

15 There's something to do with maybe your
 16 institution didn't want to have the association,
 17 but I think that the real reason that this happened
 18 is because of the data that were being generated,
 19 and there were a lot of people in the '60s who
 20 wanted to continue doing research that they'd been
 21 doing in the '50s, but there was a change in the
 22 law.

Page 119

1 In 1962, there were amendments to the Food,
 2 Drug, and Cosmetic Act that instituted the IND
 3 system that we have, and one of the main things
 4 that you had to do was to get the chemistry, and
 5 nobody could get the chemistry right to get the LSD
 6 because Sandoz had it all.

7 So that just eliminated a lot of it. Then
 8 the people who could get it were doing studies that
 9 were interesting, but they were not always to the
 10 highest quality science. his was known even at
 11 that time, that people were saying, "Yeah, this
 12 isn't --" the people who were doing it were going,
 13 "This isn't the greatest research."

14 So what happened is that in the '60s and the
 15 late '60s, NIMH, who was the main funder of this
 16 and the access point for LSD at that point, said
 17 this is not going well. We've invested many
 18 millions of dollars. There were congressional
 19 hearings about how wonderful this could be and
 20 what's going on, and it was not showing the
 21 research outcomes that people wanted.

22 Then the death note came in 1975, when it

Page 120

1 was revealed that the government had been given LSD
 2 illicitly to a lot of people without their
 3 knowledge. So NIMH just said that's it; we're out
 4 of this. But there were people that were
 5 continuing on to do this research through 1987, and
 6 then the DMT started up in 1990.

7 So there's a lot of reasons why we want to
 8 do the studies right this time, based on, let's
 9 call it pilot data, or understanding how the '60s
 10 should be interpreted. Okay. That's a lot.

11 DR. STRAIN: Thank you. I think we'll go
 12 about five more minutes or so. I don't have
 13 anybody on my list, so let me just say, I want to
 14 kind of reorient us back. It's a really
 15 interesting discussion, a lot of broad ranging, but
 16 there are two things that actually were brought up
 17 very early in this conversation that I think it
 18 would be good to return back to.

19 One was Celia's question about the REMS. I
 20 don't think we really answered that. We kind of
 21 alluded to it, the esketamine REMS and things like
 22 that. The other was Michael's comment early on

Page 121

1 about opiate-use disorder, which is what we're
 2 supposed to be talking about.
 3 Where does this fit in, in terms of like, is
 4 it something that's done post-detox? Is it done
 5 during treatment with an agonist? Should we be
 6 doing this because we've got effective therapies
 7 out there? I've got thoughts as well I could add
 8 to that about it. But I think that's also
 9 something to get us back focused on the opioid use.
 10 Any thoughts about either of those, specific
 11 thoughts to Celia on the REMS, or the FDA -- not to
 12 personalize it -- or how it fits into opiate use.
 13 Tom, and then Sandy.
 14 DR. KOSTEN: I think how it fits into opiate
 15 use is probably the most critical question because
 16 I don't really see how you can possibly, in good
 17 faith, take somebody who's an opiate user and not
 18 put them on something that's going to prevent
 19 overdoses, whenever. They've got to be on
 20 buprenorphine, methadone, or naltrexone, or maybe a
 21 vaccine, but they've got to be on something.
 22 Now, on the other hand, that many of these

Page 122

1 patients have craving that continues on all of our
 2 existing treatments is an interesting question.
 3 Craving is not an outcome that anybody wants to
 4 face up to, clearly, but if you look at what
 5 happens with these treatments, it seems like once
 6 you're stabilized, for even a couple of weeks on
 7 some kind of treatment, whether it's any one of
 8 those four, thinking about doing this with patients
 9 who still feel uncomfortable, and craving, and may
 10 in fact relapse one way or another by discontinuum,
 11 that would be a reasonable population.
 12 But as a first-line treatment, I don't see
 13 it, and as my rather provocative suggestion of
 14 giving it during detox, as far as that goes, it's
 15 hard to not agree with the medication director of
 16 NIDA to say, "What a perfect way to produce a bad
 17 trip," meaning it probably wouldn't work for that.
 18 That sort of where we fit in.
 19 As far as the REMS goes, though, I'm just
 20 concerned on the REMS, how enforceable is the REMS
 21 program? I don't know of any teeth that it has in
 22 it, and I certainly know what's going on in Houston

Page 123

1 with ketamine. All of the clinics that were giving
 2 intravenous ketamine before are continuing to give
 3 intravenous ketamine, and none of them are
 4 psychiatrists. They're all docs that just inject
 5 you, and you walk out the clinic, and that's it.
 6 So first off, the REMS doesn't apply to
 7 them, but I don't understand how the REMS is going
 8 to be enforced with the private practice people in
 9 the community that don't have CARF and don't have
 10 JCAHO. They're just doing it, and maybe FDA can
 11 answer that question; how do you do that? So those
 12 are my two comments.
 13 DR. STRAIN: Sandy?
 14 DR. COMER: I agree with what Tom is saying,
 15 and I think something that Mike said really
 16 captured my attention because I think that's a
 17 really nice compromise in terms of giving
 18 psilocybin to somebody who's a stable patient on
 19 Vivitrol. We know that there's a certain relapse
 20 rate after several months of treatment, so in that
 21 situation, you could give the medication, I don't
 22 know, after 2 or 3 months of treatment with

Page 124

1 Vivitrol, and then hope that the patient stays on
 2 Vivitrol.
 3 But then for the ones who relapse, it's not
 4 your fault. There's nothing that we're doing to
 5 increase the risk of overdose; it's the patient's
 6 decision to stop, and, hopefully, the treatment
 7 with psilocybin would reduce the risk of relapse;
 8 and if they do relapse, that the use will be lower
 9 or whatever. That's a situation, I think just
 10 clinically, where it seems like it would meet the
 11 ethical concerns.
 12 DR. STRAIN: Matt?
 13 DR. JOHNSON: And fortunately, everyone
 14 who's thinking about this that I know of, and the
 15 discussion surrounding it, and the stuff that we've
 16 been thinking about for years, they all fall in
 17 this category; so an agonist treatment or
 18 antagonist treatment being part of the mix, and
 19 being very mindful about the loss of tolerance and
 20 pushing people away from effective treatments.
 21 I'll tell you, it's not easy. The folks,
 22 including the philanthropists that have funded this

Page 125

1 and many of the people supportive of this work,
 2 it's like they don't get it. You've got to fight
 3 against this, "Well, people are still addicted,"
 4 and it's like you haven't really addressed when
 5 someone has a psychedelic, they're going to be
 6 liberated. It's like, no; people die. They lose
 7 their tolerance.
 8 Fortunately, right now, it seems like
 9 everyone is approaching this very mindfully. With
 10 respect to REMS, the IV use of ketamine is not
 11 falling under the Spravato REMS, so I think that's
 12 part of the answer there because that's been
 13 approved for treatment for decades, and they're
 14 using it off label. It was approved as an
 15 anesthetic.
 16 So as far as I know, some of these things,
 17 GHB has had a really good track record in terms of
 18 diversion and abuse; the sodium oxybate, Xyrem
 19 formulation.
 20 I have a question for folks here. I know
 21 the restrictions on methadone, in particular,
 22 preexists the whole concept of REMS. Is that

Page 126

1 directly legislatively mandated? And if so, maybe
 2 part of that is what we're dealing with, what could
 3 be part of the future here; so multiple mechanisms,
 4 including REMS and beyond, that could help to keep
 5 this safely contained.
 6 DR. STRAIN: So we're going to need to wrap
 7 up because we've run over a little bit because we
 8 started a little late a little bit.
 9 Celia, there was something directed towards
 10 an FDA question or a couple there. I don't know if
 11 you had a thought or not, and if not, I'll wrap --
 12 DR. WINCHELL: Nothing definitive.
 13 DR. STRAIN: Okay. Let me take the
 14 prerogative, as the moderator, to just say I've
 15 been struck by how, with respect to opiate-use
 16 disorder, we've been moving more and more toward a
 17 model where we give people a medication to
 18 hopefully decrease their opiate use and decrease
 19 their risk of using illicit opioids, but we're
 20 really not focusing much on trying to get them
 21 better as people to have meaningful change in their
 22 lives.

Page 127

1 I think that's really what we want to do as
 2 healthcare providers, is we want people to be more
 3 fulfilled in their lives. I'm not getting choked
 4 up on the point; it's a peanut.
 5 (Laughter.)
 6 Group Discussion - Vaccines
 7 DR. STRAIN: I see this as an opportunity to
 8 perhaps do that, which is what intrigues me. I
 9 don't think, Matt, I've told you this. I ran into,
 10 a few weeks ago at a social function, a
 11 cardiologist who was a care provider for a patient
 12 who had been through one of the psychedelic studies
 13 at Hopkins.
 14 This guy said to me, when he found out what
 15 I did, "I've got this patient who went through
 16 this," he said, "and this guy was a --" and he
 17 called him a jerk, but he used something that
 18 started with the letter A, and it was a lot more
 19 stronger than that. And I was like, "Oh."
 20 [Inaudible - mic fades]. He says, "I used to dread
 21 seeing him, and now he's just a great guy."
 22 It's an N of 1, it's anecdotal, but there's

Page 128

1 something meaningful that changed in his life by
 2 going through this, and that's really intriguing.
 3 I think that's what we strive for when we take care
 4 of people, regardless of whether it's with a
 5 psychedelic, or if it's with an antidepressant, or
 6 whatever. We want something more than simply
 7 relieving a target symptom.
 8 Anyway, on that note, let's switch gears
 9 again, and we're on the home stretch, but we're
 10 going to talk about vaccines. As we've been doing,
 11 Sandy or Marco, either of you, if you want to tag
 12 team, if you have any opening thoughts about the
 13 topic before we dive into it.
 14 DR. COMER: I do, and then maybe Marco can
 15 add some of his comments. I think the vaccine
 16 approach is different in a lot of ways from the
 17 other approaches that we've been talking about the
 18 last couple of days. One of the big ones is that
 19 the vaccines are not expected to have any abuse
 20 liability or risk of diversion, so that's a huge
 21 one.
 22 We're not really anticipating that they will

Page 129

1 be used for treating opioid withdrawal. We're
 2 really focusing on the treatment of opioid-use
 3 disorder. There is a concern about overdose risk
 4 in people who are on the vaccine as a stand-alone
 5 medication, so that's similar to some of the other
 6 approaches. But the vaccine approach is very much
 7 one where we could envision it as an adjunct
 8 medication to buprenorphine, methadone, or
 9 naltrexone.

10 I wanted to focus a little bit on some of
 11 the unique risks and issues associated with the
 12 vaccine. One is, something that we don't really
 13 know how it will play out clinically -- and it has
 14 to do with how to transition a patient onto the
 15 vaccine -- there's not clear data to suggest that
 16 putting somebody on the vaccine will result in
 17 precipitated withdrawal. We're not expecting that
 18 to happen because the antibody response will
 19 increase gradually, so we don't think that will
 20 happen.

21 At least in the early development of it with
 22 the single vaccine, if we block the effects of one

Page 130

1 opioid, it's easy for a patient to switch to
 2 another opioid, so that's going to be an issue. I
 3 think once we develop a multivalent vaccine, then
 4 that becomes more of a moot point, but that's a
 5 unique issue.

6 One of the biggest concerns with vaccine
 7 development, to date, has been the individual
 8 variability and antibody response. I think that's
 9 what has led to the decline in interest in
 10 vaccines, in general, with the nicotine vaccine and
 11 with the cocaine vaccine. I think Marco's approach
 12 of trying to find a biomarker by looking at either
 13 B cells or toll-like receptors is a really
 14 interesting one.

15 Then finally, I think one of the things that
 16 I'm sort of still struggling with a little bit is
 17 how to measure the duration of action of the
 18 vaccine. If we're expecting it to last for
 19 3 months, 6 months, or longer, it's not that it's a
 20 question of ability to measure that, but it's
 21 feasibility. So those are kind of the main points
 22 that I have.

Page 131

1 Marco, do you have anything else to add?
 2 DR. PRAVETONI: Yes, just a couple of
 3 things. One, also I would like to spend on the
 4 overdose scenario and prevention of overdose.

5 DR. STRAIN: Turn the volume up on your
 6 voice. No, it's on your voice; it's not on your
 7 mic.

8 (Laughter.)

9 DR. PRAVETONI: Yeah. In terms of
 10 prevention of overdose, a vaccine obviously won't
 11 prevent a relapse. But upon relapse, especially if
 12 you are relapsing with preferably lower doses of
 13 opioids, the vaccine would prevent actually getting
 14 the [indiscernible] off or the potential for
 15 toxicity. So that could have a role.

16 As a monotherapy, one thing that we see,
 17 especially with the case of fentanyl, carfentanil,
 18 and all the analogs that are very potent, they're
 19 also very easy to block by antibodies because the
 20 antibodies do need light to counteract only a very
 21 small dose, or plasma concentration, or whatever,
 22 of fentanyl.

Page 132

1 For instance, even other substance-use
 2 disorders, such as, for example, cocaine users that
 3 may encounter fentanyl because it's mixed or it's
 4 laced with fentanyl, may benefit from a fentanyl or
 5 carfentanil vaccine, and that would be different
 6 from an oxycodone or heroin vaccine.

7 So that's one point. We really have to
 8 define who's going to be, essentially, the good
 9 population to target with these vaccines.

10 DR. COMER: And just to add on to that
 11 point, this is something that we didn't really
 12 discuss yesterday, so I'm glad you reminded me.
 13 This is a unique approach not only for patient
 14 populations, but for other -- well, in the patient
 15 population, one other unique aspect of this is that
 16 it potentially has the ability to prevent the
 17 development of opioid-use disorder that is not a
 18 possibility with some of the other medication
 19 approaches. But then also, for other populations,
 20 this vaccine could be given to first responders,
 21 people like in a mass casualty situation. Somebody
 22 who's vaccinated may be less sensitive to the toxic

Page 133

1 effects of carfentanil or fentanyl.
 2 So there are other applications, and the
 3 Department of Defense is really interested in this
 4 kind of approach for those reasons as well.
 5 DR. STRAIN: Okay. Let's open it. Celia,
 6 then Rob, and then Tom.
 7 DR. WINCHELL: Earlier this week, NIDA held
 8 a very, very interesting and informative symposium
 9 about the risks of opioids taken together with
 10 stimulants. And some of the information that was
 11 presented, if I understood it correctly, it seemed
 12 that many of the effects of opioids occur outside
 13 the brain, and they're not necessarily mu mediated,
 14 and that there are direct effects on the lung and
 15 on gas exchange in the lung that are separate from
 16 the central depression, the drive to breathe.
 17 So that was a surprise to me, and it made me
 18 think about the vaccine approach and how the
 19 vaccine approach focuses on keeping the drug in the
 20 periphery and out of the brain. To what extent do
 21 we understand what the drug does when it stays in
 22 the periphery? Because we are driving the

Page 134

1 concentrations up quite a bit and slowing the
 2 clearance.
 3 DR. PRAVETONI: Yes. I guess I can address
 4 that, mainly from the preclinical standpoint. So
 5 we did a lot of experiments, where we showed that
 6 the vaccines are very effective in blocking
 7 respiratory depression and bradycardia. We do
 8 these studies where we expose -- and mostly they're
 9 oxycodone, fentanyl, and carfentanil, and so forth.
 10 We keep increasing, essentially, the dose until the
 11 controls are unconscious, and the vaccinated
 12 animals most likely are not. One of things that
 13 also we do is we reverse respiratory depression by
 14 naltrexone and nalmafene to essentially show that
 15 the vaccine doesn't prevent death.
 16 In regards to periphery, one of the things,
 17 actually, that we had to show to the FDA as part of
 18 our pre-IND application, was that, essentially,
 19 once the opioids are bound to the antibodies, they
 20 no longer have activity at opioid receptors. So we
 21 are driving -- high, like you say -- the serum
 22 concentration of opioids, but most of those are

Page 135

1 bound.
 2 So when you look at bound and unbound
 3 fraction, you reduce the unbound, so the frequency
 4 to collect [indiscernible] fraction. In fact,
 5 specifically, in the context of respiratory
 6 depression, not so much in these type of meetings,
 7 but when I go to DoD, et cetera, they are very
 8 concerned about renal catherization and how the
 9 unbound may recirculate across the barrier.
 10 So the antibodies being outside could act as
 11 a sponge, if you will, that will actually soak up
 12 that unbound. Once the opioids are bound, it takes
 13 quite a while, like before they're unbound, and
 14 then clear; so you're increasing the circulatory
 15 half-life of opioids, but you're kind of like
 16 tapering that. But also, once they're bound,
 17 they're no longer active.
 18 DR. STRAIN: Thank you. Rob, and then Tom.
 19 MR. BARROW: Just a general question about
 20 the risks and benefits of going down a vaccine
 21 route, which I realize is the topic, versus
 22 approaching the same kind of issue with a

Page 136

1 monoclonal antibody. Why go the vaccine route as
 2 opposed to just developing an antibody to
 3 administer?
 4 DR. PRAVETONI: That's a very good question.
 5 We develop, our group and others, of course, both
 6 vaccines and mAbs. Especially in the substance-use
 7 disorder space, the main issue against mAbs would
 8 be the cost. mAbs are very effective. If you give
 9 a mAb against any drug of abuse, it will be very
 10 effective in blocking its effect, toxicity
 11 overdose, et cetera.
 12 One of the issues would be sustained
 13 treatment. You would have to give a mAb, let's
 14 say, every, I don't know, once a month, et cetera.
 15 So mAbs are probably more indicated in overdose or
 16 the at-risk population. For example, again, using
 17 the example of Department of Defense, they're very
 18 interested in mAbs probably because they can afford
 19 it, and their enforcement process would be very
 20 different for the national stockpile and for
 21 military versus opioid users, but they are equally
 22 working.

Page 137

1 One of the advantages of the vaccine is that
 2 the protective effect would last longer, so the
 3 preclinical response would last longer, and it
 4 would be much cheaper to give, and that would be
 5 preventive, so it would beat there; and even
 6 minimizing events, a relapse event or an accidental
 7 exposure. So there are pros and cons with both
 8 approaches.
 9 DR. STRAIN: Tom?
 10 DR. KOSTEN: Thank you. I think Marco's now
 11 said a bunch of the things of why a vaccine and why
 12 not monoclonals. Monoclonals certainly will work
 13 for everyone that you give them to, but how long
 14 they're going to last is quite short, relatively
 15 speaking, to the risk period you're talking about.
 16 I want to emphasize, there's only one
 17 vaccine that I feel like we absolutely have to have
 18 as soon as possible, and that's fentanyl because
 19 fentanyl is not blocked by naltrexone. It's not
 20 blocked by buprenorphine, and it's not blocked by
 21 methadone. Those people are still dying with that
 22 combination.

Page 138

1 So the fentanyl vaccine is extremely likely
 2 to work. Why? Tiny amounts of fentanyl go a very
 3 long way to killing you, but, in fact, that has
 4 been the problem with the vaccine so far. We can
 5 make antibodies in just about everybody, but we
 6 can't make enough to block because it's a
 7 competitive antagonist. Nicotine, you take in huge
 8 amounts of nicotine, but with fentanyl, you can
 9 block it.
 10 The fentanyl vaccines that we have in
 11 animals right now. not only does it block
 12 self-administration and all that usual stuff, it
 13 blocks death. We give lethal dosages of fentanyl
 14 to the animals, and they don't say hello, how are
 15 you doing, but their respiratory rate definitely
 16 goes down somewhat, but it then comes right back up
 17 again.
 18 So I think that we have a public health
 19 crisis, and we've got to focus on something, we've
 20 got to focus on a fentanyl vaccine getting out
 21 there sort of tomorrow because we don't have a
 22 treatment.

Page 139

1 MALE VOICE: But also the analogs, rights?
 2 DR. KOSTEN: Oh, yeah. It works on
 3 carfentanil. In fact, it works better on
 4 carfentanil. The higher the potency, the lower the
 5 amount that goes in you. So the antibodies all
 6 cross-react to all of these fentanyls, and that's
 7 all they react to, fentanyl derivatives. And there
 8 are literally, not just dozens, but many, many more
 9 derivatives that are active, and you will in fact
 10 bind to them.
 11 I want to emphasize that. We are already
 12 getting some money from the Department of Defense
 13 to do it. I know that Gary Matyas has been getting
 14 money from the Army for a while to do this.
 15 DR. COMER: Marco is, too.
 16 DR. KOSTEN: And Marco is, too. The time to
 17 pull these resources together is now. But for the
 18 defense issue, I assume many of you know that what
 19 happened with Chechnya, it was the Russians, but
 20 they aerosolized fentanyl into a theater --
 21 DR. COMER: Carfentanil.
 22 DR. KOSTEN: Thank you. I guess some of you

Page 140

1 heard of this before.
 2 (Laughter.)
 3 FEMALE VOICE: Carfentanil's more than a
 4 story, just fill in a bad story with this one.
 5 MALE VOICE: It's not a good outcome.
 6 DR. KOSTEN: It killed a lot of people in
 7 there, and the Department of Defense is quite
 8 worried about that terrorists will take this and
 9 spray it.
 10 I feel like I don't want to make this too
 11 academic a discussion. This is an emergency, and
 12 we need to do something about it. I think help is
 13 coming from a lot of directions, but the other
 14 place that help is going to have to come is going
 15 to be the FDA because the approval process of this
 16 may need to be a little accelerated.
 17 There's been a bunch of things that have
 18 stood as an issue in this. Who do we test the
 19 vaccine on first, as opposed to normal versus
 20 everybody, who they have to be identified as a
 21 fentanyl abuser? They're hard to find, a quote,
 22 "fentanyl abuser," and they're going to abuse other

Page 141

1 things. Are we going to be able to do the
 2 laboratory studies, where we vaccinate people and
 3 we actually give them fentanyl? That's going to be
 4 important to do.
 5 So I think there are very practical issues
 6 on this that are quite not pie in the sky kind of
 7 tomorrow, but like right now. And DEA has to be
 8 brought on board because as make these things, the
 9 DEA made this crazy regulation so that our
 10 intermediate products and our final products that
 11 are components of these vaccines are now Schedule I
 12 drugs. That's the way their nutsy rule works.
 13 We're working very hard with NIAAA and other
 14 places. No factory will make a Schedule I drug,
 15 unless they're in China or they're in Mexico. I'm
 16 getting some of this work done in Europe because
 17 it's just impossible to do it in the U.S..
 18 DR. STRAIN: Kit, you wanted to comment?
 19 Thanks, Tom.
 20 DR. BONSON: My question has to do with
 21 ethics questions because if there is a vaccine for
 22 this, are we going to put it into at-risk

Page 142

1 communities? I'm just kind of musing this through.
 2 It could be like the Gardasil, where all teenage
 3 people now are encouraged to get it, regardless of
 4 whether you're sexually active, because you're
 5 supposed to really get it before you are sexually
 6 active; so that's good.
 7 So my concern is that it would only go into
 8 populations that are poor or of color, and they
 9 would say they're at risk, and then that's not
 10 necessarily the right community. But can we
 11 neutralize this and say everyone's at risk? Then
 12 it sort of changes to dialogue a little bit about
 13 how we think about drug abuse.
 14 You see where I'm going with that?
 15 DR. COMER: Yeah --
 16 DR. KOSTEN: Sorry.
 17 DR. COMER: Go ahead.
 18 DR. KOSTEN: We wrote a whole book about
 19 this from the National Academy of Sciences, and now
 20 the book's about 20 years old, practically, when
 21 the first started to come out about these depot
 22 medications. The parents groups all wanted it in

Page 143

1 the drinking water. The ACLU people all wanted it
 2 highly restricted, and you couldn't possibly give
 3 it to prisoners and all these other groups.
 4 DR. COMER: It's mandatory in prisons, for
 5 example.
 6 DR. KOSTEN: Half of them are in there for
 7 substance abuse, so why shouldn't you vaccinate
 8 them or something before they go out the door? Why
 9 shouldn't you inject naltrexone into them?
 10 Then the other issue that came up was a
 11 quite controversial issue, which was can we
 12 identify high-risk people for overdoses for dye and
 13 for becoming dependent? The consensus was, at the
 14 end of the day, that there were a lot of unexpected
 15 consequences, and it was clearest with the nicotine
 16 vaccine; that is you vaccinate a whole bunch of
 17 adolescents. Why do adolescents smoke? Do they
 18 smoke to really get high from nicotine? No, they
 19 sort of smoke to be antagonistic to their parents
 20 and everything else.
 21 So what are they going to do? They're going
 22 to override this vaccine. If that takes 10

Page 144

1 cigarettes in their mouth all at the same time,
 2 they'll smoke the 10 cigarettes at the same time.
 3 What will you then do? You'll expose them to 10
 4 times the amount of carcinogens that they would've
 5 been exposed to before. Is that great idea? No.
 6 Even the parents groups would agree, no, that's
 7 kind of stupid.
 8 So I think that we're going to have to think
 9 about this. I think from the standpoint of
 10 fentanyl, in particular, since we have nothing
 11 else, I'm quite concerned that there are probably
 12 more risk groups than we think. It's not just
 13 opiate addicts, they're cutting methamphetamine,
 14 and cocaine, and everything else with fentanyl, so
 15 it may be just every drug abuser, period.
 16 Then the other thing will be, what about the
 17 military? It depends what level of military you
 18 talk to. If you talk to the generals and the
 19 colonels, they say, "When you got it; you tell us.
 20 We're going to vaccinate everybody." They see it
 21 as a huge preparedness mission.
 22 DR. BONSON: Let me just say one more word,

Page 145

1 which is this mandatory aspect I think I'm getting
 2 at with the ethics. I didn't say that word, but
 3 it's not just what populations do we bring it to;
 4 it's whether or not it's mandated, and I think that
 5 that's where the ACLU came in, problematically,
 6 about prisoners.
 7 DR. STRAIN: David, and then Frances.
 8 DR. SHURTLEFF: Thank you. I'm intrigued by
 9 the fentanyl. I think if you carved out a niche, I
 10 think that's relevant here that maybe deserves more
 11 discussion or thinking. But I'm just curious, and
 12 I agree with you, the lacing of if it's heroin or
 13 stimulants, I think that's potentially another
 14 public health use for this type of approach.
 15 But I'm wondering -- and I don't know; maybe
 16 the NIDA people know. But what is the level of
 17 fentanyl in these products? Is it at a point where
 18 even though a little bit goes a long way, as you
 19 said, are these large amounts where you could run
 20 into the same problem with a challenge that you
 21 have with nicotine and other opioids, where even
 22 though a small amount will kill you, but there's 10

Page 146

1 times or 20 times that amount, lethal dose, within
 2 the product that these folks are taking that have
 3 you overwhelmed again, and you're back to the same
 4 problem.
 5 So I'm just wondering from a practical
 6 perspective, if it's, in fact, the case that
 7 there's very little in the products that are being
 8 used out on the street.
 9 DR. STRAIN: Bob, do you want to answer
 10 that, and then we'll go to Frances.
 11 DR. KOSTEN: Yes, just to --
 12 DR. STRAIN: No. Bob was chomping at the
 13 bit to say something.
 14 MR. WALSH: I was going to say I can't
 15 really say quantitatively what's being seen in
 16 things; I just don't know that off the top of my
 17 head. But one of the things I have heard, too, as
 18 part of the problem with this, is that things
 19 aren't necessarily mixed real well either.
 20 So as people are taking samples and shooting
 21 up, they may get one that has a much heavier dose
 22 of fentanyl in that area out of the bag, or

Page 147

1 whatever they're taking it from, as opposed to
 2 another area.
 3 I think that's another high risk that's
 4 there that because you don't really know what
 5 you're getting when you're taking these things.
 6 They're obviously not doing a pharmaceutical grade
 7 mixture of making sure everything is equal.
 8 DR. SHURTLEFF: Again, I don't know if
 9 there's a way to address that, but I think that's
 10 the variability in the street use or street
 11 availability that could potentially make or break
 12 this approach. Just conceptually, I think it's an
 13 excellent way to target a very specific application
 14 as needed, but I'm just wondering if we're going to
 15 be in that situation where --
 16 DR. STRAIN: Tom, did you want to say
 17 something to that as well? Then we'll do Frances,
 18 and then Andrew.
 19 DR. KOSTEN: The people who are coming into
 20 the emergency rooms now in Houston, that are
 21 saying, "I'm a methamphetamine abuser, and so are
 22 all my friends." And one of them friends brings

Page 148

1 them in and says, "I don't know why he stopped
 2 breathing." For the longest time, we couldn't
 3 convince the ER staff, "Look at his pupils." When
 4 the pupils are pinpoint, that ain't
 5 methamphetamine; give 'em something. And then what
 6 they would do is load them up with naloxone,
 7 essentially, which sooner or later might work. I
 8 think how much fentanyl is in there, though, is an
 9 extremely difficult situation.
 10 Now, the only thing I can say is that the
 11 rodents are extremely resistant. It's almost a
 12 thousand-fold difference in a rodent dose to make
 13 them stop breathing compared to humans, and these
 14 are rodents that we're doing the fentanyl vaccine
 15 and giving the fentanyl on top of. And Janda's got
 16 the same results. We are using somewhat different
 17 technologies, but the concept is the same. You
 18 just seem to make high affinity antibodies to this
 19 vaccine.
 20 I don't know how yours have been, but
 21 measuring the affinity, we're just [inaudible - mic
 22 distortion] -- kind of affinity. I think it will

Page 149

1 work, and I don't think that's going to be a huge
2 problem. The only problem I worry about -- it's
3 one that's a little different, which is if this
4 makes it safe on the street, does this mean that
5 they're now going to do it all the time?
6 Fentanyl's very cheap to make, and there are lots
7 of different ways of making it.
8 MALE VOICE: It will escalate.
9 DR. KOSTEN: Yeah. We get into a
10 competition.
11 DR. STRAIN: Frances?
12 DR. LEVIN: I think Tom said what I was
13 going to say, in between all the times you've
14 talked --
15 (Laughter.)
16 DR. KOSTEN: Oh, come on!
17 (Laughter.)
18 DR. LEVIN: But the point that the target
19 group is worried about mandated treatment, and the
20 ACLU, and all that stuff, that starting, at least,
21 with any illicit substance user, if you're cocaine,
22 or heroin, or whatever, that is a group. They'll

Page 150

1 have more of the cocaine -- hospital admissions
2 will have overdoses due to -- overdoses are related
3 to fentanyl, so I think that is a group to some
4 degree.
5 I think what the military does -- I don't
6 know military law and whether every recruit that's
7 going in the field has to agree to have an
8 injection of fentanyl before they go over to
9 Russia, and they would wind up going. I think
10 that's another question. But yes, DoD is extremely
11 interested in all ways of dealing with this
12 potential terrorism threat, whether it's mechanical
13 devices and other kinds of stuff they're also
14 interested in.
15 DR. STRAIN: Andrew?
16 DR. HUHN: I just wanted to mention,
17 regarding the prevalence of fentanyl, that at least
18 in our clinical trials that we're doing in
19 Baltimore, I think there's very little heroin left
20 in Baltimore --
21 FEMALE VOICE: Yeah, the same with New York.
22 DR. HUHN: -- that most people are coming in

Page 151

1 testing positive only for fentanyl.
2 DR. LEVIN: Only for fentanyl?
3 DR. HUHN: Yeah.
4 FEMALE VOICE: Do they think they're
5 shooting heroin?
6 DR. HUHN: Yeah.
7 MALE VOICE: That's the problem.
8 (Crosstalk.)
9 DR. HUHN: There have been a few things
10 published recently about how this really rapidly
11 shifting landscape is happening in other places,
12 too, where fentanyl is becoming the only available
13 drug or the drug of choice around the country.
14 DR. LEVIN: And the other thing we're not
15 talking about today, and Tom mentioned it, because
16 80-90 percent of our clinic is positive, heroin
17 users are positive for fentanyl. But they're
18 saying they're using heroin, but whatever.
19 We're having a much harder time with
20 induction to even view. We can't do home
21 inductions the same way, getting people on to
22 Vivitrol. Everything is a lot harder. I think

Page 152

1 that's not the discussion today, but all the
2 algorithms -- I'm responsible for training
3 throughout the country on buprenorphine
4 administration and all that sort of stuff through
5 SAMHSA's PCSS program, and all these induction
6 things we're writing aren't really holding true
7 when there's fentanyl on board. So that's a whole
8 other discussion, but we're back to the drawing
9 board with these opiate medications.
10 DR. HUHN: Also, just thinking this all the
11 way through, especially for application in the
12 military, but really for anybody who was vaccinated
13 against fentanyl, if they were to be in like an
14 emergency situation where they needed emergency
15 medical care, fentanyl is usually a go-to drug for
16 that to be used to control pain.
17 So then are we really going to end up
18 eliminating fentanyl from that mix as an analgesic?
19 I'm just throwing that out there. I don't have an
20 opinion one way or another.
21 DR. STRAIN: Yeah, although we had other
22 analgesics before fentanyl. Morphine's been

Page 153

1 around.

2 Roger? Oh, I'm sorry. Sandy wanted to

3 comment, then Roger.

4 DR. COMER: I just wanted to comment on

5 something that someone said about, well, once we've

6 vaccinated everybody, it's just going to drive the

7 dose up. I think that the pharmacology of fentanyl

8 is unique in that the dose that produces the

9 euphoric effect and the dose that produces severe

10 respiratory depression is very narrow. So the

11 safety margin is more narrow for fentanyl than for

12 heroin, for example.

13 I think if somebody gets vaccinated, they

14 may end up using higher doses, but I don't think

15 that the street doses of fentanyl will change much

16 because in a non-vaccinated person, if the dealer

17 drags it up, then he's going to kill all of his

18 customers --

19 MALE VOICE: Which they don't want to do.

20 DR. COMER: -- which they, obviously, don't

21 want to do.

22 DR. PRAVETONI: In fact, the effect of the

Page 154

1 vaccine in shifting the dose response for both

2 reward and respiratory depression goes hand in

3 hand, so it's equally effective; or respiratory

4 depression and bradycardia, as well as reward.

5 As Sandy was saying, we've been doing this

6 for quite a while. When I started, oxycodone was

7 the big thing, so I started with the oxycodone

8 vaccine 10 years ago, and now finally we are seeing

9 the IND.

10 Obviously, now things are going to be a lot

11 faster. We started working with fentanyl, and one

12 of the things that we saw was that, as Tom was

13 saying, vaccines are very effective as mAb, and

14 probably has to do with the kinetics of the drug

15 and the volume of distribution.

16 For example, we do self-administration

17 studies where we have animals self-administering

18 for weeks, and then we start vaccinating them. And

19 what happened is that usually everybody asks the

20 question about compensation. We don't see any

21 compensation. We see that with control animals

22 will compensate, so increase their intake, while

Page 155

1 instead the vaccinated animals, they will drop.

2 Fentanyl is relatively like a short

3 half-life as far as like rewarding, but then it

4 sticks around for much longer than heroin, and

5 morphine, or oxycodone. If you change the kind of

6 first peak that is rewarding, that seems to be very

7 effective, and with fentanyl more so, and it

8 probably has to do with fentanyl itself and how

9 it's interfacing with the distribution, and

10 metabolism, and all that.

11 DR. STRAIN: Thank you. Roger, I think, and

12 then Matt.

13 DR. WEISS: Just a quick point. Boston is

14 the same as Baltimore, that a number of patients

15 said you can't get heroin in Boston; it's all

16 fentanyl.

17 DR. STRAIN: We like to think Boston is

18 emulating us in Baltimore, yeah.

19 (Laughter.)

20 DR. WEISS: That's actually what they say,

21 that we've heard that it all came from Baltimore.

22 (Laughter.).

Page 156

1 DR. STRAIN: Yeah.

2 DR. WEISS: The other thing, though, is if

3 you had a vaccine -- I'd just respond to something

4 that Tom said, that if people thought it was safe,

5 they'd keep using it, though it would be safe but

6 ineffective. So maybe they wouldn't keep using it

7 if it didn't work. Maybe they'd switch to

8 something safe like methamphetamine or something

9 like that.

10 DR. STRAIN: Matt?

11 DR. JOHNSON: I just want to add, my best

12 guess is that the big picture, a future for this is

13 going to be in those people who are truly treatment

14 seeking. So I see things from a delayed

15 discounting lens, and it really fits in well. This

16 is like as long as you can get up the gumption a

17 few times or with whatever frequency, this is

18 Ulysses tying himself to the mast of the ship,

19 knowing he's going to be tempted by the sirens.

20 In terms of broad scale use, on top of the

21 ethical questions Kit brought up and the medical

22 issue that that Andrew brought up, I think it's

Page 157

1 going to also just be ineffective in the broad
 2 scale, in the sense of it's just going to be one
 3 more aspect of this game of Whac-A-Mole. They're
 4 going to be other scaffolds. Even if it
 5 generalizes the carfentanil, remifentanil, and the
 6 rest, it's going to be a continued Whac-A-Mole game
 7 with other basic structures. But at the individual
 8 level, for those that at least get the gumption up
 9 to quit, some time, it seems like there's a lot of
 10 promise.
 11 DR. STRAIN: Tom?
 12 DR. KOSTEN: Just one thing that did come up
 13 during those 20-years-ago meetings that was kind of
 14 interesting, and it was from a mayor of a
 15 relatively large urban area who had a public health
 16 background. His position was quite interesting,
 17 which was the concept of herd immunity, which has
 18 to do with cattle and veterinary things, where if
 19 you vaccinate a proportion of a population with an
 20 infectious disease, you only have to get about a
 21 third of them, and the spread then stops.
 22 That's what his concept was for the

Page 158

1 vaccines, that even if you've got a third of the
 2 users -- and I said, "Okay. Well, that's great.
 3 What usually happens then?" He says, "Well, the
 4 infection then spreads to someplace else." And I
 5 said, "Oh, okay. So then you just keep chasing
 6 it?" And he said, "Well, not exactly. I want to
 7 vaccinate the inner city people, where this is a
 8 huge problem right now, and then what will happen
 9 is the dealers will move to the middle class
 10 neighborhoods outside. Those people pay taxes, and
 11 they want to do something about it. So instead of
 12 leaving this is a problem in my inner city, they
 13 will in fact get motivated to do something."
 14 Now, obviously, you have to be a cynical
 15 politician to come up with something that
 16 interesting, but I think there is something to
 17 that, that in fact what you would do is you may
 18 start with high concentration areas of vaccination,
 19 but then what will happen is that all of the
 20 surrounding areas, as they see the epidemic spread,
 21 which unfortunately is already happening, will say,
 22 "I want my kids vaccinated, too."

Page 159

1 I think it will spread with a natural
 2 process that has something to do with herd
 3 immunity, even though you're far from getting a
 4 hundred percent of the people. And this is going
 5 to be important because these vaccines, they will
 6 last -- with the cocaine vaccine, it will last
 7 about 3 months, and then you have to revaccinate.
 8 They're saying the opiate ones will last longer.
 9 They might go out to 6 months, but they're not
 10 going to go out -- I mean, it's impossible, with
 11 current ways that we do vaccines, to make this work
 12 more than about 6 months, and then you'd have to
 13 give -- then we make them up with other kinds of
 14 depot formulations.
 15 This is a repeated thing. It's not
 16 something you can sort of say -- like measles,
 17 mumps, rubella, you get it as a kid, and then
 18 you're immune for the rest of your life. You've
 19 got to keep chasing it.
 20 DR. STRAIN: Well, we're winding down
 21 towards the end of this session. Other thoughts on
 22 vaccines?

Page 160

1 DR. KOSTEN: And money.
 2 DR. STRAIN: If not, thank you both for this
 3 discussion, as well as the psychedelic discussion,
 4 which both were certainly very intriguing and I
 5 think certainly worked for what I was hoping to
 6 hear out of them.
 7 We'll take about a 5- to 10-minute break so
 8 that people can do a bio break. As I said, and
 9 hopefully most of you heard, there'll be sandwiches
 10 and lunch things down where we had breakfast. Grab
 11 something and bring it back.
 12 In the next roughly 45 minutes, or
 13 whatever -- an hour, and we've got an hour blocked
 14 off, and we'll see how it goes -- I think there are
 15 a couple things to be thinking about. One is we've
 16 covered, obviously, four topics over the last day
 17 and a half.
 18 As we were planning this meeting, a question
 19 in my mind was do we have all that we want to? Are
 20 these the main four or are there other things that
 21 we should be considering? Are there other agents?
 22 Are you sitting there going, "Geez, these are

Page 161

1 really interesting, but I can't believe they didn't
 2 talk about X as a non-mu approach that's on the
 3 horizon." So that's one thing, and that's a major
 4 aspect, I think.
 5 The second thing is future ACTTION items
 6 related to substance abuse, and you can either
 7 bring that up to the group when we're having lunch
 8 or certainly reach out to me as well. For those of
 9 you who haven't been intimately involved with
 10 ACTTION, we've done meetings on stimulants, on
 11 cannabis, on craving, on medical devices; and
 12 obviously now on non-mu agents.
 13 This is sort of the typical process that we
 14 go through in terms of a day and a half, some talks
 15 that highlight it, but also ample time to have
 16 discussion like this. So if you find something
 17 that you're thinking, "Gee, going forward, it would
 18 be really interesting," we're certainly willing to
 19 entertain it, I think. Bob's nodding yes and
 20 Dennis is smiling. Then we'll talk also about next
 21 steps that's related to this meeting.
 22 So on that note, the big hand's on the 12,

Page 162

1 so let's break, and we'll start back up in about 10
 2 minutes.
 3 (Whereupon, at 12:00 p.m., a lunch recess
 4 was taken.)
 5
 6
 7
 8
 9
 10
 11
 12
 13
 14
 15
 16
 17
 18
 19
 20
 21
 22

Page 163

1 AFTERNOON SESSION
 2 (12:23 p.m.)
 3 General Discussion
 4 DR. STRAIN: Let's go ahead and get started.
 5 This is really an opportunity -- if people need to
 6 get up and go grab a brownie or something, please
 7 feel free to do so. This is really a chance now
 8 for us to -- if you've had any lingering thoughts
 9 that have come up; ideas, questions; and as I
 10 mentioned before, other drugs that we didn't
 11 consider; or classes of drugs that might be
 12 relevant to this; other ACTTION topics; nature of a
 13 paper that might come out of this if we move
 14 forward, Tom, go ahead.
 15 DR. KOSTEN: Once I unfill my mouth. I
 16 realize we probably did stimulants already, but
 17 that is the up and coming epidemic with
 18 methamphetamine. It seems like having maybe kind
 19 of an epidemiology presentation of how that's kind
 20 of spread all over the place, and how it's getting
 21 mixed in -- as I think [indiscernible] or someone
 22 was saying about a meeting they had at NIDA later

Page 164

1 on about stimulants and opiates being kind of the
 2 drug for sure at this point -- cocaine and opiates
 3 were bad enough, but methamphetamine and opiates
 4 are actually quite a bit messier because the
 5 methamphetamine lasts so much longer, and you can
 6 take it in every route of administration
 7 imaginable, and you still get high.
 8 DR. WINCHELL: I'll mentioned that FDA is
 9 working on a -- the Duke Margolis folks are putting
 10 together a workshop for us on stimulant-use
 11 disorder. Then there will be a patient-focused
 12 drug development meeting on stimulant-use disorder
 13 as well.
 14 DR. KOSTEN: Good. That's coming back to
 15 the forefront, and we have nothing for stimulants.
 16 DR. STRAIN: Actually, that Duke Margolis
 17 meeting I think is like in two weeks or something.
 18 It's early December.
 19 MALE VOICE: December 16th, I think.
 20 DR. STRAIN: 16th is it?
 21 DR. KOSTEN: Oh, okay. I made a mistake;
 22 they invited me to that already.

Page 165

1 DR. WINCHELL: I honestly don't know. I've
 2 been boostfully uninvolved.
 3 (Laughter.)
 4 DR. WINCHELL: I'm just going to show up.
 5 DR. STRAIN: You can go online and register
 6 to attend it if you want to go to it.
 7 We probably do need to -- and I'm looking
 8 over at Brian now. Brian spearheaded the paper we
 9 did on stimulant-use outcome measures. Didn't you?
 10 Yeah. Brian's now eating.
 11 DR. WINCHELL: You have a recent one about
 12 risk levels, right?
 13 DR. KILUK: Yeah.
 14 DR. STRAIN: What journal was that in?
 15 DR. KILUK: Studies of alcohol and drugs.
 16 DR. STRAIN: But we need to revisit
 17 stimulants at some point, probably, and I'm looking
 18 at Bob. We've got a lot that we've got to do.
 19 Other thoughts? Are there any drugs that we
 20 missed, that you sort of say, "Gee. We really
 21 should have thought about X," besides obviously
 22 stimulants.

Page 166

1 DR. WINCHELL: Well, we've seen a variety of
 2 drugs that are purported to have like a
 3 pan-addiction effect. People will come in, and
 4 they say we think this drug does everything, and
 5 then they'll pick one thing to start with based on
 6 where the money is, or where they think they can
 7 get fast-track designation, or where they think the
 8 low-hanging fruit is. They're all over the place,
 9 just all kind of everything, unrelated to anything
 10 we've seen, of course.
 11 DR. COMER: What about like kratom, and
 12 mitragynine, and 7-hydroxymitragynine? Those are
 13 kind of interesting and controversial.
 14 DR. WEISS: That's a big one.
 15 DR. STRAIN: Yeah.
 16 DR. WEISS: We're seeing a good bit of it,
 17 of kratom. The population we're seeing it in, in
 18 particular, is we have a specialty program for law
 19 enforcement and firefighters, and we're seeing it
 20 in that population because it doesn't show up in
 21 urine tests.
 22 DR. KOSTEN: Not only that; it's easy to

Page 167

1 get. It's not controlled or anything. Certainly,
 2 when we were running an opiate detox study a couple
 3 of years ago, some patients were doing remarkably
 4 well on the study. And we said, "Geez, this is
 5 great." And they said, "Well, you know, I've been
 6 taking this thing. I can't remember. Is it
 7 krocktiom [ph]?"
 8 They were doing kratom during the whole
 9 thing, and it really does work very well for opiate
 10 withdrawal. I'm not sure whether you're still
 11 opiate dependent at the end of it, but we did give
 12 them naltrexone at the end. They didn't say thank
 13 you or anything, but they weren't particularly
 14 sick.
 15 DR. WEISS: We've had people, A, who have
 16 used it as a treatment and people who have come in
 17 addicted to kratom or that was their drug of
 18 choice. It's one of those things that's very
 19 controversial because some people see it as the
 20 cure and other people see it as the problem.
 21 DR. KOSTEN: It's like Juul, right?
 22 FEMALE VOICE: Exactly.

Page 168

1 DR. KOSTEN: The eyes of the beholder.
 2 DR. WEISS: Yeah.
 3 DR. SHURTLEFF: Just from a basic science
 4 perspective, we're launching a program looking at
 5 her drug interactions, and kratom is the lead
 6 compound. It's looking at how it affects
 7 transporters --
 8 DR. STRAIN: Can you get closer to the mic?
 9 DR. SHURTLEFF: Just to say that we're
 10 looking at kratom in an herb drug interaction
 11 profile to see how it affects transporters, liver
 12 enzymes, and other things; so just some basic
 13 information that may be useful moving forward.
 14 DR. KOSTEN: So you have that information or
 15 you're --
 16 DR. SHURTLEFF: We're now gearing up. We
 17 actually have -- believe it or not, it took a long
 18 time to find the appropriate compound online, and
 19 there was a reliable source that our group in North
 20 Carolina, University of North Carolina, Greensboro,
 21 was able to find. They purchased large quantities.
 22 Now, the next step is to develop a profile and

Page 169

1 program to do this in human subjects.
 2 So we're making progress at the very
 3 beginning. We have the standardized kratom now.
 4 They looked across the board, and this was the most
 5 consistent product they could find.
 6 FEMALE VOICE: And you're going to put an
 7 IND in for this?
 8 DR. SHURTLEFF: I think they already do have
 9 FDA approval, yes, to do this. So we've already
 10 cleared the FDA component, so we're now moving to
 11 the interaction studies.
 12 DR. KOSTEN: They've been doing those in
 13 animals. My wife, Terry, has been doing those,
 14 essentially, kratom studies with the ingredient,
 15 which we found the place that you can get it from.
 16 It's not that cheap, but we can get it. We started
 17 by thinking you would have bad interactions with
 18 alcohol, and it ends up what's happening is the
 19 animals are reducing their alcohol use when they
 20 get it. So we're not sure how much George Koob
 21 will get enthusiastic about giving kratom to
 22 alcoholics, but you never know.

Page 170

1 DR. STRAIN: Matt?
 2 DR. JOHNSON: I certainly agree that kratom
 3 is very promising. My bet is it's essentially an
 4 agonist treatment, and people report it like a very
 5 new opioid profile with subjective effects. One of
 6 the big picture things is there might be something
 7 very special about mitragynine pharmacologically,
 8 and I'm open to that.
 9 One part of the package that is important
 10 now is that no one has figured out how to get a
 11 high potency extract that's injectable and
 12 sniffable. So you have a mu agonist that has to be
 13 taken orally and in a form that if you take more
 14 than 4 grams or so, it's very aversive. So those
 15 kind of non-pharmacological factors alone might be
 16 limiting, not preventing, its abuse potential,
 17 which might be why folks are reporting that it's
 18 essentially a do-it-yourself agonist treatment.
 19 DR. SHURTLEFF: It's used in East Asia.
 20 Chris McCurdy can give you a really good accounting
 21 of this. But my understanding is it's used in
 22 Eastern Europe among field workers, and they sip it

Page 171

1 all day, from morning till night. So they're
 2 titrating their dose and using this as sort of a
 3 beverage all day, and maintain their stamina, so I
 4 guess it probably reduces pain to some extent.
 5 DR. JOHNSON: People talk about the
 6 stimulant effects, but it's not unlike the railroad
 7 workers using opium, perhaps.
 8 DR. STRAIN: Andrew, did you have something
 9 you wanted to say?
 10 DR. HUH: Just to mention, a lot of those
 11 benefits sound a lot like the work on tramadol,
 12 where changing the route of administration causes
 13 bad effects and taking too much causes bad effects.
 14 And that's already FDA approved, at least for pain,
 15 so that might be something with similar advantages,
 16 but much closer.
 17 MALE VOICE: Yes, a weak mu agonist.
 18 DR. STRAIN: Bob?
 19 DR. DWORKIN: I was just curious whether any
 20 human abuse liability studies have been done. Has
 21 the abuse liability been looked at systematically?
 22 MALE VOICE: No.

Page 172

1 DR. STRAIN: There's somebody actually at
 2 Columbia, a chemist who makes 6-mitragynine.
 3 DR. COMER: Andrew Kruegel.
 4 DR. STRAIN: What's his name?
 5 DR. COMER: Andrew Kruegel.
 6 DR. STRAIN: Yeah. Is it laborious to make
 7 it or something? I forget.
 8 DR. COMER: We have to extract it from the
 9 plant.
 10 DR. KOSTEN: Yes, it's laborious. I can
 11 tell you, we tried to do it, and we decided it was
 12 cheaper to just buy it.
 13 DR. STRAIN: But I think that's probably the
 14 critical thing, is to do the abuse liability
 15 studies with 6-mitragynine, which somebody in our
 16 group wanted to do that.
 17 Did Al put a grant in to do that? Didn't
 18 he?
 19 DR. JOHNSON: I don't think the grant has
 20 gone in.
 21 DR. STRAIN: I thought he put an R21 in.
 22 DR. JOHNSON: A big old giant bag of kratom

Page 173

1 that was bought, just in case it was scheduled.
 2 DR. STRAIN: Well, that's a good thought,
 3 although I'm not sure I would bill kratom as a
 4 non-mu opioid approach. I think it's probably just
 5 a --
 6 DR. BONSON: Definitely a mu opioid.
 7 DR. STRAIN: -- mu opioid that's primarily
 8 available in brewed tea, is my understanding. I
 9 think that's how typically it's taken.
 10 DR. BONSON: Well, you can buy --
 11 DR. STRAIN: What's that?
 12 DR. BONSON: You can buy the botanical.
 13 DR. STRAIN: Yes, you buy the botanical, but
 14 I think a lot of people brew it, don't they?
 15 DR. BONSON: The difficulty in doing
 16 abuse-potential studies with mitragynine is that we
 17 don't really know what the plasma levels are in
 18 humans. You can say, oh, they take this leaf, and
 19 they do this, and they take this much, but there's
 20 that Tarrawalla thing about how much mitragynine or
 21 7-hydroxymitragynine are in that particular leaf.
 22 Then we don't know what the levels of those

Page 174

1 2 compounds are in the people who abuse them. So
 2 we don't know that for humans, so we don't know how
 3 to run a human abuse-potential study. And we don't
 4 know what it is in humans, so we can't extrapolate
 5 down for plasma levels in animal studies, where we
 6 do the typical self-administration, drug
 7 discrimination, and whatever it is. So it's very
 8 hard at this stage to know what conclusions to be
 9 drawing other than it's an unregulated mu opioid
 10 agonist.
 11 (Laughter.)
 12 DR. STRAIN: That's all.
 13 Other thoughts? Yeah, Dustin?
 14 DR. LEE: I have a general thought. This is
 15 my second ACTTION meeting, and what I find most
 16 intriguing about ACTTION is that you break down
 17 everything to the most individual level. Yesterday
 18 morning, we heard a little bit about this, but
 19 anyone that was at the canvas meeting like a year
 20 and a half ago, I think the general consensus
 21 coming out of that is we have no clue what we're
 22 looking for with regards to outcome measures.

Page 175

1 So I think a future ACTTION built totally
 2 around outcome domains and really trying to figure
 3 out across drug classes and within drug classes. I
 4 know that's a hard topic, but I think it's one
 5 that's really necessary and could improve clinical
 6 trials for substance-use disorders across the
 7 board.
 8 It could have something to do with general
 9 technological developments to prevent the loose
 10 cannon sort of behavioral treatment aspect that we
 11 sometimes see, and just like the basic foundations,
 12 then we can more easily transfer data -- or
 13 translate data across clinical trials to look at
 14 these secondary outcome domains.
 15 DR. STRAIN: I was having a little
 16 difficulty hearing you in the beginning. I did
 17 hear the part where you said you really liked
 18 ACTTION meetings, though.
 19 (Laughter.)
 20 DR. STRAIN: Were you saying a meeting that
 21 focuses on outcome measures for opiate-use disorder
 22 specifically?

Page 176

1 DR. LEE: Across drug class.
 2 DR. STRAIN: Across drug class.
 3 DR. LEE: We were talking about this in
 4 cannabis as well, and we're running into, it seems
 5 to me with very few exceptions, that abstinence is
 6 our default outcome of record, but is it the best?
 7 I think it's an interesting discussion that we
 8 dance around at these meetings, and then we kind of
 9 filter back in, okay, let's see which drug works
 10 now; where if we really focused on improving and
 11 pooling together unique and novel outcomes, we
 12 might have a general consensus on how do you
 13 approach trial design in a larger respect.
 14 DR. STRAIN: It's kind of related. Annie
 15 and I meet regularly and kind of brainstorm ideas
 16 and things. We meet in person. Bob, Dennis, and I
 17 talk on the phone as well, and Annie. But an idea
 18 we had batted around was actually quality of life
 19 as it related to substance-use disorder. It kind
 20 of goes back to something I was saying before lunch
 21 about abstinence is good, but abstinence isn't the
 22 only thing.

Page 177

1 DR. LEE: You leave it to the folks who are
2 writing the systematic reviews, and we're going to
3 tell you the problems because we write the
4 systematic reviews, and then we figure out, and
5 there's really no consensus about any of this
6 stuff. In that respect, you can break down almost
7 every single drug class and just determine that
8 there's a mess of outcome measures.
9 I know Brian has done a ton of work in this,
10 and I think we need more emphasis on that type of
11 pooling together across studies, and I think we
12 could probably make pretty good use of time if we
13 do that.
14 DR. STRAIN: Well, doing a systematic review
15 of outcome measures across substance-use
16 disorders --
17 DR. LEE: No, I wasn't talking about that.
18 DR. STRAIN: Do you want to hit Dustin now?
19 DR. LEE: I'm not touching those for a
20 while. But you could take just one substance. And
21 I think for the cannabis meeting, and 65 different
22 cannabinoids comes across 58 trials. I don't think

Page 178

1 it's that much different if you look at opiate-use
2 disorders. Even if it's abstinence, it's defined
3 drastically different.
4 DR. DWORKIN: Dustin, and actually everybody
5 in the room. is there a need for that kind of
6 systematic review of OUD primary outcome measures?
7 Kyle's presentation obviously presented a whole lot
8 of variability across studies in terms of what the
9 primary outcome or primary outcomes were. Should
10 that be done systematically? ACTTION could
11 certainly provide support for a systematic review
12 of outcomes in OUD clinical trials.
13 DR. KLEYKAMP: Al and I were just talking
14 about doing that because I flagged his presentation
15 as really helpful to me; not being within OUD, but
16 I defer to anyone else. Are there guidelines? Is
17 there a consensus, statements out there, on primary
18 outcome in OUD studies that have already been
19 published?
20 DR. WINCHELL: We did release a guidance,
21 two guidances. I would say I'm not sure it would
22 be fruitful to review the literature on outcomes

Page 179

1 that have been used because we know that they've
2 been variable. They've been specific to that
3 particular study, that particular population.
4 Studies are anywhere from 6 weeks to 6 years long.
5 Obviously, they're all over the place.
6 What would be better, I think, is to try to
7 articulate what we think they should be going
8 forward. We all know what the endpoints have been.
9 We reviewed all the protocols, so we know what the
10 endpoints are. We know how many there are. And we
11 also know that many protocols say that the endpoint
12 is urine toxicology.
13 Now, urine toxicology is not an endpoint,
14 and EKG is not an endpoint. You have to say what
15 you're going to do with it, and there are literally
16 an infinite number of things you can calculate with
17 the urine toxicology data that you have collected.
18 So you will probably find in much of the
19 published literature, they don't even tell you what
20 the endpoint is. I don't think that's going to be
21 particularly fruitful. I don't mean to rain on
22 anyone's parade.

Page 180

1 DR. DWORKIN: Celia, so what would be
2 helpful?
3 DR. WINCHELL: Some of the discussions,
4 we've had to identify what treatment response looks
5 like. We've tried to incorporate some of that in
6 our guidance to talk about functional outcomes,
7 people feeling better, doing better, functioning
8 better. These are all of interest for people who
9 meet criteria for remission from opioid-use
10 disorder because opioid-use disorder diagnosis
11 doesn't include any quantitation of
12 self-administration at all.
13 So if you had a magic drug that you could
14 give to people, that would let them use heroin
15 willy-nilly, and they would be fine, upstanding
16 citizens, and it wouldn't interfere with their
17 lives at all, that's fine.
18 (Laughter.)
19 DR. BONSON: And that's the harm question
20 thing that I was talking about.
21 DR. WINCHELL: If they don't meet diagnostic
22 criteria for opioid-use disorder, they don't have a

Page 181

1 problem. And if they don't have a problem, then
 2 they're adequately treated. We've articulated
 3 these things.
 4 Now, the problem is that there is a tension
 5 between wanting studies to be brief and efficient,
 6 and wanting outcomes to be global, because it takes
 7 a long time to move the needle on a global outcome.
 8 I've said this before. Obesity studies are
 9 15 months long, I think, because that's how long it
 10 takes to lose 7 percent of your body weight. They
 11 can't do a 12-week obesity study because nobody
 12 loses enough weight in that time to move the
 13 needle.
 14 We often have this tension. People will
 15 simultaneously say they want less challenging to
 16 achieve endpoint and a shorter study. We end up
 17 perhaps demonstrating very little clinical movement
 18 in that patient. I think we just need to have a
 19 little more help articulating what could the
 20 endpoints be.
 21 I'd also like to say that we've moved quite
 22 a long way from the original design of these

Page 182

1 opioid-use disorder studies that were done in
 2 patients who were getting face-to-face treatment
 3 and on-site dispensing of medication on a daily
 4 basis. When you go back to those -- I know I've
 5 said this before, so go get a brownie.
 6 The every other day urine testing schedule
 7 was based on the window of detectability of heroin
 8 because that's what people were using. They were
 9 using heroin, and that's what we wanted them to
 10 stop using. If you tested them every day, you
 11 would get false positives, but if you tested them
 12 less often, you might miss some use, so we got this
 13 every other day testing.
 14 Well, that got carried over to every other
 15 drug use scenario, every other study, everything
 16 else. And then people would say, "It's really hard
 17 to get people to come 3 times a week." And we
 18 would say, "Why are you doing that?" "Well, that's
 19 how it's always been done." So we did allow these
 20 registration trials with much less frequent urine
 21 testing.
 22 Now on the other side, we know that much

Page 183

1 less frequent urine testing, we're going to miss a
 2 lot. There's probably a lot of positives we're not
 3 seeing, especially because their scheduled. The
 4 patients know when they have to be negative. So
 5 for us to say we expect all the urine tests to be
 6 negative isn't the same thing as saying we expect a
 7 patient to be a hundred percent abstinent. I mean,
 8 we only tested them 1 out of 30 days.
 9 So we thought, well, we know they could
 10 still be using pretty frequently, but if they got
 11 their act together enough to submit a negative
 12 sample at every one of these widely spaced visits,
 13 that's pretty good. I mean, that's an indicator
 14 that they got their lives together.
 15 So even if we're still saying that we expect
 16 every urine sample you collect to be negative,
 17 that's not the same thing as saying the FDA
 18 requires complete abstinence when we've gotten it
 19 down to one sample a month. So I would just
 20 implore, stop saying that.
 21 FEMALE VOICE: It's in the guidance, though.
 22 DR. WINCHELL: Yes, it's in the guidance.

Page 184

1 (Crosstalk.)
 2 FEMALE VOICE: I read it at CPED [ph].
 3 DR. WINCHELL: It's in the guidance. Read
 4 the guidance.
 5 DR. BONSON: There's a widely
 6 misunderstanding. Why do we have misunderstanding
 7 that you have to have abstinence? This is not
 8 true.
 9 DR. STRAIN: Tanya, you wanted to raise
 10 something.
 11 DR. RAMEY: I just wanted to suggest again,
 12 and maybe it will be useful for the field to look,
 13 cross-diagnostically, at measures by domain. Would
 14 it be useful to see addictions by the domain, and
 15 maybe agree on measures that would be most useful
 16 domain. Then you would be able to construct an
 17 endpoint on this specific domain; like for example,
 18 your secondary endpoint, just for example. That
 19 would be useful, I think.
 20 DR. STRAIN: Give me an example of what you
 21 think what that might be. Who?
 22 DR. RAMEY: Well, it could be, for example,

Page 185

1 negative effect, there's a domain.
 2 DR. STRAIN: I see. Okay.
 3 DR. RAMEY: For example, reward in the task,
 4 which could be kind of sensitive to change, that
 5 could be like you had that baseline, and in the
 6 end, you had the task and the change. So that's
 7 your endpoint, so this has changed. You won't
 8 sleep; again, I'm talking about inter-reception,
 9 even like executive functions by domain.
 10 DR. STRAIN: Thanks. David?
 11 DR. SHURTLEFF: This may sound self-serving,
 12 but I'll say it anyway. What I'm going to talk
 13 about is part of the HEAL initiative. I think the
 14 combination of behavioral interventions with
 15 medication -- so we have this program through the
 16 HEAL initiative called BRIM, Behavioral Research
 17 for Improving MAT Adherence.
 18 But to get back at some of the comments you
 19 made, Eric, about improving overall qualities and
 20 other things that may be more important, medication
 21 alone is not likely to do it. I think it's a
 22 challenge, too, about how to combine -- which we

Page 186

1 discussed a little bit of it today -- behavioral
 2 interventions, particularly in this population, and
 3 what the right time and what the right duration.
 4 There are a lot of things to unpack there,
 5 but I think if we're going to have a comprehensive
 6 program, it needs to involve both medication and
 7 behavioral interventions, and how to do that
 8 effectively would be a good discussion.
 9 DR. STRAIN: Music to my ears.
 10 DR. KLEYKAMP: This is Annie. I just wanted
 11 to follow up on something Celia said so I
 12 understand, just being tasked with writing up if we
 13 have something. When I was saying what I liked
 14 about Kyle -- the way I envision if, say, we get
 15 led with a review of what's out there is that we
 16 would document what's been done, like in some
 17 streamlined way, a snapshot of outcomes, but within
 18 that manuscript, there would include what you've
 19 mentioned, which are expert recommendations for OUD
 20 endpoints.
 21 Is that something that would be valuable or
 22 is that too redundant with what you already know?

Page 187

1 Is that catching to what you feel like would be
 2 helpful?
 3 DR. WINCHELL: Well, I think our goal for
 4 this particular meeting was to explore whether the
 5 types of endpoints that we've articulated in our
 6 existing guidances would be in some way appropriate
 7 or inappropriate if we were not talking about
 8 agonists. So I think one of the issues is
 9 always -- and I know I've said this before -- that
 10 the risk-benefit calculation, when you're treating
 11 somebody with an opioid, is, well, they're going to
 12 be taking an opioid anyway, so it's this opioid or
 13 their illicit drug of choice. So all of these
 14 opioid adverse effects, they're unavoidable; it's
 15 pick your poison.
 16 Well, if you're going to choose a medication
 17 that has a completely different mechanism of
 18 action, you might expect something different. You
 19 might say this introduces a whole new set of risks,
 20 and therefore our expectation for efficacy should
 21 be higher, or this introduces no risks, and our
 22 expectation for efficacy should be lower.

Page 188

1 In talking about going beyond mu receptors
 2 in a way people have been thinking about these
 3 medications for my lifetime, that was kind of the
 4 place where we were interested in hearing some
 5 expert opinion; what should we do differently?
 6 DR. STRAIN: Bob, you and I had a very brief
 7 chat here, where you were articulating some
 8 thoughts about a paper that would encompass the
 9 four topic areas, and you articulated that very
 10 well. So I'm going to put you on the spot to
 11 repeat that, if you would.
 12 DR. DWORKIN: So what I asked Eric is did he
 13 think the following kind of paper might be a
 14 reasonable outcome of this meeting, an article
 15 perhaps for an addiction journal, but perhaps also
 16 for a pharmacology or a clinical trials journal, on
 17 kind of novel emerging treatments for OUD, and the
 18 ones that we've discussed, but the focus on the
 19 paper is what are the clinical trial challenges
 20 going forward?
 21 It's really what Celia said. When we move
 22 away from the mu receptor and start studying novel

Page 189

1 agents, and these four are the example, what are
 2 the clinical trial challenges in terms of patients
 3 enrolled outcome measures and research designs? It
 4 wouldn't be a systematic review, and it would be
 5 longer than an editorial. So it's kind of an
 6 extended commentary on what's on the horizon, and
 7 what are the challenges, and what should people be
 8 thinking about.

9 Does that sound like a reasonable paper for
 10 all of us to prepare and think about a substance
 11 abuse journal, or a pharmacology journal, or a
 12 clinical trials journal?

13 DR. JOHNSON: It's probably going to be
 14 little integration. This might be fine, but I
 15 think there's probably going to be little
 16 integration across these four things. The really
 17 interesting stuff is what makes them not just
 18 different from mu agonists, but different from each
 19 other, but that might be fine. It ends up being a
 20 laundry list, but it might have a lot of value.

21 DR. DWORKIN: The way I was thinking about
 22 it is we'd pick and choose four examples of

Page 190

1 challenges. The challenges in moving psychedelic
 2 agents forward are clearly different, and you'd use
 3 those as examples where it was most relevant; then
 4 the challenges of sleep agents.

5 So we would use these four emerging
 6 treatments really is as examples of challenges.
 7 The point of the paper would be to identify the
 8 clinical trial challenges that we see emerging on
 9 the horizon.

10 DR. WEISS: Would you focus it specifically
 11 on the clinical trial part? Because a lot of the
 12 discussion over the last couple of days has been
 13 on -- particularly, with the psychedelics, how
 14 would you roll this out if it were -- that's
 15 different from a clinical trial challenge. A lot
 16 of it is where would we go from here? And we've
 17 done that even some with the vaccine.

18 DR. DWORKIN: So Roger, it could be two
 19 papers.

20 DR. WEISS: I think it would be better to
 21 keep it with the clinical trials because you could
 22 go on for a long time with these other things, and

Page 191

1 that's where they really get different from each
 2 other.

3 DR. DWORKIN: I agree about that, starting
 4 with the clinical trial challenges, and then we
 5 could think about a paper -- in some ways this is
 6 actually more interesting. The drug development
 7 commercialization challenge is where we talk about
 8 things like REMS. We've had ACTTION meetings where
 9 there are actually two articles that come out of
 10 the meeting. But the lower hanging fruit is
 11 certainly clinical trials, and outcome measures,
 12 and related issues.

13 DR. WEISS: And I think with the clinical
 14 trials, you could talk about shared versus unique
 15 challenges, based on what you're dealing with.

16 DR. STRAIN: And there may also be a feature
 17 of opportunities as well. I'm thinking with the
 18 sleep aids, the technology that's emerging is an
 19 opportunity that is specific to sleep aids, but it
 20 would be nice to acknowledge that there are also
 21 these aspects; that we're not stuck with urine
 22 testing as the only non-self report.

Page 192

1 Other thoughts?

2 (No response.)

3 DR. STRAIN: What time is it? We still have
 4 4 minutes, but we could end 4 minutes early.

5 (Laughter.)

6 DR. STRAIN: Oh, no. Dennis wants to say
 7 something.

8 DR. TURK: I want to fill up one of those
 9 minutes, anyhow.

10 The way these things have worked in the
 11 past -- and I'm not sure that's what the plan
 12 is -- is that somebody identified as a rapporteur,
 13 which I guess is Annie, drafts up a review paper, a
 14 summary paper, of what we talked about. That then
 15 gets distributed first to Eric, and maybe to Bob,
 16 and any of the organizers, just look at it, then
 17 refine, maybe add things.

18 Then all of you will be invited to be
 19 authors of that paper, to review the paper, to add
 20 your comments. You don't have to feel when you
 21 leave the meeting today, "Oh rats, I should have
 22 talked about X, Y, or Z," but you'll have an

Page 193

1 opportunity. In fact, you'll have
2 several -- assuming you, number one, want to, and
3 number 2, legally can. I know there are some
4 regulatory agency issues for some of you. That may
5 be something you have to get approved for. Then
6 you'll get a chance, and then we'll refine
7 something.
8 For those that can be authors and want to be
9 authors, they'll be included as authors. For those
10 that attended the meeting, but for whatever
11 purpose, either choose not to or are not allowed
12 to, we will ask you permission to acknowledge you
13 were at the meeting, so there will be
14 acknowledgment you were here. Then we will
15 finalize it. You'll approve it. It will get
16 submitted to journal X, Y, or Z.
17 Inevitably, reviewers will have comments
18 back to us. Annie will take those comments, try to
19 address them, and typically tend to highlight what
20 we've changed and to address those. The caution
21 is, if you look at the number of people here, all
22 of whom are busy, if we send each one of these

Page 194

1 versions out, and it takes you six months to get it
2 back to us, this is never going to see the light of
3 day, so we encourage you to try to look at it
4 fairly quickly. Then when it gets to the point of
5 revisions being made is to focus specifically on
6 the revisions. So typically we've had red font, so
7 you can see this is what we've changed since the
8 last time you've seen this; so to save you some
9 time, we can move it along.
10 That's the goal and the process we try to
11 go to. So each of you will have an opportunity to
12 see the drafts. You will have an opportunity to
13 contribute. You will have an opportunity to decide
14 yes or no, if you want to, or willing to, or able
15 to participate as an author. If you're not, we'll
16 ask, obviously with your permission,
17 hopefully -- there would be no issue about that,
18 that at least you were acknowledging you attended
19 the meeting, so we can put that out there.
20 We then hope to publish these things. As
21 Bob said, there's over a hundred ACTTION
22 publications. If you are good, we'll have 102 the

Page 195

1 next time Bob talks about this --
2 DR. DWORKIN: 120.
3 DR. TURK: -- 120. From this meeting, we'll
4 have at least two, so Bob, next week when he goes,
5 or next month when he goes, he'll be saying,
6 ACTTION now has 102 manuscripts that have been
7 published or in the process.
8 So I just want you to understand, you don't
9 have to feel like everybody's going to run out the
10 door, and then you're going to inevitably think of
11 something we didn't talk about. And you will see
12 this. You're not signing off and stamping that
13 this is the final discussion.
14 DR. DWORKIN: To give an example of what
15 Dennis is talking about, we have another manuscript
16 right now that we're working on, that's not related
17 to this group, where we've gone back and forth for
18 the last 3 or 4 weeks, about 5 times, with a
19 renowned Scottish statistician --
20 (Laughter.)
21 DR. DWORKIN: -- about our section on what
22 is number needed to treat and what are its

Page 196

1 advantages and limitations. So it is possible you
2 would get very sick of this manuscript --
3 (Laughter.)
4 DR. DWORKIN: -- before it gets submitted
5 for publication, because we try to make everybody
6 happy, and sometimes that takes a bit of work.
7 DR. STRAIN: Well, I'm a firm believer that
8 we aren't a Quaker meeting, where we have to have
9 consensus before we can move forward.
10 DR. BONSON: Just the majority, right?
11 Adjournment
12 DR. STRAIN: Yeah.
13 On that note, thanks, everybody. Thanks to
14 those of you who've stuck it out to the bitter end.
15 We've had a little bit of attrition, but great
16 staying power by all of you. Safe travels, and
17 we'll be in touch.
18 (Applause.)
19 (Whereupon, at 1:01 p.m., the meeting was
20 adjourned.)
21
22

	79:14	84:2;88:7;95:5;98:17; 117:11;120:16; 131:13;134:17; 135:11;141:3;155:20; 164:4,16;168:17; 172:1;176:18;178:4; 191:6,9	92:1;98:9;117:3; 136:3 administered (4) 9:15;79:5;97:21; 116:16 administration (6) 19:21;21:12; 101:10;152:4;164:6; 171:12 admissions (1) 150:1 admittedly (1) 27:7 adolescents (2) 143:17,17 adopted (1) 44:9 advanced (1) 86:14 advantages (4) 11:21;137:1; 171:15;196:1 adverse (3) 97:16;117:4;187:14 advocacy (1) 22:9 advocate (1) 117:16 advocating (2) 103:5;116:5 aerosolized (1) 139:20 affect (1) 92:13 affects (3) 12:16;168:6,11 affinity (3) 148:18,21,22 afford (1) 136:18 afraid (3) 24:13;25:7;87:22 afterglow (1) 111:10 again (21) 7:19;11:3;31:16; 49:10;50:8;57:20; 73:21;81:13;83:17; 88:19;89:6;104:12; 105:20;106:4;128:9; 136:16;138:17;146:3; 147:8;184:11;185:8 against (6) 52:12;117:15; 125:3;136:7,9;152:13 agency (1) 193:4 agency's (1) 78:10 agent (3) 17:2;18:8;38:10 agents (12) 16:6;20:3;53:15;	54:14;55:4;56:8; 67:18;160:21;161:12; 189:1;190:2,4 ago (9) 14:14;72:17; 102:13;105:21;118:3; 127:10;154:8;167:3; 174:20 agonism (1) 110:10 agonist (15) 38:11;39:7,7;46:19, 20;75:5;91:18;92:10; 121:5;124:17;170:4, 12,18;171:17;174:10 agonists (4) 26:7,8;187:8; 189:18 agree (21) 20:10;25:8;28:21; 33:9;39:5,19;42:17; 46:14;69:17;80:22; 81:17,18;90:14; 122:15;123:14;144:6; 145:12;150:7;170:2; 184:15;191:3 agreement (1) 101:6 agrees (1) 61:3 agriculture (1) 21:18 ahead (10) 37:4,7;41:1;76:15; 88:13;113:21;115:8; 142:17;163:4,14 AI (1) 84:11 aids (2) 191:18,19 Aimee (1) 15:18 aiming (1) 61:12 ain't (1) 148:4 airline (1) 38:14 aisle (1) 59:9 al (3) 79:1;172:17;178:13 alcohol (4) 107:8;165:15; 169:18,19 alcoholics (1) 169:22 algorithms (1) 152:2 alike (1) 82:11 allow (2) 117:18;182:19
\$	accepting (1) 82:7			
\$3 (1) 41:15	access (5) 5:8;43:20;46:16; 100:1;119:16			
[accidental (1) 137:6	acute (3) 17:14;82:2;92:14		
[inaudible (6) 73:9;80:3;110:17; 113:13;127:20;148:21	accidents (1) 94:10	adamantly (1) 92:17	admissions (1) 150:1	
[indiscernible] (5) 54:5;102:12; 131:14;135:4;163:21	accomplish (1) 3:12	Adam's (1) 47:18	admittedly (1) 27:7	
[ph] (3) 78:18;167:7;184:2	accounting (1) 170:20	add (16) 7:17;29:15;33:20, 22;36:7;56:12;60:12, 13;85:11;121:7; 128:15;131:1;132:10; 156:11;192:17,19	adolescents (2) 143:17,17	
A	acetylcholine (1) 67:7	addicted (3) 40:13;125:3;167:17	adopted (1) 44:9	
	ache (1) 63:1	addiction (6) 12:17;103:19; 107:5,21;108:1; 188:15	advanced (1) 86:14	
	achieve (1) 181:16	additions (2) 37:13;184:14	advantages (4) 11:21;137:1; 171:15;196:1	
ability (3) 54:11;130:20; 132:16	acknowledge (2) 191:20;193:12	addictive (1) 64:13	adverse (3) 97:16;117:4;187:14	
able (7) 9:5;27:16;79:15; 141:1;168:21;184:16; 194:14	acknowledging (1) 194:18	addicts (1) 144:13	advocacy (1) 22:9	
above (1) 109:9	acknowledgment (1) 193:14	adding (5) 7:4;35:22;36:2,2; 63:13	advocate (1) 117:16	
absent (1) 32:15	ACLU (3) 143:1;145:5;149:20	addition (1) 36:17	advocating (2) 103:5;116:5	
absolutely (4) 30:4;49:12;108:6; 137:17	across (14) 82:3;111:1;135:9; 169:4;175:3,6,13; 176:1,2;177:11,15,22; 178:8;189:16	add-on (1) 14:20	aerosolized (1) 139:20	
abstaining (2) 74:7,12	Act (3) 119:2;135:10; 183:11	address (11) 43:1;58:6;65:9; 73:17;94:17;115:3; 118:9;134:3;147:9; 193:19,20	affect (1) 92:13	
abstinence (9) 70:13,16;76:12; 176:5,21,21;178:2; 183:18;184:7	actigraphy (2) 83:12;85:4	addressed (3) 71:15;99:4;125:4	affects (3) 12:16;168:6,11	
abstinence-induced (1) 71:10	action (3) 112:9;130:17; 187:18	addresses (1) 94:22	affinity (3) 148:18,21,22	
abstinent (1) 183:7	active (8) 22:10;108:16; 113:14;114:13; 135:17;139:9;142:4,6	addressing (2) 43:6;57:19	afford (1) 136:18	
abuse (19) 11:20;22:17;29:2; 41:5,7;93:21;125:18; 128:19;136:9;140:22; 142:13;143:7;161:6; 170:16;171:20,21; 172:14;174:1;189:11	actively (1) 68:2	adequately (1) 181:2	afraid (3) 24:13;25:7;87:22	
abuse-potential (2) 173:16;174:3	activity (3) 82:22;110:9;134:20	Adherence (1) 185:17	afterglow (1) 111:10	
abuser (4) 140:21,22;144:15; 147:21	ACTTION (13) 5:11;59:20;161:5, 10;163:12;174:15,16; 175:1,18;178:10; 191:8;194:21;195:6	adjourned (1) 196:20	again (21) 7:19;11:3;31:16; 49:10;50:8;57:20; 73:21;81:13;83:17; 88:19;89:6;104:12; 105:20;106:4;128:9; 136:16;138:17;146:3; 147:8;184:11;185:8	
academic (1) 140:11	actual (1) 56:14	adjunct (6) 24:7;25:4;33:8; 56:10;116:11;129:7	against (6) 52:12;117:15; 125:3;136:7,9;152:13	
Academy (1) 142:19	actually (42) 4:17;5:6;8:20;9:1; 10:5;14:15;16:2;23:7; 28:22;34:12;35:18; 42:1;50:17;59:5,18; 61:6;66:9,11;67:4; 81:5;82:9;83:19,22;	Adjourment (1) 196:11	agency (1) 193:4	
accelerated (1) 140:16		administer (4)	agency's (1) 78:10	
acceptable (4) 38:10,12;52:21;			agent (3) 17:2;18:8;38:10	

<p>allowed (3) 98:9,10;193:11</p> <p>alluded (2) 100:10;120:21</p> <p>almost (4) 16:14;103:4; 148:11;177:6</p> <p>alone (6) 25:7;37:11;56:7; 57:20;170:15;185:21</p> <p>along (2) 108:22;194:9</p> <p>alright (2) 34:18;43:8</p> <p>alternative (1) 46:1</p> <p>although (2) 152:21;173:3</p> <p>always (8) 7:19;32:17;80:21; 103:4;117:4;119:9; 182:19;187:9</p> <p>amazing (1) 42:14</p> <p>Ambien (6) 55:7,7;70:7,18; 85:14,16</p> <p>amenable (1) 37:21</p> <p>amendments (1) 119:1</p> <p>American (2) 46:3;103:14</p> <p>among (2) 95:22;170:22</p> <p>amount (8) 9:1;26:1,13;106:22; 139:5;144:4;145:22; 146:1</p> <p>amounts (3) 138:2,8;145:19</p> <p>ample (1) 161:15</p> <p>analgesic (1) 152:18</p> <p>analgesics (1) 152:22</p> <p>analog (1) 107:18</p> <p>analogous (1) 20:2</p> <p>analog (4) 107:16;110:13; 131:18;139:1</p> <p>analysis (2) 20:11;50:5</p> <p>analyzed (1) 49:17</p> <p>ancillary (1) 14:21</p> <p>Andrew (16) 54:16;55:10,21; 59:21;66:15;67:4,21;</p>	<p>68:18;81:4,16;147:18; 150:15;156:22;171:8; 172:3,5</p> <p>anecdotal (1) 127:22</p> <p>anesthetic (1) 125:15</p> <p>angles (1) 19:4</p> <p>animal (4) 13:10;107:3,20; 174:5</p> <p>animals (8) 134:12;138:11,14; 154:17,21;155:1; 169:13,19</p> <p>Annie (8) 59:19;63:12;84:17; 176:14,17;186:10; 192:13;193:18</p> <p>answered (1) 120:20</p> <p>antagonist (6) 46:19,21;67:5; 91:18;124:18;138:7</p> <p>antagonistic (1) 143:19</p> <p>anthropological (1) 102:10</p> <p>antibodies (7) 131:19,20;134:19; 135:10;138:5;139:5; 148:18</p> <p>antibody (4) 129:18;130:8; 136:1,2</p> <p>anti-cannabinoids (2) 48:14;49:1</p> <p>anticholinergic (1) 67:8</p> <p>anticipating (1) 128:22</p> <p>anticompetitive (1) 99:1</p> <p>antidepressant (3) 74:10;110:4;128:5</p> <p>antidepressants (1) 100:4</p> <p>anxiety (11) 14:20;20:22;21:3; 24:11,12;28:12;45:2; 50:14,19;51:5;52:20</p> <p>anxiolytic (1) 20:3</p> <p>anymore (1) 45:14</p> <p>apart (1) 16:8</p> <p>apnea (5) 74:17,22;75:3,7,8</p> <p>app (1) 86:10</p> <p>appear (3)</p>	<p>94:7,8;113:2</p> <p>appears (3) 102:19;103:11; 107:19</p> <p>appetite (1) 48:15</p> <p>Applause (1) 196:18</p> <p>Apple (2) 86:8,13</p> <p>application (4) 65:15;134:18; 147:13;152:11</p> <p>applications (3) 14:4;106:16;133:2</p> <p>apply (3) 64:11;82:19;123:6</p> <p>applying (1) 40:7</p> <p>appreciate (1) 51:21</p> <p>appreciative (1) 53:19</p> <p>approach (19) 21:4;40:12;42:9; 100:11;105:4,10; 106:10;128:16;129:6; 130:11;132:13;133:4, 18,19;145:14;147:12; 161:2;173:4;176:13</p> <p>approaches (12) 30:19;42:2,3;59:4; 78:16;79:13,22;105:8; 128:17;129:6;132:19; 137:8</p> <p>approaching (2) 125:9;135:22</p> <p>appropriate (8) 17:2,3;35:20;38:9; 42:22;98:7;168:18; 187:6</p> <p>appropriately (1) 81:1</p> <p>approval (4) 100:2;101:19; 140:15;169:9</p> <p>approve (1) 193:15</p> <p>approved (6) 65:19;100:14; 125:13,14;171:14; 193:5</p> <p>apropos (1) 51:22</p> <p>archeological (1) 102:10</p> <p>area (10) 19:2;35:16;48:12; 49:12;89:12;97:5; 104:19;146:22;147:2; 157:15</p> <p>areas (5) 11:13;109:1;</p>	<p>158:18,20;188:9</p> <p>argue (3) 98:22;108:17;117:2</p> <p>argued (1) 102:7</p> <p>argument (1) 60:8</p> <p>arm (1) 97:18</p> <p>Army (1) 139:14</p> <p>around (15) 17:21;21:18;27:12; 39:22;48:22;81:19; 88:11,12;110:1; 151:13;153:1;155:4; 175:2;176:8,18</p> <p>arrived (1) 60:3</p> <p>article (1) 188:14</p> <p>articles (1) 191:9</p> <p>articulate (3) 90:21;91:1;179:7</p> <p>articulated (4) 91:16;181:2;187:5; 188:9</p> <p>articulating (3) 91:9;181:19;188:7</p> <p>artificial (1) 26:2</p> <p>Asia (1) 170:19</p> <p>aside (1) 52:2</p> <p>asleep (4) 73:17;84:22;87:13, 13</p> <p>aspect (10) 37:21;65:11;66:6,7; 72:8;132:15;145:1; 157:3;161:4;175:10</p> <p>aspects (5) 65:12,16;89:2; 115:12;191:21</p> <p>assessments (2) 3:19,22</p> <p>assign (1) 40:8</p> <p>assistants (1) 109:7</p> <p>assisted (1) 51:20</p> <p>associated (2) 97:17;129:11</p> <p>association (1) 118:16</p> <p>assume (3) 18:4;72:2;139:18</p> <p>assuming (2) 52:9;193:2</p> <p>assure (1)</p>	<p>91:2</p> <p>astronomical (1) 100:3</p> <p>astronomically (1) 107:2</p> <p>at-risk (2) 136:16;141:22</p> <p>attend (1) 165:6</p> <p>attended (2) 193:10;194:18</p> <p>attention (2) 111:22;123:16</p> <p>attenuate (1) 11:5</p> <p>attenuation (1) 10:22</p> <p>attractive (1) 75:20</p> <p>attributes (1) 107:13</p> <p>attrition (1) 196:15</p> <p>audience (1) 94:14</p> <p>author (1) 194:15</p> <p>authorized (1) 99:7</p> <p>authors (4) 192:19;193:8,9,9</p> <p>Avahuasca (1) 103:14</p> <p>availability (2) 105:5;147:11</p> <p>available (10) 4:19;36:22;44:7; 45:18;46:16,21;66:2; 88:8;151:12;173:8</p> <p>average (1) 75:15</p> <p>aversive (1) 170:14</p> <p>award (1) 41:17</p> <p>aware (1) 69:15</p> <p>awareness (1) 102:15</p> <p>away (6) 71:3;116:8;118:10, 13;124:20;188:22</p>
B				
<p>back (46) 4:8,10;6:14;12:11; 14:22;16:5;28:15,18; 32:21;42:7;54:7;57:7; 68:20;70:20;82:14; 88:8,10;90:12;91:13; 95:18;99:12;105:1,18, 20,21;106:4;113:22;</p>				

114:7;115:10;118:3; 120:14,18;121:9; 138:16;146:3;152:8; 160:11;162:1;164:14; 176:9,20;182:4; 185:18;193:18;194:2; 195:17 backdrop (1) 102:5 background (3) 31:20;52:12;157:16 bad (16) 7:21;12:16;24:14; 43:12;45:2;56:6;95:9, 20;97:19;113:2; 122:16;140:4;164:3; 169:17;171:13,13 bag (2) 146:22;172:22 ball (1) 99:9 Baltimore (5) 150:19,20;155:14, 18,21 band-aid (1) 71:1 barrier (1) 135:9 BARROW (4) 99:14;115:6,10; 135:19 based (6) 24:1;115:16;120:8; 166:5;182:7;191:15 baseline (1) 185:5 bases (1) 86:12 basic (6) 31:10;107:3;157:7; 168:3,12;175:11 basis (1) 182:4 batted (1) 176:18 batteries (2) 112:1,2 battery (3) 85:10;112:4,14 beat (1) 137:5 become (3) 22:15;105:19;108:5 becomes (4) 43:12;52:22;56:4; 130:4 becoming (2) 143:13;151:12 bed (3) 72:21;73:7;85:9 beg (1) 94:18 beginning (4) 54:16;94:16;169:3; 175:16 behavior (2) 13:14;60:5 behavioral (10) 56:8;70:2;76:5; 79:22;86:3;175:10; 185:14,16;186:1,7 behaviors (1) 53:6 behold (1) 70:19 beholder (1) 168:1 believer (1) 196:7 believing (1) 113:10 belly (1) 63:1 below (1) 90:7 benefit (11) 3:22;27:6;29:1,3, 10;51:10;85:21; 102:22;106:2;116:2; 132:4 benefits (4) 6:10;20:22;135:20; 171:11 benign (1) 31:5 benzodiazepines (2) 20:3;69:16 benzo-like (1) 69:16 benzos (1) 67:10 besides (1) 165:21 best (9) 19:19;20:5;32:13; 41:6;62:21;110:21; 111:16;156:11;176:6 bet (1) 170:3 better (19) 46:6;49:7,20,21; 55:17;63:18;64:1; 85:22;89:22;90:2; 104:3;107:13;126:21; 139:3;179:6;180:7,7, 8;190:20 beverage (1) 171:3 beyond (3) 77:22;126:4;188:1 biased (1) 110:10 big (16) 7:18;45:22;46:18; 56:4;71:10,11;88:11; 93:4;109:16;128:18; 154:7;156:12;161:22; 166:14;170:6;172:22 biggest (5) 19:7;71:7;99:18; 101:17;130:6 bill (2) 44:2;173:3 bind (1) 139:10 bio (1) 160:8 biological (2) 110:18;111:11 biologics (1) 27:2 biomarker (1) 130:12 bit (18) 20:2;27:18;43:15; 61:21;126:7,8;129:10; 130:16;134:1;142:12; 145:18;146:13;164:4; 166:16;174:18;186:1; 196:6,15 bitter (1) 196:14 bizarre (1) 26:5 blind (1) 113:18 blinding (5) 114:19;115:4,14; 117:1,9 block (6) 99:3;129:22; 131:19;138:6,9,11 blocked (4) 137:19,20,20; 160:13 blocking (2) 134:6;136:10 blocks (1) 138:13 blood (1) 11:17 blunt (1) 13:17 board (8) 82:3;86:3;92:13; 141:8;152:7,9;169:4; 175:7 Bob (14) 3:7;34:15,17;35:7; 146:9,12;165:18; 171:18;176:16;188:6; 192:15;194:21;195:1, 4 Bob's (2) 35:7;161:19 body (1) 181:10 BOGENSCHUTZ (5) 13:5;30:15,15; 91:13;106:13 BOL-148 (1) 107:21 BONSON (18) 14:3;67:22;82:4; 90:3;95:4;98:22;99:5; 115:8;116:22;141:20; 144:22;173:6,10,12, 15;180:19;184:5; 196:10 book (2) 83:13;142:18 book's (1) 142:20 boostfully (1) 165:2 bored (1) 113:12 borne (1) 72:5 Boston (3) 155:13,15,17 botanical (5) 14:4,10,11;173:12, 13 both (20) 3:7;32:5;37:9;60:9; 72:13;77:3;91:5; 92:12;93:15;100:11; 104:15;111:16; 114:12;117:13;136:5; 137:7;154:1;160:2,4; 186:6 bottle (2) 72:22;73:7 bottom (2) 10:16;94:5 bought (1) 173:1 bound (5) 134:19;135:1,2,12, 16 bounds (2) 116:2,16 BPRU (1) 85:14 bradycardia (2) 134:7;154:4 brain (2) 133:13,20 brainstorm (1) 176:15 break (13) 38:5;54:19;86:22; 88:4,4,13;96:21; 147:11;160:7,8;162:1; 174:16;177:6 breakfast (2) 88:8;160:10 breaking (1) 21:5 breathe (1) 133:16 breathing (2) 148:2,13 brew (1) 173:14 brewed (1) 173:8 Brian (5) 70:5;71:19;165:8,8; 177:9 Brian's (1) 165:10 bridge (2) 73:12;74:2 brief (2) 181:5;188:6 BRIM (1) 185:16 bring (8) 29:17;32:20;37:15; 75:7;88:10;145:3; 160:11;161:7 brings (2) 75:3;147:22 broad (4) 65:14;120:15; 156:20;157:1 broaden (1) 106:14 broader (1) 62:19 broadly (3) 29:13;105:11; 106:20 brom (1) 107:21 brought (7) 68:21;85:16; 115:19;120:16;141:8; 156:21,22 Brown (1) 93:5 brownie (2) 163:6;182:5 BSR (1) 78:18 buckets (1) 61:1 bucks (1) 87:9 Building (1) 99:14 built (3) 78:19;110:8;175:1 bunch (6) 45:19;88:1;116:22; 137:11;140:17;143:16 bup (2) 39:1;44:15 buprenorphine (20) 6:19;7:16;10:19; 11:2;12:1;20:17,20; 23:11;24:18;33:18; 34:1;55:14;57:16;

75:11;93:7;97:12; 121:20;129:8;137:20; 152:3 business (1) 43:22 busy (1) 193:22 buy (7) 31:3;36:1,8;172:12; 173:10,12,13	16:18;7;33:8,12,21, 22;34:4,7;35:22; 44:18;45:5;51:21; 52:5,10,18;104:13 Cannabinoids (31) 6:6,8,8,12;7:14,20; 8:3;12:9;13:8;15:3; 16:7;18:17;19:12; 21:14;26:2;28:16; 29:5,10;30:11;31:1; 33:4;39:6;40:21;41:4, 9,16;49:5;54:16;61:4; 91:15;177:22 cannabis (46) 9:9,13,14,17,17; 10:1,8,15,19;11:5; 12:7;13:6;14:5,5,10; 15:2;20:1,12;21:7,15; 24:21,22;28:5,21; 29:6,18;30:1,17;39:3; 40:21;42:13,21;43:2, 3,17,20;44:16;50:13; 55:1;71:9;92:16; 102:18;104:13; 161:11;176:4;177:21 cannabis-use (1) 70:8 cannon (1) 175:10 canvas (1) 174:19 captured (1) 123:16 captures (1) 69:3 carcinogens (1) 144:4 card (2) 34:15;55:7 cardiologist (1) 127:11 care (7) 30:5;71:6;95:15; 102:16;127:11;128:3; 152:15 careful (5) 17:20;44:20,22; 91:8;103:1 carefully (2) 44:11;45:4 CARF (1) 123:9 carfentanil (8) 131:17;132:5; 133:1;134:9;139:3,4, 21;157:5 Carfentanil's (1) 140:3 Carolina (2) 168:20,20 carried (1) 182:14 carved (1)	145:9 case (11) 10:22;43:22;62:20, 22;64:16;82:5;99:6; 103:14;131:17;146:6; 173:1 cases (2) 44:8;103:7 casualty (1) 132:21 catching (1) 187:1 catch-up (1) 39:19 categories (1) 3:13 category (8) 3:13,16,18;6:15; 63:21;96:2;110:14; 124:17 catherization (1) 135:8 cattle (1) 157:18 causation (1) 103:1 caused (2) 24:11;74:18 causes (2) 171:12,13 causing (1) 111:3 caution (2) 102:16;193:20 CBD (12) 13:9;19:22;20:21; 21:2;28:10,11,22; 31:2,12;41:4,18; 105:17 CBT-I (3) 71:5;76:1,9 CDI (1) 27:3 Celia (16) 37:3;51:18;61:9; 63:9;78:14;80:1; 90:11;96:5;97:1; 112:21;121:11;126:9; 133:5;180:1;186:11; 188:21 Celia's (1) 120:19 cells (1) 130:13 center (1) 41:1 central (3) 74:21;75:2;133:16 certain (4) 9:1;11:21;86:17; 123:19 certainly (25) 29:8;37:12;40:4;	57:5;65:12;66:1; 67:22;68:3;74:20; 78:9,11;89:3;99:6,16; 103:2;122:22;137:12; 160:4,5;161:8,18; 167:1;170:2;178:11; 191:11 certification (3) 98:13,14,14 certify (1) 98:8 cessation (1) 114:15 cetera (6) 22:20;23:2;36:9; 135:7;136:11,14 challenge (6) 71:4;100:15; 145:20;185:22; 190:15;191:7 challenges (14) 71:8;99:15,18; 115:13;188:19;189:2, 7;190:1,1,4,6,8;191:4, 15 challenging (1) 181:15 chance (3) 6:9;163:7;193:6 chances (1) 29:19 change (12) 29:20;60:16;66:8; 69:1;96:16;112:12; 118:21;126:21; 153:15;155:5;185:4,6 changed (5) 106:3;128:1;185:7; 193:20;194:7 changes (5) 21:1;45:10;112:11, 19;142:12 changing (1) 171:12 characteristics (1) 6:21 characterized (2) 30:18;32:7 chasing (2) 158:5;159:19 chat (1) 188:7 cheap (3) 87:7;149:6;169:16 cheaper (2) 137:4;172:12 Chechnya (1) 139:19 check (1) 87:1 checked (1) 3:7 chemical (1)	16:6 chemist (1) 172:2 chemistry (2) 119:4,5 chicken (1) 72:12 China (3) 26:22;87:8;141:15 choice (5) 46:11,12;151:13; 167:18;187:13 choked (1) 127:3 chomping (1) 146:12 choose (3) 187:16;189:22; 193:11 Chris (1) 170:20 chronic (11) 16:11,17;17:15; 20:15,17;32:1;51:8; 66:18;75:2;104:20,21 chronically (2) 67:15,17 chronologic (1) 73:9 chunk (1) 39:3 church (1) 103:15 cigarette (1) 79:3 cigarettes (2) 144:1,2 circle (2) 90:12;91:13 circulatory (1) 135:14 citizens (1) 180:16 city (2) 158:7,12 claim (5) 43:12;61:17;62:5,6, 16 class (8) 9:21;60:20;94:4; 107:1;158:9;176:1,2; 177:7 classes (3) 163:11;175:3,3 classic (1) 106:20 clean (2) 43:21;60:18 clear (10) 34:11;61:2;101:6; 103:4,9;115:12,21,22; 129:15;135:14 clearance (1)
C				
calculate (1) 179:16 calculation (1) 187:10 call (2) 116:3;120:9 called (3) 111:10;127:17; 185:16 calling (1) 43:11 came (9) 70:20;72:17;91:14; 95:10;109:15;119:22; 143:10;145:5;155:21 camel's (1) 79:11 can (96) 10:9;11:9;12:3; 16:1;20:7,15;22:14; 23:5,12;29:21;32:13; 36:1;38:6;39:22;40:8; 41:10;42:17;43:5,16; 47:2;50:18;55:5,7; 58:12,22;59:14;61:15; 62:10;64:15,15,19,20; 65:1;73:17;77:9;79:2, 3,6,16;80:8;82:21; 92:4,7,94:12;95:1; 96:5,8,11,20;98:7,11; 99:5;100:18;102:15; 110:8;114:11;115:3; 116:16;117:3,8,12,22; 121:16;123:10; 128:14;134:3;136:18; 138:4,8;142:10; 143:11;148:10; 156:16;159:16;160:8; 161:6;164:5;165:5; 166:6;168:8;169:15, 16;170:20;172:10; 173:10,12,18;175:12; 177:6;179:16;193:3,8; 194:7,9,19;196:9 canabinoids (1) 17:7 candidates (2) 38:13;39:7 cannabinoid (20) 6:17;12:7,20;14:7,				

134:2 cleared (1) 169:10 clearest (1) 143:15 clearly (4) 65:13;75:5;122:4; 190:2 clinic (2) 123:5;151:16 clinical (45) 8:5;11:22;19:1,11, 15;29:10;32:3,12; 33:7;40:20;41:2,12, 14,21;46:8,10,13; 47:7;56:5,14;57:11; 66:8;70:7;77:17;79:4; 82:18;106:16;109:1; 118:3;150:18;175:5, 13;178:12;181:17; 188:16,19;189:2,12; 190:8,11,15,21;191:4, 11,13 clinically (8) 9:7;43:7;66:9,11; 71:22;106:18;124:10; 129:13 clinician (4) 24:22;47:1;73:10; 108:19 clinics (1) 123:1 clonidine (1) 84:20 closed (1) 98:12 closer (3) 80:8;168:8;171:16 closest (1) 97:7 closing (1) 48:6 clue (1) 174:21 co-administration (1) 93:6 Coca-Cola (2) 73:1,7 cocaine (12) 23:21,22;49:19,22; 63:17;130:11;132:2; 144:14;149:21;150:1; 159:6;164:2 code (1) 90:6 coding (2) 83:7,9 coffee (2) 31:3;105:18 cognition (3) 69:6;112:5,7 cognitions (1) 112:12	cognitive (7) 54:12;70:2;72:4,8; 76:5;81:11;85:17 coherently (1) 86:1 cold (1) 59:11 colleagues (2) 5:7;97:14 collect (2) 135:4;183:16 collected (2) 114:5;179:17 collecting (1) 83:1 colonels (1) 144:19 color (1) 142:8 Colorado (1) 40:6 Columbia (3) 8:10;59:6;172:2 combination (5) 17:17;44:13;75:1; 137:22;185:14 combinations (1) 26:5 combine (3) 20:18;28:17;185:22 combined (1) 41:9 COMER (24) 10:4;11:13;32:20; 33:2;37:9;51:17;58:9, 22;62:10,12;123:14; 128:14;132:10; 139:15,21;142:15,17; 143:4;153:4,20; 166:11;172:3,5,8 comfortable (3) 5:20;30:20;80:10 coming (12) 7:18,19;26:4;39:16; 48:2;82:8;140:13; 147:19;150:22; 163:17;164:14;174:21 comment (29) 20:7;28:7,21;29:4; 30:12;31:14;34:19,20; 35:14,19;36:13;42:8; 45:8;48:10;51:18; 52:4;65:4;66:19; 78:11,16;82:12;95:6; 101:1;105:14,15; 120:22;141:18;153:3, 4 commentary (2) 60:2;189:6 comments (15) 3:6;7:1;14:13;28:1; 71:21;78:12;99:14; 105:1;115:7;123:12;	128:15;185:18; 192:20;193:17,18 commercial (2) 26:10;27:10 commercialization (1) 191:7 Commission (1) 27:13 commitment (1) 78:19 commonalities (1) 20:4 communities (1) 142:1 community (9) 68:6;71:16;95:7,10, 14,22;96:1;123:9; 142:10 comorbidities (2) 28:8;45:1 comorbidity (2) 23:15;58:1 companies (1) 26:18 company's (1) 32:7 comparable (1) 98:18 comparative (3) 11:4;36:18;114:18 comparator (1) 115:16 compare (4) 35:19,21,21;36:9 compared (7) 10:1;11:6,6;63:16; 107:1;109:19;148:13 compensate (1) 154:22 compensation (2) 154:20,21 competition (2) 99:4;149:10 competitive (1) 138:7 competitor (1) 96:15 complain (3) 58:5;81:2;82:7 complaining (1) 81:20 complaint (3) 57:5;73:17;77:5 complaints (3) 55:12;61:22;73:11 complement (1) 77:8 complete (2) 79:17;183:18 completely (5) 33:9;39:5;89:16; 94:13;187:17 complicated (3)	31:7;52:3;63:5 component (5) 18:9;49:9;100:9; 116:9;169:10 components (4) 16:7;21:5,6;141:11 composed (1) 112:15 compound (4) 3:18;20:14;168:6, 18 compounds (12) 6:9,17;21:10,11,20; 26:6;31:12;67:3,10; 107:12,15;174:1 comprehensive (1) 186:5 compromise (1) 123:17 compulsive (1) 94:6 concentration (3) 131:21;134:22; 158:18 concentrations (1) 134:1 concept (5) 95:9;125:22; 148:17;157:17,22 conceptually (1) 147:12 concern (7) 66:17;67:5,13;80:4; 117:9;129:3;142:7 concerned (4) 68:9;122:20;135:8; 144:11 concerning (2) 67:1;97:16 concerns (8) 39:5;48:21,21; 67:17;85:19;103:21; 124:11;130:6 conclusions (1) 174:8 concomitant (1) 61:22 concrete (1) 20:19 concurrent (1) 92:9 condition (2) 20:12;54:5 conditions (6) 18:16;21:3;28:9,15; 104:20;116:12 conducted (1) 114:6 confounds (1) 54:3 confused (1) 17:22 congressional (1)	119:18 conjunction (1) 74:2 cons (1) 137:7 consensus (8) 80:3;106:1;143:13; 174:20;176:12;177:5; 178:17;196:9 consequence (1) 58:10 consequences (1) 143:15 consider (8) 11:12;17:13;18:7; 53:17;58:12;112:18; 117:18;163:11 consideration (2) 29:17;77:19 considering (3) 3:20;64:8;160:21 consistent (2) 94:4;169:5 consistently (3) 89:16;93:17;94:5 constantly (1) 17:22 construct (1) 184:16 contact (1) 5:18 contacting (1) 26:17 contained (1) 126:5 context (5) 13:18;76:10;90:18; 102:14;135:5 continue (4) 55:15;68:8;104:6; 118:20 continued (2) 47:21;157:6 continues (3) 89:14;103:12;122:1 continuing (2) 120:5;123:2 contraceptive (1) 97:15 contribute (1) 194:13 contributes (1) 80:16 control (5) 36:6;100:17;113:9; 152:16;154:21 controlled (4) 100:8,9,21;167:1 controlling (1) 20:22 controls (1) 134:11 controversial (3)
--	---	---	--	--

143:11;166:13; 167:19 conundrum (2) 68:10;75:21 conveniently (1) 101:22 conversation (5) 30:16;55:1;64:4; 89:1;120:17 conversations (1) 88:18 convey (3) 3:9;7:7;89:6 convince (1) 148:3 convincing (3) 67:2;102:9;114:16 cool (1) 93:3 cooperate (1) 98:18 copious (1) 4:4 core (1) 68:21 correctly (3) 55:6;114:10;133:11 correlational (1) 110:22 cortex (1) 110:12 Cosmetic (1) 119:2 cost (3) 32:2;87:8;136:8 costs (1) 44:1 counteract (1) 131:20 counter-culture (1) 106:3 counting (1) 91:21 country (4) 30:9;54:3;151:13; 152:3 couple (14) 14:13;28:1;48:7; 73:4;84:4;85:11; 104:11;122:6;126:10; 128:18;131:2;160:15; 167:2;190:12 course (8) 39:21;60:4;68:11; 103:1;104:21;106:3; 136:5;166:10 covered (1) 160:16 covertly (1) 93:1 CPED (1) 184:2 craving (16)	21:2,4;59:16,16,22; 60:3,9;62:17,19,21; 63:3,4;122:1,3,9; 161:11 Craving's (1) 62:20 crazy (2) 19:14;141:9 create (1) 98:11 created (2) 3:17;98:1 creating (1) 93:2 creation (1) 99:7 creative (1) 40:2 credentialing (1) 109:9 credentials (1) 109:6 credibility (1) 43:5 criminalization (1) 103:20 crisis (1) 138:19 criteria (5) 16:18;50:1;81:19; 180:9,22 critical (3) 100:9;121:15; 172:14 cross-diagnostically (1) 184:13 cross-react (1) 139:6 Crosstalk (2) 151:8;184:1 CTN (1) 46:11 cultivar (1) 14:8 cultural (1) 55:8 cure (1) 167:20 curious (4) 10:5;64:7;145:11; 171:19 current (2) 40:1;159:11 currently (2) 114:2,11 customers (1) 153:18 cut (1) 31:13 cutting (1) 144:13 cynical (1) 158:14	D daily (1) 182:3 damage (1) 97:19 dampening (1) 13:12 dance (1) 176:8 dangerous (3) 26:3;52:14;68:2 data (27) 4:13;11:4;28:4; 47:6,6;49:18;51:14; 55:15;75:10;78:3,22; 83:1,8,15;89:16; 94:14;104:16;110:11, 22;111:18;114:5; 118:18;120:9;129:15; 175:12,13;179:17 date (2) 78:8;130:7 daughter (2) 83:18;84:2 David (15) 20:8;23:8;25:15; 27:21;39:12,15;78:13; 95:3;97:2;99:13; 102:2;104:9;110:10; 145:7;185:10 Davis (1) 110:10 Day (25) 3:3,4,4,8;9:15,16; 37:14;68:16;70:9; 79:4;82:22;85:3,22; 87:20,21;92:6;143:14; 160:16;161:14;171:1, 3;182:6,10,13;194:3 days (4) 111:10;128:18; 183:8;190:12 daytime (2) 84:22;85:5 DEA (2) 141:7,9 deal (3) 64:1;71:10,12 dealer (1) 153:16 dealers (1) 158:9 dealing (5) 91:22;105:7;126:2; 150:11;191:15 death (3) 119:22;134:15; 138:13 decades (2) 105:21;125:13 December (2)	164:18,19 decide (1) 194:13 decided (1) 172:11 decision (2) 43:6;124:6 decisions (1) 23:3 decline (1) 130:9 decrease (5) 26:10;48:14;76:1; 126:18,18 decriminalization (1) 103:16 decriminalized (1) 104:14 deep (3) 112:1,1,3 default (1) 176:6 Defense (5) 133:3;136:17; 139:12,18;140:7 defer (1) 178:16 define (3) 45:20;46:15;132:8 defined (1) 178:2 definitely (3) 78:3;138:15;173:6 definitive (1) 126:12 degree (1) 150:4 delayed (1) 156:14 delivering (1) 101:13 delivery (3) 100:12,20;115:11 dementia (2) 67:2,11 demonstrate (1) 62:1 demonstrated (1) 50:13 demonstrating (2) 61:18;181:17 Dennis (6) 3:6;16:3;161:20; 176:16;192:6;195:15 Denver (2) 103:16;104:14 Department (4) 133:3;136:17; 139:12;140:7 depend (1) 13:8 dependence (1) 49:19	dependent (5) 22:16;52:18;69:21; 143:13;167:11 depending (3) 6:19;17:7;21:16 depends (1) 144:17 depot (2) 142:21;159:14 depressed (1) 74:6 depression (16) 14:20;45:3;49:1; 52:20;65:20;76:4; 99:20;106:7;116:10; 133:16;134:7,13; 135:6;153:10;154:2,4 depressive (1) 99:17 derivatives (2) 139:7,9 describe (1) 93:17 describing (1) 97:9 deserves (1) 145:10 design (20) 3:15;6:10;7:2,13; 8:6;9:13;17:6;23:6; 33:15;34:9,12;38:17; 42:16,22;43:4;52:4,9; 53:10;176:13;181:22 designation (1) 166:7 designed (1) 46:8 designs (4) 9:20;19:15;93:8; 189:3 desire (1) 53:5 despite (1) 97:21 detail (1) 109:12 detectability (1) 182:7 determine (2) 64:22;177:7 detox (5) 11:15;26:16;52:11; 122:14;167:2 detoxified (1) 92:3 develop (6) 33:17;42:15;43:21; 130:3;136:5;168:22 developed (5) 26:9;27:9;78:20; 108:2;112:2 developing (4) 93:5;107:5;112:3;
---	--	---	--	--

<p>136:2 development (13) 27:10;33:17;43:17; 77:1;85:12;104:5; 107:14;108:9;129:21; 130:7;132:17;164:12; 191:6 developments (1) 175:9 device (1) 85:7 devices (3) 86:19;150:13; 161:11 diagnosis (1) 180:10 diagnostic (1) 180:21 dialogue (3) 27:5,20;142:12 dicey (1) 92:16 die (1) 125:6 difference (4) 46:18;51:3;109:19; 148:12 differences (1) 20:5 different (59) 3:20;8:17;9:14,16, 17;11:20;13:21;14:1; 16:6,7,9,12,17;17:12; 19:20,21;20:2;22:3,3, 6,7,22;24:1,2;30:7; 32:1;35:21;36:16; 37:16,17;38:18;49:12; 52:8;55:4,8;58:12; 59:4;63:21;77:10; 108:8;113:6;115:15; 117:17;128:16;132:5; 136:20;148:16;149:3, 7;177:21;178:1,3; 187:17,18;189:18,18; 190:2,15;191:1 differently (1) 188:5 difficult (2) 93:17;148:9 difficulty (2) 173:15;175:16 digested (1) 55:22 diphenhydramine (1) 114:13 direct (3) 62:12;111:11; 133:14 directed (1) 126:9 direction (5) 49:6;63:2;72:2,10; 76:13</p>	<p>directions (4) 92:12;108:8; 111:17;140:13 directly (2) 110:18;126:1 director (1) 122:15 discern (1) 54:9 discontinuum (1) 122:10 discounting (1) 156:15 discouraged (1) 68:2 discovered (2) 83:19,21 discrete (1) 61:1 discrimination (1) 174:7 discuss (1) 132:12 discussed (4) 22:2;29:16;186:1; 188:18 discussion (28) 4:4;6:6;8:6;17:21; 32:21;53:15;56:12; 86:6;88:16;90:10,13; 106:14;108:17; 120:15;124:15;127:6; 140:11;145:11;152:1, 8;160:3,3;161:16; 163:3;176:7;186:8; 190:12;195:13 discussions (1) 180:3 disease (6) 65:11,12,16;66:7,7; 157:20 disorder (62) 6:13,22;7:15,20; 8:2;10:16;14:18; 15:10;16:14,19;17:18; 19:13;24:13;33:11; 37:19,21;45:12,15,21; 50:2,17,19;59:2,12, 22;61:18;62:4,5,7,18; 64:7;66:21;69:5;70:8; 71:1;73:16;74:1,18, 19;76:10;78:21; 79:14;80:5,12,16,20; 81:2;99:17;106:17; 121:1;126:16;129:3; 132:17;136:7;164:11, 12;175:21;176:19; 180:10,10,22;182:1 disorders (11) 28:19;29:11;56:6; 61:21;67:19;69:20; 99:20;132:2;175:6; 177:16;178:2</p>	<p>dispensaries (2) 36:9;55:6 dispensary (3) 29:22;36:1;54:6 dispense (1) 98:10 dispensing (1) 182:3 displayed (1) 30:6 disruptions (1) 87:22 distinction (2) 12:6;62:9 distortion] (1) 148:22 distracted (1) 88:17 distributed (1) 192:15 distribution (3) 98:12;154:15;155:9 disturbance (5) 56:6,9;74:13;81:20; 82:7 disturbances (3) 80:4;81:3;95:16 dive (1) 128:13 diversion (2) 125:18;128:20 diving (2) 74:14;75:20 Division (1) 76:16 divorced (1) 20:1 DMT (1) 120:6 docs (1) 123:4 doctoral (2) 101:7;108:18 doctors (2) 45:17,18 document (1) 186:16 DoD (2) 135:7;150:10 do-it-yourself (1) 170:18 dollars (1) 119:18 domain (6) 184:13,14,16,17; 185:1,9 domains (2) 175:2,14 done (28) 4:11;14:15;20:13; 49:17;53:20;79:4,20; 99:22;101:3;106:22; 107:3,6,10;114:1;</p>	<p>115:3;117:14;118:1; 121:4,4;141:16; 161:10;171:20;177:9; 178:10;182:1,19; 186:16;190:17 door (3) 48:2;143:8;195:10 dopamine (1) 110:16 dosages (1) 138:13 dose (17) 21:12;41:9;44:13; 114:4,13;117:12,12; 131:21;134:10;146:1, 21;148:12;153:7,8,9; 154:1;171:2 dose-related (2) 12:16,19 dose-response (1) 31:10 doses (8) 9:16;34:7;108:4,5; 114:14;131:12; 153:14,15 dosing (3) 11:11;55:5;101:9 dovetails (1) 65:4 down (15) 21:5;54:6;83:13; 84:3;88:9;98:5;113:2; 135:20;138:16; 159:20;160:10;174:5, 16;177:6;183:19 dozens (2) 10:14;139:8 DR (436) 3:4;4:16,21,21;5:1, 12,15,18,21;6:2,4,7; 7:9,12,17,22;8:1,8; 9:11;10:3,4,11;11:13; 12:11;13:5;14:2,3,12; 15:4,6,7,10,12,13,15, 18,19;16:3,4;18:18, 21,22;20:7,8,10,10; 21:22;22:1;23:8,9; 25:8,11,12,14,16,18, 20;27:21,22;29:14,15; 30:12,13,14,15;31:13, 15;32:19,20;33:1,2; 34:11,17,18,20,22; 35:2,4,6,8,10,11,13, 14;37:1,3,4,5,7,8,9,9; 38:21;39:12,13,15,16; 42:5,7;45:6,8;48:6,10; 49:15,16;50:4,18,22; 51:2,7,10,13,16,17; 53:16;56:2,19,20,22; 58:8,9,21,22;59:19; 61:9,11,12;62:10,11, 12,20;63:2,4,8,11; 64:2,3;65:7,9;66:14,</p>	<p>16;67:20,22;68:18,19; 70:5,6,12;71:19,20; 72:15;73:3,10,13,14; 74:5,8,9,16;75:1,16; 76:4,7,9,15,16;78:5,7, 13,15;80:1,2,8,9;81:4, 5,16,17;82:4,5,10,11, 14;83:6,17;84:2,6,10, 12,13,14,18;85:4,6,8, 11;86:21;87:4,17,19; 88:2,17;89:9,19,21; 90:1,2,3,5,7,9,10,12; 91:11,13;93:12,14; 95:2,4;96:20,21;97:5; 98:22;99:2,5,6,12; 101:22;102:4;104:9, 11;106:11,13;108:11, 15;111:19,20;113:4,6, 20,21;114:1;115:5,8; 116:21,22;120:11; 121:14;123:13,14; 124:12,13;126:6,12, 13;127:7;128:14; 131:2,5,9;132:10; 133:5,7;134:3;135:18; 136:4;137:9,10;139:2, 15,16,21,22;140:6; 141:18,20;142:15,16, 17,18;143:4,6;144:22; 145:7,8;146:9,11,12; 147:8,16,19;149:9,11, 12,16,18;150:15,16, 22;151:2,3,6,9,14; 152:10,21;153:4,20, 22;155:11,13,17,20; 156:1,2,10,11;157:11, 12;159:20;160:1,2; 163:4,15;164:8,14,16, 20,21;165:1,4,5,11,13, 14,15,16;166:1,11,14, 15,16,22;167:15,21; 168:1,2,3,8,9,14,16; 169:8,12;170:1,2,19; 171:5,8,10,18,19; 172:1,3,4,5,6,8,10,13, 19,21,22;173:2,6,7,10, 11,12,13,15;174:12, 14;175:15,20;176:1,2, 3,14;177:1,14,17,18, 19;178:4,13,20;180:1, 3,19,21;183:22;184:3, 5,9,11,20,22;185:2,3, 10,11;186:9,10;187:3; 188:6,12;189:13,21; 190:10,18,20;191:3, 13,16;192:3,6,8; 195:2,3,14,21;196:4,7, 10,12 drafting (1) 76:22 drafts (2) 192:13;194:12 drags (1)</p>
--	--	---	--	--

<p>153:17 drastically (1) 178:3 drawing (2) 152:8;174:9 dread (1) 127:20 drinking (3) 72:22;73:7;143:1 drive (2) 133:16;153:6 driven (2) 89:16;94:14 drives (1) 74:22 driving (3) 57:6;133:22;134:21 dronabinol (5) 8:11;9:3,4;11:5,19 drop (1) 155:1 dropout (1) 47:13 dropping (2) 23:18;47:9 drug (60) 9:15,18;22:17; 31:10;38:3;60:20; 61:13,14,17;63:19; 65:13;70:15;71:14; 72:19;76:22;77:15; 80:17;92:11;94:4,6; 96:14;98:2,6,9,10,16; 104:5;107:14,22; 108:9;113:14;114:14; 119:2;133:19,21; 136:9;141:14;142:13; 144:15;151:13,13; 152:15;154:14;164:2, 12;166:4;167:17; 168:5,10;174:6;175:3, 3;176:1,2,9;177:7; 180:13;182:15; 187:13;191:6 drug- (1) 92:11 drug-drug (2) 34:6;92:4 drugs (29) 9:21;17:17;22:20; 23:2,12,17;29:2; 67:15;69:16,17;81:1; 92:5,20;95:11;96:3; 97:18,21;98:17; 103:20;107:1;113:1; 117:2;118:8;141:12; 163:10,11;165:15,19; 166:2 drug-seeking (1) 13:14 drug-use (1) 76:10 drug-using (1)</p>	<p>95:22 due (1) 150:2 Duke (2) 164:9,16 duration (2) 130:17;186:3 during (13) 58:18;60:22;70:15; 84:19,22;87:13,20,22; 101:9;121:5;122:14; 157:13;167:8 Dustin (6) 25:15;29:14;32:14; 174:13;177:18;178:4 Dustin's (1) 70:9 Dworkin (12) 4:21;171:19;178:4; 180:1;188:12;189:21; 190:18;191:3;195:2, 14,21;196:4 Dworkin's (1) 34:15 dye (1) 143:12 dying (1) 137:21 dysfunction (2) 69:6;117:6</p>	<p>effect (18) 12:15;30:19;50:8; 61:18;62:3;65:2; 92:14,14;107:9; 111:11,14;115:1; 136:10;137:2;153:9, 22;166:3;185:1 effective (18) 10:17;20:15;23:10; 31:21;49:9;61:17; 62:16;91:20;107:20; 108:1;121:6;124:20; 134:6;136:8,10;154:3, 13;155:7 effectively (3) 101:8;116:17;186:8 effectiveness (2) 36:5,19 effects (25) 12:19;13:13;28:11; 49:13;50:12;51:15; 52:13;63:13;67:8; 68:8;69:12;107:18; 110:4,21;111:4; 115:16;129:22;133:1, 12,14;170:5;171:6,13, 13;187:14 efficacy (10) 6:19;11:4;21:8; 36:11;50:13;77:17; 114:18;117:11; 187:20,22 efficient (1) 181:5 efforts (1) 48:13 egg (1) 72:12 either (17) 3:17;14:16;21:19; 24:2,11;35:22;46:5; 53:20;65:14;66:5; 74:3;121:10;128:11; 130:12;146:19;161:6; 193:11 EKG (1) 179:14 elaborate (1) 96:11 elements (2) 21:7;91:1 eligible (1) 100:5 eliminated (1) 119:7 eliminating (1) 152:18 elimination (2) 69:2,9 Els (4) 20:8;21:22;34:19; 35:5 else (14)</p>	<p>10:1;19:8;21:17; 25:6;36:2;52:6;83:20; 131:1;143:20;144:11, 14;158:4;178:16; 182:16 em (1) 148:5 EMA-approved (1) 21:20 embolism (1) 97:19 embrace (1) 100:6 emergency (5) 95:21;140:11; 147:20;152:14,14 emerges (1) 49:3 emerging (5) 64:12;188:17; 190:5,8;191:18 emotion (1) 69:6 emphasis (1) 177:10 emphasize (2) 137:16;139:11 empirically (1) 116:7 emulating (1) 155:18 encompass (1) 188:8 encounter (1) 132:3 encourage (1) 194:3 encouraged (1) 142:3 encouraging (1) 94:20 end (12) 77:16;78:10; 143:14;152:17; 153:14;159:21; 167:11,12;181:16; 185:6;192:4;196:14 ended (1) 70:17 endorse (1) 100:6 endorsed (1) 71:17 endotypes (1) 24:2 endpoint (9) 53:1;179:11,13,14, 20;181:16;184:17,18; 185:7 endpoints (9) 38:17;53:13;58:12; 62:4;179:8,10;181:20; 186:20;187:5</p>	<p>ends (2) 169:18;189:19 enforceable (1) 122:20 enforced (2) 90:17;123:8 enforcement (2) 136:19;166:19 engage (1) 76:1 enhance (1) 47:2 enough (14) 19:5;32:3;42:16; 45:18;46:17;56:4,6; 57:16;74:8;118:4; 138:6;164:3;181:12; 183:11 enrolled (1) 189:3 entering (2) 111:21;112:19 entertain (1) 161:19 entertains (1) 65:12 enthusiastic (1) 169:21 entities (1) 37:16 environment (2) 102:18,20 envision (3) 91:10;129:7;186:14 enzymes (1) 168:12 epidemic (2) 158:20;163:17 epidemiological (1) 28:4 epidemiology (1) 163:19 Epidiolex (1) 44:6 episodic (1) 92:6 equal (2) 99:7;147:7 equally (3) 60:6;136:21;154:3 ER (1) 148:3 Eric (8) 3:3;56:2;78:20; 95:2;96:20;185:19; 188:12;192:15 Eric's (1) 12:11 escalate (1) 149:8 esketamine (5) 109:18,20;115:18, 20;120:21</p>
E				
<p>Earlier (3) 107:7;108:8;133:7 early (5) 120:17,22;129:21; 164:18;192:4 ears (1) 186:9 easier (1) 34:3 easily (1) 175:12 East (1) 170:19 Eastern (1) 170:22 easy (5) 82:19;124:21; 130:1;131:19;166:22 eating (3) 72:21;73:6;165:10 echo (1) 78:15 editorial (1) 189:5 educate (1) 5:16 educated (1) 19:9 eerie (1) 35:6</p>				

<p>especially (9) 3:20;54:22;69:19; 92:20;131:11,17; 136:6;152:11;183:3</p> <p>espouse (1) 68:13</p> <p>Essentially (10) 43:2,11;132:8; 134:10,14,18;148:7; 169:14;170:3,18</p> <p>et (7) 22:20;23:2;36:9; 79:1;135:7;136:11,14</p> <p>ethical (3) 39:5;124:11;156:21</p> <p>Ethically (1) 93:3</p> <p>ethics (2) 141:21;145:2</p> <p>euphoric (1) 153:9</p> <p>Europe (2) 141:16;170:22</p> <p>evaluate (1) 104:2</p> <p>evaluated (1) 43:19</p> <p>evaluating (1) 17:2</p> <p>evaluations (1) 38:18</p> <p>even (34) 5:13;9:8;12:1;31:2; 33:10;43:21;48:4,4; 55:16;67:1,18;79:2; 82:19;86:14;92:15; 100:3;114:5;115:13; 119:10;122:6;132:1; 137:5;144:6;145:18, 21;151:20;157:4; 158:1;159:3;178:2; 179:19;183:15;185:9; 190:17</p> <p>event (1) 137:6</p> <p>events (3) 97:17;117:5;137:6</p> <p>everybody (10) 38:19;56:19;138:5; 140:20;144:20;153:6; 154:19;178:4;196:5, 13</p> <p>everybody's (1) 195:9</p> <p>everyone (7) 60:17;64:11;109:4, 11;124:13;125:9; 137:13</p> <p>everyone's (2) 101:19;142:11</p> <p>evidence (5) 32:15;102:10,22; 108:7;114:21</p>	<p>exactly (7) 13:10;22:4,7;38:21; 70:21;158:6;167:22</p> <p>example (34) 5:22;11:16;13:9; 16:11;20:13,14;21:3; 22:15;28:11,12;31:2; 35:21;48:21;49:7; 57:13;65:17;76:1; 78:18;79:1;107:18; 109:13;132:2;136:16, 17;143:5;153:12; 154:16;184:17,18,20, 22;185:3;189:1; 195:14</p> <p>examples (3) 189:22;190:3,6</p> <p>excellent (1) 147:13</p> <p>exceptions (1) 176:5</p> <p>exchange (1) 133:15</p> <p>excited (2) 11:10;58:13</p> <p>exciting (1) 89:10</p> <p>exclusionary (1) 9:5</p> <p>executive (4) 86:2;112:5,12; 185:9</p> <p>exercise (3) 33:14;53:11;54:11</p> <p>exist (1) 3:17</p> <p>existing (3) 6:18;122:2;187:6</p> <p>expand (1) 90:20</p> <p>expanded (1) 112:3</p> <p>expect (4) 183:5,6,15;187:18</p> <p>expectation (2) 187:20,22</p> <p>expectations (1) 92:21</p> <p>expected (1) 128:19</p> <p>expecting (2) 129:17;130:18</p> <p>expensive (1) 108:21</p> <p>experience (11) 60:6;69:4,7;82:2; 92:13;97:6,8,15; 111:2,7;113:19</p> <p>experiment (2) 28:2;54:3</p> <p>Experimental (9) 13:1;19:1,1,11; 20:6;32:3,9,12,15</p>	<p>experiments (2) 110:1;134:5</p> <p>expert (4) 35:15;89:8;186:19; 188:5</p> <p>expertise (1) 97:6</p> <p>experts (1) 8:2</p> <p>explain (1) 99:5</p> <p>explore (1) 187:4</p> <p>exploring (2) 101:2;108:10</p> <p>expose (2) 134:8;144:3</p> <p>exposed (1) 144:5</p> <p>exposure (1) 137:7</p> <p>extended (1) 189:6</p> <p>extensive (1) 118:3</p> <p>extent (2) 133:20;171:4</p> <p>extract (2) 170:11;172:8</p> <p>extrapolate (1) 174:4</p> <p>extreme (1) 102:16</p> <p>extremely (6) 32:6;97:16;138:1; 148:9,11;150:10</p> <p>eyes (1) 168:1</p>	<p>factors (3) 58:2;89:17;170:15</p> <p>factory (1) 141:14</p> <p>fades] (4) 73:9;110:17; 113:14;127:20</p> <p>failed (4) 25:10;48:17,19; 49:11</p> <p>fairly (2) 22:19;194:4</p> <p>faith (1) 121:17</p> <p>fall (2) 87:13;124:16</p> <p>falling (3) 84:22;87:13;125:11</p> <p>false (1) 182:11</p> <p>familiar (3) 76:20;86:11;118:8</p> <p>far (8) 60:18;65:12; 122:14,19;125:16; 138:4;155:3;159:3</p> <p>fashion (1) 66:19</p> <p>fashionable (1) 108:6</p> <p>faster (1) 154:11</p> <p>fast-track (1) 166:7</p> <p>fatal (2) 12:18;94:11</p> <p>fault (1) 124:4</p> <p>FDA (24) 14:3;27:16;53:22; 58:11,19,21;62:15; 65:12;68:1;90:17; 96:7;100:12;115:11; 117:17;121:11; 123:10;126:10; 134:17;140:15;164:8; 169:9,10;171:14; 183:17</p> <p>FDA-approved (2) 21:11,20</p> <p>FDA's (1) 83:6</p> <p>fear (1) 24:21</p> <p>feasibility (3) 105:2;112:16; 130:21</p> <p>feasible (1) 33:22</p> <p>feature (1) 191:16</p> <p>features (1) 75:20</p>	<p>Federal (6) 27:13;39:17;40:1; 41:20;68:1,12</p> <p>feedback (1) 60:11</p> <p>feel (11) 25:1;61:1;74:6; 86:17;122:9;137:17; 140:10;163:7;187:1; 192:20;195:9</p> <p>feeling (2) 92:19;180:7</p> <p>feels (1) 38:19</p> <p>felt (1) 118:4</p> <p>FEMALE (7) 140:3;150:21; 151:4;167:22;169:6; 183:21;184:2</p> <p>fentanyl (48) 131:17,22;132:3,4, 4;133:1;134:9;137:18, 19;138:1,2,8,10,13,20; 139:7,20;140:21,22; 141:3;144:10,14; 145:9,17;146:22; 148:8,14,15;150:3,8, 17;151:1,2,12,17; 152:7,13,15,18,22; 153:7,11,15;154:11; 155:2,7,8,16</p> <p>fentanyls (1) 139:6</p> <p>Fentanyl's (1) 149:6</p> <p>few (6) 69:13;84:4;127:10; 151:9;156:17;176:5</p> <p>field (11) 19:8;22:11;23:20; 35:20;48:18;97:15; 111:1;116:1;150:7; 170:22;184:12</p> <p>fight (1) 125:2</p> <p>figure (4) 54:8;84:10;175:2; 177:4</p> <p>figured (1) 170:10</p> <p>figuring (1) 71:6</p> <p>fill (2) 140:4;192:8</p> <p>filter (1) 176:9</p> <p>final (6) 29:4;50:11;87:2; 106:5;141:10;195:13</p> <p>finalize (1) 193:15</p> <p>finally (2)</p>
		F		
		<p>face (2) 100:15;122:4</p> <p>faced (1) 101:17</p> <p>face-to-face (1) 182:2</p> <p>facilitated (1) 110:2</p> <p>facilitation (1) 116:18</p> <p>facilitator (1) 116:4</p> <p>facilities (2) 98:8,8</p> <p>fact (15) 15:8;27:12;81:10; 91:16;97:21;122:10; 135:4;138:3;139:3,9; 146:6;153:22;158:13, 17;193:1</p> <p>factor (3) 53:9;57:21;105:12</p>		

130:15;154:8 Finan (1) 64:5 find (12) 23:22;43:9;47:12; 93:10;130:12;140:21; 161:16;168:18,21; 169:5;174:15;179:18 finding (4) 9:2;23:14;81:7; 92:17 findings (3) 10:8;86:20;94:2 fine (8) 18:13;25:18;61:13; 91:6;180:15,17; 189:14,19 firefighters (1) 166:19 firm (1) 196:7 first (24) 5:4;14:14;15:1; 28:14;38:5;46:7;47:2, 16,17;48:3;52:11; 59:19;72:13;95:5; 102:8;107:7;111:9; 114:3;123:6;132:20; 140:19;142:21;155:6; 192:15 first-line (2) 92:18;122:12 fit (2) 121:3;122:18 Fitbit (4) 83:18,20;86:9;87:7 fits (3) 121:12,14;156:15 five (1) 120:12 fix (2) 80:18;84:8 fixing (1) 84:14 flagged (1) 178:14 flattered (1) 6:2 flexibility (2) 44:17;54:12 flipping (1) 17:21 focus (13) 56:15;60:18;63:22; 64:8;65:5;79:10; 85:17;129:10;138:19, 20;188:18;190:10; 194:5 focused (4) 82:20;106:15; 121:9;176:10 focuses (2) 133:19;175:21	focusing (4) 29:11;107:10; 126:20;129:2 fold (1) 84:3 Folding (1) 83:21 folks (18) 25:13;38:22;39:3; 70:17;71:4,11;89:13; 99:21;100:3;102:17, 19;108:20;124:21; 125:20;146:2;164:9; 170:17;177:1 follow (6) 4:16;27:22;51:17; 70:6;94:2;186:11 followed (1) 50:7 following (2) 104:12;188:13 follow-up (2) 101:11;112:21 fond (1) 103:19 font (1) 194:6 Food (1) 119:1 fooled (1) 114:8 foot (1) 44:2 force (2) 105:6,10 forefront (1) 164:15 forget (1) 172:7 form (1) 170:13 formulation (1) 125:19 formulations (1) 159:14 forth (3) 38:17;134:9;195:17 fortunately (2) 124:13;125:8 forward (16) 4:13;19:3;31:20; 40:3;41:12,21;60:9; 106:9;114:17;161:17; 163:14;168:13;179:8; 188:20;190:2;196:9 found (9) 8:13,19;26:8;46:4; 49:19;63:15;70:12; 127:14;169:15 foundations (1) 175:11 four (8) 122:8;160:16,20;	188:9;189:1,16,22; 190:5 fourth (1) 108:3 fraction (2) 135:3,4 frame (1) 6:14 Frances (14) 10:7;11:22;20:9; 23:8;33:10;39:15; 42:6;45:6;56:21; 91:15;145:7;146:10; 147:17;149:11 Frances' (1) 39:13 free (1) 163:7 frequency (2) 135:3;156:17 frequent (2) 182:20;183:1 frequently (2) 45:10;183:10 friend (1) 95:19 friends (2) 147:22,22 front (1) 84:16 fruit (2) 166:8;191:10 fruitful (2) 178:22;179:21 fulfilled (1) 127:3 full (5) 26:7;59:9;69:4; 112:13,18 fuller (1) 109:8 function (4) 72:4,8;86:2;127:10 functional (1) 180:6 functioning (1) 180:7 functions (1) 185:9 fund (2) 90:4,8 funded (1) 124:22 funder (1) 119:15 funding (1) 90:8 funny (1) 74:11 future (5) 105:22;126:3; 156:12;161:5;175:1 fuzzy (2)	37:20;53:3 G game (2) 157:3,6 Gardasil (1) 142:2 Garland (1) 78:20 Gary (1) 139:13 gas (1) 133:15 gather (1) 102:15 gave (5) 8:11;46:4;52:18; 70:18;87:6 gearing (1) 168:16 gears (3) 48:8;54:13;128:8 gee (3) 54:4;161:17;165:20 Geez (2) 160:22;167:4 general (16) 6:4;62:19;66:17; 75:14,14;83:2;101:3; 103:20;106:1;130:10; 135:19;163:3;174:14, 20;175:8;176:12 generalized (1) 50:19 generalizes (1) 157:5 generally (3) 45:2;76:19;80:18 generals (1) 144:18 generated (1) 118:18 generic (4) 98:16,17;99:1,8 George (1) 169:20 geriatric (1) 87:6 gets (13) 5:6;30:5;43:14,19; 52:14;53:3;77:15; 98:6;100:14;153:13; 192:15;194:4;196:4 GHB (1) 125:17 giant (1) 172:22 gift (1) 87:7 given (10) 7:7;15:8,21;24:22; 40:1;46:7,17;98:19;	120:1;132:20 gives (1) 83:22 giving (9) 3:7;57:13;59:6; 67:15;122:14;123:1, 17;148:15;169:21 glad (1) 132:12 glean (1) 48:11 glitch (1) 84:8 global (2) 181:6,7 goal (4) 34:11;80:6;187:3; 194:10 goals (1) 108:16 goes (13) 31:21;47:14;98:16; 122:14,19;138:16; 139:5;145:18;154:2; 160:14;176:20;195:4, 5 gold (4) 48:1;77:8;78:17; 116:19 good (38) 7:13;10:15;12:21; 16:1;18:14;24:14; 33:5,19;38:2;39:2; 42:4,19;43:9,12,22; 44:7;46:1;68:19; 75:14;77:20;89:19; 107:13;120:18; 121:16;125:17;132:8; 136:4;140:5;142:6; 164:14;166:16; 170:20;173:2;176:21; 177:12;183:13;186:8; 194:22 Google (1) 84:8 gosh (2) 24:22;109:16 go-to (1) 152:15 government (4) 29:7;68:1,12;120:1 grab (3) 88:9;160:10;163:6 grade (5) 21:10;26:19;30:10; 55:5;147:6 gradually (1) 129:19 graduate (1) 109:2 grams (1) 170:14 grand (1)
--	--	--	---	---

54:2 grant (2) 172:17,19 granted (1) 78:17 great (19) 11:16;12:4;27:1; 30:3;42:14;43:3; 58:14;61:15;82:11; 88:2;96:13;101:13; 116:11;117:20; 127:21;144:5;158:2; 167:5;196:15 greater (1) 70:13 greatest (2) 101:19;119:13 greatly (1) 24:19 green (2) 72:21;73:6 Greensboro (1) 168:20 groove (1) 55:2 Group (19) 6:6;7:12;36:10; 45:20;46:15;53:15; 56:16;82:17;88:16; 115:17;127:6;136:5; 149:19,22;150:3; 161:7;168:19;172:16; 195:17 groups (8) 22:10;25:20;91:10; 116:15;142:22;143:3; 144:6,12 growing (2) 82:17;107:2 grown (2) 14:8;21:17 guess (15) 8:1;9:11;10:13; 15:13;19:19;20:5; 39:2;41:22;74:20; 110:21;134:3;139:22; 156:12;171:4;192:13 guesses (2) 19:9;32:13 guessing (1) 114:9 guidance (8) 76:22;78:7;178:20; 180:6;183:21,22; 184:3,4 guidances (2) 178:21;187:6 guidelines (1) 178:16 guiding (1) 116:18 gumption (2) 156:16;157:8	guy (3) 127:14,16,21 GW (2) 20:14;21:10 <hr/> H <hr/> Half (4) 143:6;160:17; 161:14;174:20 half-life (2) 135:15;155:3 hallucinogens (1) 104:14 halted (1) 49:4 hand (3) 121:22;154:2,3 handled (1) 102:16 handling (1) 101:13 hands (1) 98:6 hand's (1) 161:22 hanging (1) 191:10 happen (9) 4:9;91:3;101:20; 103:22;117:21; 129:18,20;158:8,19 happened (4) 118:17;119:14; 139:19;154:19 happening (14) 19:4;22:19;32:10, 14:70;18:97;20;104:2, 16;109:20;112:10; 114:2;151:11;158:21; 169:18 happens (5) 96:14;98:16;104:5; 122:5;158:3 happier (1) 58:7 happy (1) 196:6 hard (9) 75:6;93:1;113:17; 122:15;140:21; 141:13;174:8;175:4; 182:16 harder (2) 151:19,22 harking (1) 105:1 harm (4) 30:19;68:6;71:21; 180:19 harmed (1) 94:9 harmful (1)	68:8 harms (3) 93:21;94:4,6 hate (2) 105:18;106:4 head (2) 4:10;146:17 headache (1) 108:1 HEAL (2) 185:13,16 health (7) 10:14;49:14;83:2; 100:20;138:18; 145:14;157:15 healthcare (2) 101:12;127:2 healthy (2) 85:15;114:21 hear (12) 10:5;35:17;38:15; 39:13;50:22;56:15; 57:5;68:13;80:21; 91:4;160:6;175:17 heard (11) 3:14;35:15;36:11; 80:15;103:17;118:12; 140:1;146:17;155:21; 160:9;174:18 hearing (10) 14:13;16:5;42:8,11, 12;53:19;60:16;68:5; 175:16;188:4 hearings (1) 119:19 heart (2) 82:21;86:12 heavier (1) 146:21 heavy (2) 116:3,11 heightened (1) 67:18 held (1) 133:7 hell (1) 57:14 hello (1) 138:14 help (23) 7:14;8:3,6,11,13; 9:3;14:20;25:17; 50:17;62:1;63:22; 68:13;72:18;83:8,9; 84:15;91:8;95:19; 98:21;126:4;140:12, 14;181:19 helpful (9) 8:22;11:2;23:4; 50:20;59:13;73:20; 178:15;180:2;187:2 helping (5) 4:3;57:16;58:6;	62:2;68:15 helps (1) 95:18 HENDRICKS (2) 64:3;102:4 Henningfield (1) 93:19 herb (1) 168:10 herd (2) 157:17;159:2 heroin (13) 132:6;145:12; 149:22;150:19;151:5, 16,18;153:12;155:4, 15;180:14;182:7,9 hesitant (1) 74:13 high (15) 12:3;24:16;33:13; 47:13;52:16;114:3,13; 117:12;134:21; 143:18;147:3;148:18; 158:18;164:7;170:11 higher (5) 47:10;53:8;139:4; 153:14;187:21 highest (1) 119:10 highlight (2) 161:15;193:19 highlighting (1) 40:4 highly (3) 26:22;102:13;143:2 high-risk (1) 143:12 himself (1) 156:18 historians (1) 102:6 history (11) 22:17;23:1;49:16; 50:10,21;51:6;55:14; 95:6;114:5;118:3,10 hit (1) 177:18 hits (1) 27:3 hitting (1) 29:1 hold (2) 49:9;84:14 holding (1) 152:6 home (4) 68:16;84:16;128:9; 151:20 honest (1) 5:14 honestly (1) 165:1 hope (3)	89:14;124:1;194:20 hopefully (5) 88:18;124:6; 126:18;160:9;194:17 hoping (1) 160:5 Hopkins (5) 93:7;99:21;101:5; 116:15;127:13 horizon (3) 161:3;189:6;190:9 hospital (1) 150:1 hotel (1) 87:1 hour (2) 160:13,13 hours (7) 79:2,6;85:3,8; 87:20;112:16;115:21 Houston (2) 122:22;147:20 HOUTSMULLER (8) 22:1;34:17,20;35:2, 4,8,11,14 huge (5) 128:20;138:7; 144:21;149:1;158:8 HUHN (17) 56:2,19;63:2;68:19; 75:1;81:17;82:5,14; 85:4,8;150:16,22; 151:3,6,9;152:10; 171:10 human (4) 41:16;169:1; 171:20;174:3 humans (7) 102:8,11;103:11; 148:13;173:18;174:2, 4 hundred (5) 84:4;100:18;159:4; 183:7;194:21 hundreds (3) 26:6;107:11;114:7 Hurd (1) 21:1 Hutchinson (2) 40:5;42:3 hygiene (3) 67:16;75:12,13 hype (1) 92:21 <hr/> I <hr/> ibogaine (1) 107:18 idea (24) 7:21;8:11;10:6; 23:12;24:5,20;25:9; 26:10;38:8;42:19;
--	--	--	--	--

43:9,16;45:22;60:2; 64:10;69:12;92:16; 93:5;100:6;103:19; 113:8;117:15;144:5; 176:17 ideal (3) 90:16;97:9;116:9 ideas (5) 56:17;60:15; 108:22;163:9;176:15 identified (5) 58:18;97:16; 115:22;140:20;192:12 identify (3) 143:12;180:4;190:7 identifying (1) 33:6 ignored (1) 69:8 illicit (7) 12:18;69:3,10;94:3; 126:19;149:21;187:13 illicitly (1) 120:2 imaginable (1) 164:7 imagine (6) 20:18;29:12;33:10; 37:10;93:1;105:13 Immediately (3) 33:16,18;106:18 immune (1) 159:18 immunity (2) 157:17;159:3 impact (1) 101:14 impairment (2) 66:22,22 implantable (2) 97:12,15 implement (1) 105:10 implore (1) 183:20 implying (1) 103:1 important (30) 16:19;22:5;37:11; 42:18;43:13;44:12; 46:14;49:10;57:18,21; 60:4,7,9;62:15;63:20; 66:7;69:7;70:17;77:2, 6,12;106:17;111:7,22; 112:8,10;141:4;159:5; 170:9;185:20 impossible (3) 100:22;141:17; 159:10 impractical (1) 78:1 impression (1) 93:2	improve (8) 65:1,2;72:4,5,7,7; 80:11;175:5 improved (1) 70:15 improvement (3) 65:21;66:10;68:15 improving (9) 57:2,3;59:2;65:1; 80:6,11;176:10; 185:17,19 impulsivity (1) 23:15 inappropriate (1) 187:7 include (2) 180:11;186:18 included (2) 65:22;193:9 includes (1) 112:4 including (6) 19:4;31:12;56:13; 101:7;124:22;126:4 incorporate (2) 23:5;180:5 incorporating (1) 83:5 increase (5) 67:2,11;124:5; 129:19;154:22 increased (1) 111:12 increasing (2) 134:10;135:14 IND (5) 101:4;118:5;119:2; 154:9;169:7 independently (1) 28:19 indicate (1) 102:21 indicated (1) 136:15 indicating (1) 102:10 indication (7) 63:3;64:9;65:14; 66:6;69:1;76:19; 115:15 indications (3) 29:13;50:16;66:1 indicator (1) 183:13 indigenous (1) 103:13 individual (4) 28:15;130:7;157:7; 174:17 individuals (2) 20:20;98:11 INDs (1) 101:5	inducted (1) 24:8 induction (3) 8:16;151:20;152:5 inductions (1) 151:21 industry (8) 25:22;29:7;42:11, 21;43:2;48:11,12; 49:11 ineffective (2) 156:6;157:1 Inevitably (2) 193:17;195:10 infection (1) 158:4 infectious (1) 157:20 infinite (1) 179:16 influencing (1) 58:4 inform (1) 8:6 information (10) 22:14;23:6;31:20; 42:1,17;66:1,4; 133:10;168:13,14 informative (1) 133:8 ingredient (1) 169:14 initial (2) 65:15;70:16 initially (1) 10:6 initiate (1) 76:12 initiative (2) 185:13,16 initiatives (2) 103:16,21 inject (2) 123:4;143:9 injectable (1) 170:11 injection (1) 150:8 inner (2) 158:7,12 innovator (1) 99:9 inpatient (2) 9:6;13:18 input (2) 23:4;66:12 inserted (1) 98:2 insertion (1) 98:3 inside (1) 13:7 insight (2)	40:17;61:12 insomnia (6) 62:22;70:3;71:10; 77:1,5,15 instance (2) 100:2;132:1 instead (3) 93:3;155:1;158:11 institute (1) 74:9 instituted (1) 119:2 institutes (1) 40:22 institution (2) 25:12;118:16 institutional (1) 98:14 instruments (1) 77:21 intake (1) 154:22 integrate (1) 93:10 integration (2) 189:14,16 intensity (1) 79:7 intensive (1) 105:3 intent (1) 104:7 interacting (1) 94:9 interaction (4) 31:11;34:6;168:10; 169:11 interactions (5) 31:7;92:4,12;168:5; 169:17 interception (2) 112:6,11 interchanging (1) 12:8 interest (11) 11:14;15:8;19:6; 39:11;53:19;75:17; 85:18;89:10;104:22; 130:9;180:8 interested (23) 32:8;37:8,18;38:7, 11;39:1,10;40:20; 41:3;48:16;56:15; 64:3;74:16;78:4; 104:19,20;106:19; 117:20;133:3;136:18; 150:11,14;188:4 interesting (37) 8:4;9:2,10,20;10:8; 12:13,14;14:12;23:9; 30:16;46:2;48:13; 53:11;61:5;63:14; 64:22;68:10;81:16;	109:21;110:6,11; 115:19;116:15;119:9; 120:15;122:2;130:14; 133:8;157:14,16; 158:16;161:1,18; 166:13;176:7;189:17; 191:6 interfacing (1) 155:9 interfere (1) 180:16 intermediate (1) 141:10 interpret (1) 78:2 interpreted (1) 120:10 inter-reception (1) 185:8 intervention (1) 69:22 interventions (5) 56:9;86:4;185:14; 186:2,7 interviews (1) 103:6 intimately (1) 161:9 into (43) 6:17;7:4,18,19; 12:18;19:11;23:6; 28:7;29:15;34:4;38:6; 40:17;41:10,13;47:19; 61:12;70:2;74:2,4,14; 75:20;76:19;82:8; 89:13;93:10;96:8; 97:18;98:6;113:10; 117:22;118:5;121:12, 14;127:9;128:13; 139:20;141:22;142:7; 143:9;145:20;147:19; 149:9;176:4 intractable (1) 104:21 intravenous (2) 123:2,3 intrigued (1) 145:8 intrigues (1) 127:8 intriguing (3) 128:2;160:4;174:16 introduces (2) 187:19,21 introductory (1) 3:6 invested (3) 95:8;96:1;119:17 invited (2) 164:22;192:18 involve (1) 186:6 involved (3)
--	---	---	--	--

<p>21:18;101:9;161:9 involvement (2) 101:7;116:4 iPads (1) 112:17 isolated (2) 14:7;36:20 isolation (1) 101:21 issue (26) 10:12;16:22;31:18; 43:1;45:9;46:12; 55:13;57:9;59:17; 61:16;75:9,18;85:10; 91:14,19;99:2;130:2, 5;135:22;136:7; 139:18;140:18; 143:10,11;156:22; 194:17 issues (23) 3:15;8:6;11:17,19; 16:21;20:17;33:4; 39:18;41:5;47:10; 51:4;52:3;69:6,17; 71:17;89:11;100:20; 129:11;136:12;141:5; 187:8;191:12;193:4 items (1) 161:5 IV (1) 125:10</p>	<p>jump (1) 19:10 jumping (1) 89:13 junk (1) 27:17 Juul (1) 167:21</p>	<p>17;109:10;110:17; 111:10;116:17; 120:14,20;122:7; 130:21;133:4;135:15, 22;141:6;142:1; 144:7;148:22;155:5; 157:13;163:18,19; 164:1;166:9,13; 170:15;176:8,14,15, 19;178:5;185:4;188:3, 13,17;189:5</p>	<p>L</p> <p>lab (3) 19:16;36:20;57:10 label (5) 65:20,22;66:5; 109:20;125:14 labeling (2) 62:14,16 labor (2) 105:6,10 laboratory (1) 141:2 laborious (2) 172:6,10 laced (1) 132:4 lacing (1) 145:12 lagged (1) 50:5 landscape (1) 151:11 large (6) 36:5;95:15;101:14; 145:19;157:15;168:21 largely (2) 32:15;94:19 larger (1) 176:13 last (14) 48:9;110:4;128:18; 130:18;137:2,3,14; 159:6,6,8;160:16; 190:12;194:8;195:18 lasts (1) 164:5 late (2) 119:15;126:8 later (4) 18:15;118:7;148:7; 163:22 latter (1) 59:6 Laughter (28) 6:3;7:11;15:5;50:3; 63:7;70:11;73:2; 82:13;84:1,5;87:16, 18;89:20;108:14; 127:5;131:8;140:2; 149:15,17;155:19,22; 165:3;174:11;175:19; 180:18;192:5;195:20; 196:3 launching (1) 168:4 laundry (3) 83:21;84:3;189:20 law (4) 96:18;118:22; 150:6;166:18 lay (1)</p>	<p>34:13 layered (1) 6:17 lead (3) 81:11;114:6;168:5 leaf (2) 173:18,21 learn (3) 32:17;42:1;111:4 learned (1) 106:6 learning (2) 110:8;111:5 least (19) 4:7;5:10;25:22; 41:16;48:16;57:1; 69:9;78:10;81:18; 82:1;86:22;98:11; 129:21;149:20; 150:17;157:8;171:14; 194:18;195:4 leave (2) 177:1;192:21 leaving (1) 158:12 lecture (1) 59:6 led (2) 130:9;186:15 LEE (7) 29:15;174:14; 176:1,3;177:1,17,19 left (5) 8:16;9:6;47:9;48:8; 150:19 legalized (2) 28:2;32:11 legally (1) 193:3 legislatively (1) 126:1 lens (2) 10:13;156:15 less (9) 12:17;13:3;112:16; 117:9;132:22;181:15; 182:12,20;183:1 lessons (2) 106:6;109:15 lethal (2) 138:13;146:1 letter (1) 127:18 level (8) 41:21;101:7; 102:21;108:18; 144:17;145:16;157:8; 174:17 levels (5) 112:4;165:12; 173:17,22;174:5 LEVIN (15) 8:8;23:9;37:9;45:8;</p>
<p>J</p> <p>Jack (1) 93:19 Janda's (1) 148:15 JCAHO (1) 123:10 jerk (1) 127:17 job (2) 33:5;77:20 JOHNSON (29) 12:11;18:18,21,22; 25:8,12,16;30:13; 31:15;37:1,4,7;38:21; 66:16;89:9;90:1,5,9; 93:14;108:15;113:20; 114:1;124:13;156:11; 170:2;171:5;172:19, 22;189:13 joint (1) 54:7 Journal (8) 46:3;165:14; 188:15,16;189:11,11, 12;193:16 journalist (1) 94:18 Juliette (1) 76:17</p>	<p>K</p> <p>K2 (1) 26:4 keep (15) 25:14;48:1;68:5; 78:5;88:19;104:8; 108:20;114:18;126:4; 134:10;156:5,6;158:5; 159:19;190:21 keeping (6) 24:9;39:8;47:16; 48:2;109:18;133:19 Kent (2) 40:5;42:3 Kenzie (7) 45:7;48:8;49:15; 61:10;62:11;63:9; 81:4 Kenzie's (2) 51:21;82:15 kept (1) 9:1 ketamine (8) 106:7;109:15,17,22; 123:1,2,3;125:10 key (4) 38:16;43:6;49:13; 71:14 kid (1) 159:17 kids (1) 158:22 kill (2) 145:22;153:17 killed (1) 140:6 killing (1) 138:3 KILUK (3) 71:20;165:13,15 kind (78) 3:18;10:20;11:18; 14:12;18:5;19:14; 21:4;30:16;34:4,8,9; 38:18;43:14;44:10,17; 48:19;49:3;52:4,20; 53:10,12,13,20;55:20, 22;56:3;58:9,14; 59:16;63:17;68:10; 70:6;72:11;76:17; 82:16;87:8;88:11; 91:4;95:15,17;96:2; 98:5;105:10;106:13,</p>	<p>kinds (19) 6:10;9:20;10:10; 21:3;23:2;37:14,16; 51:15;52:8;59:4;67:8; 69:18;79:21;87:11; 97:19;117:7,11; 150:13;159:13 kinetics (1) 154:14 Kit (15) 14:2;65:8;66:14; 67:20;91:12;93:12; 95:2;101:1;108:12; 113:5;115:5,6;116:21; 141:18;156:21 KLEYKAMP (5) 59:19,20;85:11; 178:13;186:10 knowing (1) 156:19 knowledge (3) 27:7,7;120:3 known (1) 119:10 knows (3) 66:21;84:6;110:3 Koob (1) 169:20 KOSTEN (33) 4:16;5:15,21;25:20; 82:11;84:18;85:6; 87:4,19;121:14; 137:10;139:2,16,22; 140:6;142:16,18; 143:6;146:11;147:19; 149:9,16;157:12; 160:1;163:15;164:14, 21;166:22;167:21; 168:1,14;169:12; 172:10 kratom (12) 166:11,17;167:8,17; 168:5,10;169:3,14,21; 170:2;172:22;173:3 krocktiom (1) 167:7 Kruegel (2) 172:3,5 Kyle (2) 6:2;186:14 Kyle's (2) 5:22;178:7</p>		

56:22;58:21;73:10,14; 74:8,16;76:4;149:12, 18;151:2,14 liability (8) 11:20;41:6,7;93:21; 128:20;171:20,21; 172:14 liberated (1) 125:6 licensed (1) 109:3 lieu (2) 14:19;69:9 life (7) 23:17;60:6;69:7; 91:17;128:1;159:18; 176:18 lifetime (1) 188:3 light (3) 86:13;131:20;194:2 liked (2) 175:17;186:13 likelihood (1) 44:3 likely (5) 22:3;50:1;134:12; 138:1;185:21 likewise (1) 3:21 limit (1) 90:18 limitations (1) 196:1 limited (2) 105:5;118:2 limiting (2) 105:11;170:16 lingering (1) 163:8 linked (1) 57:3 linking (1) 75:2 list (4) 10:16;108:13; 120:13;189:20 listen (3) 42:19,20;68:11 listening (3) 35:16;46:9;61:4 literally (2) 139:8;179:15 literature (5) 57:1,2;64:13; 178:22;179:19 littered (1) 48:18 little (36) 3:5;4:8;8:22;27:18; 31:1,15;35:6;37:20; 38:6;43:15;53:3; 61:20;64:7;73:21;	79:5;84:7;102:5; 126:7,8,8;129:10; 130:16;140:16; 142:12;145:18;146:7; 149:3;150:19;174:18; 175:15;181:17,19; 186:1;189:14,15; 196:15 liver (1) 168:11 lives (5) 93:11;126:22; 127:3;180:17;183:14 lo (1) 70:19 load (1) 148:6 loathe (1) 37:10 local (1) 55:6 lock (1) 98:5 lofexidine (3) 11:6,16;84:20 long (18) 12:3;21:12;55:14; 69:18;70:4;75:6; 77:16;137:13;138:3; 145:18;156:16; 168:17;179:4;181:7,9, 9,22;190:22 Long=term (1) 71:15 longer (12) 5:13;80:13;110:4; 130:19;134:20; 135:17;137:2,3;155:4; 159:8;164:5;189:5 longest (1) 148:2 long-term (9) 45:1;69:11,15; 71:17;81:11;85:20; 110:21;111:4,8 look (29) 9:18;12:10;15:15; 19:16;32:5;33:7,15; 35:18;40:9;46:22; 47:5,16;48:15;51:14; 65:10,16;76:8;78:20; 86:4;100:3;122:4; 135:2;148:3;175:13; 178:1;184:12;192:16; 193:21;194:3 looked (5) 46:13;50:4,6;169:4; 171:21 looking (19) 4:1;12:14,15;16:13; 19:11;36:20,21;39:8; 40:5;41:15,18;76:18; 130:12;165:7,17;	168:4,6,10;174:22 looks (3) 67:1,6;180:4 loose (1) 175:9 lose (3) 44:20;125:6;181:10 loses (1) 181:12 loss (1) 124:19 lost (1) 43:14 lot (75) 4:5;7:8;8:18;13:7; 16:20;19:3,6;20:13; 21:16;22:17;23:14,15; 24:10;28:3;29:20; 31:6,6,9;46:6;48:3,12; 51:14;53:17,17;57:6; 58:5;60:11;68:3,5; 69:5,14;71:13;76:20; 77:14;78:1;79:20; 83:1,11;89:1,9,11; 90:13;92:11;97:14; 108:7;109:13;117:21; 118:1,7,19;119:7; 120:2,7,10,15;127:18; 128:16;134:5;140:6, 13;143:14;151:22; 154:10;157:9;165:18; 171:10,11;173:14; 178:7;183:2,2;186:4; 189:20;190:11,15 lots (4) 78:18;83:22; 117:17;149:6 love (1) 39:13 low (3) 10:20;11:20;117:12 lower (6) 114:14;124:8; 131:12;139:4;187:22; 191:10 low-hanging (1) 166:8 LOWY (1) 65:9 LSD (5) 107:8,21;119:5,16; 120:1 lunch (7) 4:7;60:16;88:7; 160:10;161:7;162:3; 176:20 lung (3) 97:18;133:14,15 lying (2) 27:14;83:13	mAb (3) 136:9,13;154:13 mAbs (5) 136:6,7,8,15,18 magic (1) 180:13 main (5) 119:3,15;130:21; 136:7;160:20 mainly (1) 134:4 maintain (2) 58:4;171:3 maintained (4) 75:5,12;85:16; 96:16 maintenance (10) 7:16;13:16;14:19; 33:19;36:17;38:3,8, 12;75:19;85:20 major (10) 27:19;32:18;51:9; 65:19;73:17;89:11; 99:17;100:16,20; 161:3 majority (2) 45:11;196:10 makes (5) 21:12;108:21; 149:4;172:2;189:17 making (13) 7:1;12:6;26:2,5; 36:13;43:6;45:3; 52:14;60:8;95:8; 147:7;149:7;169:2 MALE (10) 12:6;35:3;139:1; 140:5;149:8;151:7; 153:19;164:19; 171:17,22 manage (1) 70:4 managed (1) 99:10 management (2) 28:6;41:19 managing (1) 21:2 mandated (3) 126:1;145:4;149:19 mandates (1) 115:20 mandatory (2) 143:4;145:1 manner (1) 103:12 manuals (1) 95:18 manufacture (1) 26:20 manufactured (1) 26:21 manuscript (3)	186:18;195:15; 196:2 manuscripts (1) 195:6 many (23) 21:13;29:2;31:4; 41:5;61:22;64:13; 65:3;72:17;102:13; 103:7,10,18;105:6; 109:13;119:17; 121:22;125:1;133:12; 139:8,8,18;179:10,11 Marco (5) 128:11,14;131:1; 139:15,16 Marco's (2) 130:11;137:10 margin (1) 153:11 Margolis (2) 164:9,16 marijuana (26) 8:13,18,20;9:5,8; 10:9;12:10;14:16; 22:22;24:14;28:2; 35:22;36:8,21;40:1, 14;47:21,21,22;49:20; 50:6,7,8;52:2;57:1,10 marijuana-use (1) 50:2 markedly (1) 26:12 market (3) 32:6,9;69:13 marketed (3) 30:6;90:15;98:17 marketing (3) 61:16;62:5,6 marketplace (1) 29:18 marry (1) 84:11 marrying (2) 20:11;21:6 mass (1) 132:21 mast (1) 156:18 MAT (1) 185:17 Matt (26) 18:21;25:11;29:14; 30:12;31:13;35:17; 37:5;42:17;54:17; 65:7;66:14;85:19; 89:5;91:11;93:12; 95:5;102:3;104:10; 106:11;108:11; 113:21;124:12;127:9; 155:12;156:10;170:1 matter (1) 104:4 Matt's (5)
M				

<p>39:18;41:11;51:18; 65:4;69:11 Matyas (1) 139:13 may (52) 7:1;9:10;13:13; 20:21;22:21;28:11,18; 29:1,2,10;37:6;50:16; 57:14,18;58:3;60:16; 64:10;66:9;74:11; 76:1,11;79:13;81:10, 12;95:20;96:13;97:3; 105:5;107:12;108:1,3; 111:9;115:14,15; 116:19,19,20;122:9; 132:3,4,22;135:9; 140:16;144:15; 146:21;153:14; 158:17;168:13; 185:11,20;191:16; 193:4 maybe (40) 8:10;11:2;14:14,22; 18:12,13;30:18;31:19; 32:7,20;36:14;44:16; 57:8,11,16;68:7;72:1, 12;79:16;84:15; 85:22;87:5;92:15; 97:2;105:14;111:14; 118:15;121:20; 123:10;126:1;128:14; 145:10,15;156:6,7; 163:18;184:12,15; 192:15,17 mayor (1) 157:14 McCRAE-CLARK (5) 15:4,7,12,15,19 McCurdy (1) 170:20 mean (15) 8:12;19:3;26:18; 36:7;53:7;54:8,14; 76:19;89:7;118:14; 149:4;159:10;179:21; 183:7,13 meaning (1) 122:17 meaningful (5) 66:9,11;71:22; 126:21;128:1 means (1) 116:5 meantime (1) 88:13 measles (1) 159:16 measure (8) 50:19;52:12;77:7,9, 22;82:21;130:17,20 measured (1) 52:19 measurements (1)</p>	<p>8:7 measures (27) 3:16;18:13,14;40:7, 15;49:21,22;50:20; 61:2;63:13;77:4;81:6, 7,15;82:15;85:2; 112:7;165:9;174:22; 175:21;177:8,15; 178:6;184:13,15; 189:3;191:11 measuring (2) 63:12;148:21 mechanical (2) 74:20;150:12 mechanics (1) 113:7 mechanism (2) 111:12;187:17 mechanisms (5) 13:22;18:8;110:11, 18;126:3 mechanistic (1) 65:3 media (1) 103:6 mediated (1) 133:13 mediator (2) 57:8,19 medical (7) 28:3;29:3;30:1; 102:6;152:15;156:21; 161:11 medication (36) 6:18;11:7,16;23:22; 33:13,20;45:13;46:5, 16;52:10,13;59:14,15; 62:16;69:1,22;71:1, 15;73:19;76:11; 79:16;81:21;92:7; 100:16;110:2;122:15; 123:21;126:17;129:5, 8;132:18;182:3; 185:15,20;186:6; 187:16 medication- (1) 51:19 medication-assisted (4) 7:4;33:9;45:13; 56:10 medications (13) 6:22;24:1;33:16; 45:14;47:17;58:16; 59:10;66:18;67:9; 69:18;142:22;152:9; 188:3 medicine (5) 72:18;73:4;75:22; 96:7;109:1 meditation (1) 79:6 meditative (1) 79:21</p>	<p>meds (3) 71:5,5;76:6 meet (6) 50:1;124:10; 176:15,16;180:9,21 meeting (29) 3:5;7:19;25:21; 32:21;58:19;59:22; 60:12,15;63:8;79:10; 160:18;161:21; 163:22;164:12,17; 174:15,19;175:20; 177:21;187:4;188:14; 191:10;192:21; 193:10,13;194:19; 195:3;196:8,19 meetings (7) 87:14;135:6; 157:13;161:10; 175:18;176:8;191:8 mention (3) 94:20;150:16; 171:10 mentioned (12) 8:9;12:8;16:11; 24:5;49:16;51:5; 88:22;105:17;151:15; 163:10;164:8;186:19 mesolimbic (1) 110:16 mess (1) 177:8 messier (1) 164:4 messy (1) 28:22 meta-analyses (1) 4:12 metabolism (1) 155:10 methadone (25) 6:18;7:16;10:18; 11:1;12:2;14:19,20; 20:16,20;23:11;24:17, 19;25:6;34:2,3,7;39:1; 44:15;55:13;75:8,11; 121:20;125:21;129:8; 137:21 methadone-maintained (1) 75:4 methamphetamine (7) 144:13;147:21; 148:5;156:8;163:18; 164:3,5 methodological (1) 115:12 methodology (1) 32:22 methylphenidate (1) 114:4 Mexico (2) 26:21;141:15 mic (9)</p>	<p>73:9;80:3,8;110:17; 113:13;127:20;131:7; 148:21;168:8 Michael (9) 30:15;71:3;91:11; 99:22;102:2;104:9; 106:11;110:5;114:12 Michael's (1) 120:22 micro (1) 108:5 microphone (1) 60:14 middle (2) 39:18;158:9 midst (1) 54:2 might (60) 3:17,19,22;4:9;8:6; 9:18;11:8;13:15,17, 22;14:22;16:12,18,20; 18:19;19:22;21:18; 27:14;34:3;44:8; 50:12,20;51:10;52:21; 56:17;61:11;66:19; 67:10,14;69:21;75:6; 83:14;85:9;92:13; 100:4;102:7;103:22; 106:8;108:20,20; 110:14;112:17; 113:15;148:7;159:9; 163:11,13;170:6,15, 17;171:15;176:12; 182:12;184:21; 187:18,19;188:13; 189:14,19,20 migration (1) 97:18 Mike (2) 30:14;123:15 military (6) 136:21;144:17,17; 150:5,6;152:12 milligram (1) 31:4 million (5) 41:15;89:15;99:19; 100:5;111:17 millions (1) 119:18 mind (8) 6:14;11:3;33:16; 39:8;53:4;58:10; 104:8;160:19 mindful (2) 89:17;124:19 mindfully (1) 125:9 minds (2) 82:11;101:20 mine (1) 85:18 mined (1)</p>	<p>51:14 minimizing (1) 137:6 minimum (1) 41:9 mining (1) 4:13 minor (5) 29:5,9;41:3,15; 109:12 minority (1) 18:20 Mintzer (1) 85:15 minutes (12) 14:13;48:7;54:13; 60:22;88:5,6;120:12; 160:12;162:2;192:4,4, 9 miracle (1) 73:5 miraculously (1) 91:20 Miriam (1) 85:15 miss (2) 182:12;183:1 missed (1) 165:20 missing (2) 27:19;88:1 mission (1) 144:21 mistake (1) 164:21 misunderstanding (2) 184:6,6 misused (1) 105:20 mitragynine (4) 166:12;170:7; 173:16,20 mix (2) 124:18;152:18 mixed (3) 132:3;146:19; 163:21 mixture (1) 147:7 model (5) 42:4;106:8;115:18; 116:18;126:17 modeling (1) 32:10 models (4) 13:10,21;107:21; 111:14 moderator (2) 97:4;126:14 modest (2) 78:22;79:12 molecular (2) 37:15,16</p>
---	--	--	---	---

molecule (1) 37:22	160:9;169:4;174:15, 17;184:15;190:3	6:1;93:19	131:20;140:12,16; 163:5;165:7,16; 177:10;178:5;181:18	night (4) 63:15;82:22;87:22; 171:1	
moment (4) 3:10;55:11;92:2; 106:14	mostly (4) 26:3;69:8;81:17; 134:8	mythology (1) 118:11	needed (6) 7:10;30:4;102:16; 147:14;152:14;195:22	nights (1) 63:16	
money (7) 37:15;44:2;90:9; 139:12,14;160:1; 166:6	motivated (1) 158:13	N	needle (2) 181:7,13	NIH (3) 39:16;40:22;68:1	
monoclonal (1) 136:1	MOUDs (1) 56:11	nalmafene (1) 134:14	needs (15) 4:13;14:7,8;27:16; 70:22;71:14;84:3; 100:7;101:19;109:5,5, 11;116:7;117:21; 186:6	NIH's (1) 53:21	
Monoclonals (2) 137:12,12	mounted (1) 5:10	naloxone (1) 148:6	negative (5) 183:4,6,11,16;185:1	NIMH (2) 119:15;120:3	
monotherapy (1) 131:16	mouth (3) 93:16;144:1;163:15	naltrexone (7) 12:2;121:20;129:9; 134:14;137:19;143:9; 167:12	negatives (1) 48:18	nobody (3) 75:7;119:5;181:11	
month (6) 5:5,10;85:17; 136:14;183:19;195:5	mouths (1) 91:5	name (5) 34:15;35:7;76:17; 96:10;172:4	neglected (1) 106:21	nodding (1) 161:19	
months (10) 47:4;123:20,22; 130:19,19;159:7,9,12; 181:9;194:1	move (13) 39:21;41:21;49:5; 79:16;80:8;106:9; 158:9;163:13;181:7, 12;188:21;194:9; 196:9	Naomi (2) 63:10;65:7	neighborhoods (1) 158:10	noise (1) 42:13	
moot (1) 130:4	moved (1) 181:21	Naomi's (1) 76:18	neither (1) 117:13	non (1) 11:6	
more (81) 8:20;9:2;10:12; 13:4;19:10;20:4,4; 21:9,13,21;25:2,3; 26:19;29:5,8,12; 31:15,21;32:17;36:11; 38:15;40:17;47:3; 48:7;50:1;51:11;57:9; 61:2;64:8;65:5;67:1; 72:6;74:13;79:17; 80:10;81:14;82:15; 83:1;84:4;85:13;86:1, 2,14;89:11,13,18,21; 90:2;92:11,16;96:5; 100:5,18;111:5,10; 116:19;118:7;120:12; 126:16,16;127:2,18; 128:6;130:4;136:15; 139:8;140:3;144:12, 22;145:10;150:1; 153:11;155:7;157:3; 159:12;170:13; 175:12;177:10; 181:19;185:20;191:6	movement (2) 86:12;181:17	narrow (3) 18:2;153:10,11	nerve (1) 97:19	non- (2) 52:15;73:8	
Morgan (1) 47:6	moving (9) 12:18;31:17;40:3; 41:1,12;126:16; 168:13;169:10;190:1	national (2) 136:20;142:19	neuropathic (1) 41:19	none (1) 123:3	
morning (2) 171:1;174:18	mu (11) 39:7;91:18;133:13; 170:12;171:17;173:6, 7;174:9;188:1,22; 189:18	Native (1) 103:14	neuroplasticity (2) 110:12;111:12	non-mu (7) 37:10,12;38:10,19; 161:2,12;173:4	
morphine (1) 155:5	much (38) 8:22;11:15;15:20; 26:13,19;29:5,6,35;4; 41:1;42:13;47:10; 66:19;74:13,17;82:12; 92:21;96:16;100:6; 110:9;126:20;129:6; 135:6;137:4;146:21; 148:8;151:19;153:15; 155:4;164:5;169:20; 171:13,16;173:19,20; 178:1;179:18;182:20, 22	natural (11) 27:2;28:1,21;40:16; 49:16;50:10,21;51:6; 102:18,19;159:1	neuropsychiatric (1) 49:13	non-pharmacologic (4) 78:16;79:9,13; 105:8	
Morphine's (1) 152:22	multiple (4) 29:1;69:21;110:11; 126:3	naturalistically (1) 19:5	neutralize (1) 142:11	non-pharmacological (1) 170:15	
most (25) 8:4;12:13;20:1; 24:6;26:7;30:8;33:6; 43:19;60:17;92:5; 99:10;106:17;107:5; 113:16;117:2;121:15; 134:12,22;150:22;	multipronged (1) 100:11	nature (2) 105:3;163:12	Nevertheless (1) 64:12	non-psychedelic (4) 107:16;108:4; 110:7,13	
	multivalent (1) 130:3	NCCIH (5) 29:8;39:16;40:19; 41:13;104:18	new (11) 31:11,12;37:15; 61:2;63:12;67:13; 93:3;100:16;150:21; 170:5;187:19	non-psychoactive (1) 107:20	
	mumps (1) 159:17	nearing (1) 78:9	newest (1) 86:13	non-self (1) 191:22	
	mushrooms (1) 102:12	necessarily (13) 9:22;13:21;14:6; 57:3,8;59:17;72:5; 84:21;95:13;116:8; 133:13;142:10;146:19	next (16) 4:9;18:11;34:2; 54:13;57:15;60:22; 85:22;86:18;114:15, 20;160:12;161:20; 168:22;195:1,4,5	non-vaccinated (1) 153:16	
	Music (1) 186:9	necessary (2) 98:20;175:5	NIAAA (2) 112:3;141:13	Nora (2) 58:11;59:5	
	musings (1) 142:1	need (59) 3:17,19;4:11,12; 5:2;6:11;7:3;14:6; 15:19,22;19:2,10,17, 18;26:13;28:17;31:9, 16;32:5,12,16;35:18; 39:21;44:19;48:16; 53:4,14;66:6;80:19; 83:15;84:10;87:1; 89:11,15,16,18;90:8; 91:8;92:11;93:9; 101:6;109:2,14; 111:17;112:13,18,22; 115:22;118:6;126:6;	neither (1) 117:13	nice (4) 43:21;44:5;123:17; 191:20	noribogaine (1) 110:15
	myself (2)		niche (1) 145:9	normal (1) 140:19	
			nicotine (6) 130:10;138:7,8; 143:15,18;145:21	normalization (1) 110:15	
			NIDA (8) 33:17;40:21;58:19; 112:3;122:16;133:7; 145:16;163:22	normally (1) 111:6	
				normals (1) 114:21	
				North (2) 168:19,20	
				nose (1) 79:11	
				note (4) 119:22;128:8; 161:22;196:13	
				notes (1) 4:5	
				nothing's (2) 113:10;115:3	

<p>noticed (1) 9:7</p> <p>novel (3) 176:11;188:17,22</p> <p>nuances (1) 93:17</p> <p>number (20) 12:14;31:22;32:4; 37:12;40:18;77:9; 79:3;87:10;96:15; 97:16;110:7;114:1; 115:8;118:2;155:14; 179:16;193:2,3,21; 195:22</p> <p>numerous (1) 118:11</p> <p>nurse (1) 109:7</p> <p>nutsy (1) 141:12</p>	<p>79:16;99:14;109:20; 123:6;125:14;131:14; 146:16;160:14;195:12</p> <p>offer (1) 100:16</p> <p>offered (1) 103:3</p> <p>off-label (1) 109:17</p> <p>often (6) 45:9;46:7,12;73:11; 181:14;182:12</p> <p>old (4) 27:8;118:14; 142:20;172:22</p> <p>older (1) 103:13</p> <p>Olson (1) 110:10</p> <p>on! (1) 149:16</p> <p>once (13) 9:6,15;47:13;49:3; 56:19;122:5;130:3; 134:19;135:12,16; 136:14;153:5;163:15</p> <p>One (91) 5:1,7;7:17;12:9; 14:9;16:21;17:6,6,17; 18:2;25:20;30:17; 38:6;40:12,18;46:14; 48:9;54:7,17;58:3; 60:20;62:15;63:14; 71:7;72:2,10,13;87:4; 92:1;93:4;94:7;98:19; 99:6,15,18;106:18; 109:13,16;111:15; 115:14,17;116:6; 119:3;120:19;122:7, 10;127:12;128:18,21; 129:7,12,22;130:6,14, 15;131:3,16;132:7,15; 134:12,16;136:12; 137:1,16;140:4; 144:22;146:17,21; 147:22;149:3;152:20; 154:11;157:2,12; 160:15;161:3;165:11; 166:5,14;167:18; 170:5,9,10;175:4; 177:20;183:12,19; 187:8;192:8;193:2,22</p> <p>ones (5) 57:22;124:3; 128:18;159:8;188:18</p> <p>ongoing (1) 52:19</p> <p>online (2) 165:5;168:18</p> <p>only (32) 27:12;31:4;38:6; 43:5;52:7;66:22; 69:13;87:8;98:2,6,8,9;</p>	<p>103:5;112:5,12;113:2; 118:2;131:20;132:13; 137:16;138:11;142:7; 148:10;149:2;151:1,2, 12;157:20;166:22; 176:22;183:8;191:22</p> <p>onset (1) 75:7</p> <p>on-site (1) 182:3</p> <p>onto (3) 33:21,22;129:14</p> <p>open (5) 39:4;41:13;90:10; 133:5;170:8</p> <p>opening (4) 54:21;55:20;89:5; 128:12</p> <p>open-label (1) 114:17</p> <p>operating (1) 109:11</p> <p>opiate (17) 47:4;50:4,9;56:22; 65:2;74:7;75:19; 121:12,14,17;126:18; 144:13;152:9;159:8; 167:2,9,11</p> <p>opiates (13) 26:11,12,13,17; 57:7,7,12;74:12; 87:10,20;164:1,2,3</p> <p>opiate-use (12) 45:11,14,21;73:16, 22;74:18,19;79:14; 121:1;126:15;175:21; 178:1</p> <p>opinion (3) 47:16;152:20;188:5</p> <p>opioid (43) 11:7;12:15;13:2; 14:17;16:18;38:3; 43:3;49:18,21;50:7; 51:3;52:20;53:5; 59:18;63:15;68:1,7; 69:2,3,10;71:11;72:3, 9;75:2;82:1,2,6;92:13; 121:9;129:1;130:1,2; 134:20;136:21;170:5; 173:4,6,7;174:9; 187:11,12,12,14</p> <p>opioid- (1) 80:19</p> <p>opioid-cannabinoid (1) 44:14</p> <p>opioid-induced (1) 59:15</p> <p>opioids (20) 12:17;13:3;15:19; 21:2;22:16,18;31:8; 40:13;52:18;64:17; 67:19;126:19;131:13; 133:9,12;134:19,22;</p>	<p>135:12,15;145:21</p> <p>opioid-use (38) 6:13,22;7:15,20; 8:2;10:15;15:10; 16:14,19;17:18;19:13; 33:11;37:19;50:17; 56:5;59:2,22;61:18, 21;62:3,5,7,17;64:6; 66:21;69:5;78:21; 80:5,12,16;81:2; 106:16;129:2;132:17; 180:9,10,22;182:1</p> <p>opium (1) 171:7</p> <p>opportunities (3) 41:20;104:2;191:17</p> <p>opportunity (11) 32:2;64:21;79:8; 104:15;127:7;163:5; 191:19;193:1;194:11, 12,13</p> <p>opposed (6) 10:6,11;26:7;136:2; 140:19;147:1</p> <p>opposite (1) 72:1</p> <p>option (1) 46:5</p> <p>orally (1) 170:13</p> <p>order (1) 66:4</p> <p>orexin (2) 67:5,6</p> <p>organization (1) 39:17</p> <p>organizers (1) 192:16</p> <p>original (1) 181:22</p> <p>originator (1) 96:14</p> <p>Others (6) 88:18;91:16;99:22; 102:7;104:22;136:5</p> <p>otherwise (1) 27:14</p> <p>OUD (12) 21:6;28:8,17;32:1; 37:14;62:8;178:6,12, 15,18;186:19;188:17</p> <p>ours (1) 87:7</p> <p>out (71) 15:20;22:12;23:18; 26:15;27:17;30:6; 31:3;34:13;43:9;47:9; 51:14;54:8;60:19; 61:8;70:9;71:7;72:5, 20;73:5;75:10,11; 82:9;84:10;87:1;91:4, 20;93:15;95:10,12; 96:15,21;97:3,18;</p>	<p>100:7,14;102:17,19; 106:6;108:20;109:14; 120:3;121:7;123:5; 127:14;129:13; 133:20;138:20; 142:21;143:8;145:9; 146:8,22;152:19; 159:9,10;160:6;161:8; 163:13;170:10; 174:21;175:3;177:4; 178:17;183:8;186:15; 190:14;191:9;194:1, 19;195:9;196:14</p> <p>outcome (29) 3:16;6:20;8:19; 17:4;40:7,15;43:7,12; 49:21,22;56:7,13; 122:3;140:5;165:9; 174:22;175:2,14,21; 176:6;177:8,15;178:6, 9,18;181:7;188:14; 189:3;191:11</p> <p>outcomes (19) 6:10;16:16,16; 17:11,13;18:6;40:10; 68:22;71:22;80:12; 111:8;119:21;176:11; 178:9,12,22;180:6; 181:6;186:17</p> <p>outpatient (1) 81:19</p> <p>outside (5) 19:16;90:22; 133:12;135:10;158:10</p> <p>outsider (2) 16:4;64:6</p> <p>over (20) 15:16;26:13;27:4; 35:1;36:6;41:15; 45:10;55:10;77:17; 99:19;126:7;150:8; 160:16;163:20;165:8; 166:8;179:5;182:14; 190:12;194:21</p> <p>overall (1) 185:19</p> <p>overdose (13) 12:18;15:20;24:16, 19;47:14;52:16; 124:5;129:3;131:4,4, 10;136:11,15</p> <p>overdosed (1) 25:1</p> <p>overdoses (4) 121:19;143:12; 150:2,2</p> <p>overdosing (1) 53:8</p> <p>overlying (1) 40:15</p> <p>overreach (1) 108:19</p> <p>overregulation (1)</p>
--	--	---	---	---

O

Oakland (2)
103:17;104:13

Obesity (2)
181:8,11

objective (5)
77:4,7;81:6,14;
82:15

objectively (1)
81:9

obscure (1)
117:19

observation (1)
115:21

observational (3)
40:6;51:11;104:16

obsessed (1)
86:8

obtaining (1)
101:19

obviate (1)
118:6

obviously (19)
34:12;53:18;55:3;
61:21;84:7;96:6;
107:2,11;131:10;
147:6;153:20;154:10;
158:14;160:16;
161:12;165:21;178:7;
179:5;194:16

occur (2)
4:13;133:12

occurrence (1)
40:16

occurs (1)
112:9

odd (2)
96:2;118:3

off (15)
22:18;26:17;27:18;
31:13;57:12;70:19;

<p>108:21 override (1) 143:22 overseeing (1) 109:6 overstate (1) 105:16 overstating (1) 19:22 overtly (1) 93:1 overwhelmed (1) 146:3 own (2) 84:8;86:8 oxybate (1) 125:18 oxycodone (5) 132:6;134:9;154:6, 7;155:5</p>	<p>99:10;107:5;124:18; 125:12;126:2,3; 134:17;146:18;170:9; 175:17;185:13;190:11 partial (3) 26:7;39:7;92:10 participants (1) 81:8 participate (1) 194:15 particular (12) 3:16;9:21;18:7; 93:22;115:18;125:21; 144:10;166:18; 173:21;179:3,3;187:4 particularly (10) 24:18;31:8;41:4; 84:19;101:13;115:19; 167:13;179:21;186:2; 190:13 parts (2) 36:21;38:6 past (2) 3:21;192:11 patents (1) 27:8 pathway (1) 98:5 pathways (1) 37:17 patient (26) 13:1;16:12,14,18, 19;22:9,12;33:11; 53:13;69:8;72:16; 73:12;78:19;80:7; 81:15;100:1;123:18; 124:1;127:11,15; 129:14;130:1;132:13, 14;181:18;183:7 patient-focused (1) 164:11 patients (49) 7:15;8:18,19;12:15; 15:1;20:16;22:5;24:7, 11;28:4;37:18;38:4, 11,12;42:12,20;45:10; 47:3,14;50:14,16; 51:8,12,19;52:17; 55:13;58:7,18;59:13; 62:8,17;66:2,12;75:4, 9,12,18;79:14;80:5; 81:2;87:6;105:6; 122:1,8;155:14;167:3; 182:2;183:4;189:2 patient's (2) 80:10;124:5 Patrick (1) 64:5 patterns (2) 72:20;83:10 pause (1) 72:18 pay (2)</p>	<p>111:22;158:10 PCORI (1) 36:3 PCSS (1) 152:5 peak (1) 155:6 peanut (1) 127:4 people (155) 5:2;9:1,7,19;10:14; 13:2;15:16;22:6,10, 15,21;23:1;24:8;25:9, 15;26:4;30:8;31:5; 35:17;36:1,6,15; 37:15;39:6,9;40:8,9, 13;43:20;44:4,14,22; 45:2,11;46:11;47:9, 17,20,22;48:1,22; 49:18,20;51:8;54:15; 55:15;57:6,12;58:1,4, 61:14,21;62:2;67:2, 15,17,19;69:19;70:2, 14;74:3;76:5,12; 80:14,16,19;82:2,7, 16;83:4;84:20;86:19; 87:14;89:7;90:13; 91:4,17;93:18;94:8; 95:9,11,16,20;97:22; 98:3,7;99:3,10,19; 100:5,18;103:7;104:5; 111:4;113:10,16; 114:4;117:5,19; 118:11,19;119:8,11, 12,21;120:2,4;123:8; 124:20;125:1,3,6; 126:17,21;127:2; 128:4;129:4;132:21; 137:21;140:6;141:2; 142:3;143:1,12; 145:16;146:20; 147:19;150:22; 151:21;156:4,13; 158:7,10;159:4;160:8; 163:5;166:3;167:15, 16,19,20;170:4;171:5; 173:14;174:1;180:7,8, 14;181:14;182:8,16, 17;188:2;189:7; 193:21 peppers (2) 72:22;73:6 per (4) 40:1;79:4;82:20; 101:16 percent (8) 20:16;47:3,7,8; 151:16;159:4;181:10; 183:7 perception (1) 15:22 perfect (3) 115:3,14;122:16</p>	<p>perfectly (1) 61:13 performance (1) 85:17 perhaps (18) 35:18;38:8;50:13, 14;57:19;64:10;65:5; 67:1,12;103:17;111:3, 13,15;127:8;171:7; 181:17;188:15,15 period (6) 13:19;70:1,16; 78:12;137:15;144:15 peripheral (1) 74:21 periphery (3) 133:20,22;134:16 permission (2) 193:12;194:16 persistently (3) 13:19;74:6,12 persisting (2) 13:13;92:14 person (6) 46:4;92:2;117:22; 118:5;153:16;176:16 personal (2) 86:7;97:8 personalize (1) 121:12 personally (1) 117:16 person-hours (1) 101:16 person's (1) 72:3 perspective (8) 47:1,15;53:22;83:6; 96:1;104:4;146:6; 168:4 Peter (7) 63:9;64:2;93:19; 97:2;99:13;102:2; 114:12 peyote (1) 103:14 pharmaceutical (12) 21:10;25:22;26:19; 29:21;30:10;43:22; 48:11,12;49:11;55:5; 90:16;147:6 pharmacies (1) 98:10 pharmacokinetic (1) 31:7 pharmacologically (1) 170:7 pharmacology (6) 105:5;107:4; 114:22;153:7;188:16; 189:11 pharmacy (3) 47:5;59:10;98:13</p>	<p>phenotypes (1) 24:2 phenotyping (3) 112:1,2,4 philanthropists (1) 124:22 phone (1) 176:17 phones (1) 83:12 physically (1) 52:17 physicians' (1) 109:7 pick (4) 18:2;166:5;187:15; 189:22 picture (4) 88:11;112:19; 156:12;170:6 pie (1) 141:6 piece (3) 27:19;70:7;76:14 piggyback (1) 76:18 pilot (1) 120:9 pilots (2) 38:14;44:21 pinpoint (1) 148:4 pipeline (1) 108:9 place (12) 12:4;15:16;27:4; 95:13;97:13;103:13; 140:14;163:20;166:8; 169:15;179:5;188:4 placebo (9) 52:19;54:5;113:8, 16;114:13;115:1; 117:1,15,16 places (2) 141:14;151:11 plan (1) 192:11 planning (1) 160:18 plant (4) 21:7,15;29:6;172:9 plasma (3) 131:21;173:17; 174:5 platform (1) 33:19 play (4) 89:17;99:9;110:18; 129:13 playing (1) 39:19 Please (6) 90:3,8,9;94:19,20;</p>
P				
<p>package (2) 44:5;170:9 page (1) 3:11 pain (35) 12:14;13:2;14:18; 16:12,17;20:15,17; 22:16;28:6;29:12; 32:1;38:4;41:19; 50:14;51:5,8;64:4,7, 10,15,16,19,20;65:1,5; 78:20;79:5,7;87:11; 104:21,21;105:9; 152:16;171:4,14 pan-addiction (1) 166:3 paper (21) 21:1;46:2;58:11; 60:15,19;61:7;70:9; 93:18;118:13;163:13; 165:8;188:8,13,19; 189:9;190:7;191:5; 192:13,14,19,19 papers (2) 4:12;190:19 parade (1) 179:22 parallel (2) 30:17;97:7 parameters (3) 34:13;55:3;109:14 parents (3) 142:22;143:19; 144:6 parse (1) 61:20 part (21) 8:17;45:16;50:21; 51:5;65:9;71:22; 72:12;73:14;95:15;</p>				

<p>163:6 plug (1) 36:3 pm (3) 162:3;163:2;196:19 point (26) 31:9;32:18;37:11; 41:11;22:56;12:68;19; 69:11;76:18;82:15; 88:2;91:21;105:19; 119:16,16;127:4; 130:4;132:7,11; 145:17;149:18; 155:13;164:2;165:17; 190:7;194:4 points (5) 4:5,15;77:2;104:11; 130:21 poison (1) 187:15 politician (1) 158:15 pooling (3) 60:14;176:11; 177:11 poor (3) 64:20;82:3;142:8 popularized (1) 105:19 population (21) 16:22;19:16;23:7; 45:5;56:7;66:20; 75:15;81:8,15;92:17; 100:1;102:21;122:11; 132:9,15;136:16; 157:19;166:17,20; 179:3;186:2 populations (12) 13:1,2;16:9;17:12; 22:3;36:16;38:17; 101:15;132:14,19; 142:8;145:3 posed (1) 96:12 position (6) 67:22;68:3,12; 103:4,8;157:16 positioned] (1) 80:4 positive (3) 151:1,16,17 positives (2) 182:11;183:2 possibilities (1) 96:18 possibility (3) 14:6;113:11;132:18 possible (6) 39:21;96:6;98:15; 117:8;137:18;196:1 possibly (3) 113:15;121:16; 143:2</p>	<p>Post-detox (2) 93:4;121:4 potency (2) 139:4;170:11 potent (2) 26:22;131:18 potential (11) 3:15;11:14;12:17; 16:15;41:5,6;99:22; 116:14;131:14; 150:12;170:16 potentially (7) 14:11;16:8;91:17; 105:12;132:16; 145:13;147:11 power (1) 196:16 practical (3) 33:4;141:5;146:5 practicality (1) 105:2 practically (2) 93:9;142:20 practice (5) 22:12;78:19;96:7,9; 123:8 practiced (1) 30:2 practitioner (1) 98:13 practitioners (2) 100:12;109:7 pragmatic (1) 30:21 PRAVETONI (5) 131:2,9;134:3; 136:4;153:22 pre- (1) 74:18 precipitated (1) 129:17 precise (1) 86:19 preclinical (2) 134:4;137:3 predominant (1) 28:6 preexists (1) 125:22 prefer (1) 56:11 preferably (1) 131:12 preference (3) 45:9,16;48:5 preferred (1) 92:7 pre-IND (1) 134:18 preliminary (2) 7:6;94:2 prepare (2) 100:13;189:10</p>	<p>preparedness (1) 144:21 prerogative (2) 96:22;126:14 prescribed (1) 64:9 prescribers (1) 66:2 prescribing (3) 45:18;69:18;74:14 prescription (1) 47:6 presentation (5) 56:1;77:20;163:19; 178:7,14 presentations (1) 3:14 presented (4) 5:2;89:8;133:11; 178:7 presenter (2) 5:18,19 presenters (1) 4:3 press (2) 15:16,21 pressure (1) 11:18 PRESTON (7) 49:16;50:4,22;51:7, 13;63:11;81:5 presumably (1) 67:7 pretty (11) 10:8;11:20;12:3; 39:2;45:2;64:3;67:2; 86:19;177:12;183:10, 13 prevalence (1) 150:17 prevent (7) 12:3;121:18; 131:11,13;132:16; 134:15;175:9 preventing (1) 170:16 prevention (4) 38:2,9;131:4,10 preventive (1) 137:5 pre-Vivitrol (1) 93:4 primarily (4) 41:3;104:20; 106:15;173:7 primary (8) 52:22;56:5;64:9; 99:16;178:6,9,17 prime (1) 73:22 prior (1) 101:9 priorities (1)</p>	<p>10:17 prisoners (2) 143:3;145:6 prisons (1) 143:4 private (1) 123:8 probably (36) 15:22;19:6;31:4,4; 38:1,1;40:13;51:13; 55:18;62:1;71:13; 74:9;75:7;89:2;94:9; 111:7;115:6;116:1; 121:15;122:17; 136:15,18;144:11; 154:14;155:8;163:16; 165:7,17;171:4; 172:13;173:4;177:12; 179:18;183:2;189:13, 15 problem (23) 8:15;10:9;56:4; 64:1;67:14;71:6; 80:15,18,20;93:4; 138:4;145:20;146:4, 18;149:2,2;151:7; 158:8,12;167:20; 181:1,1,4 problematic (2) 53:6;71:13 problematically (1) 145:5 problems (15) 10:14;16:10;50:15; 55:16;57:14;59:16; 62:2;63:22;70:20; 71:13,18;81:11,12; 100:16;177:3 probuphine (3) 97:11,12;98:1 procedure (2) 5:17;97:14 proceed (1) 71:13 process (7) 109:6;136:19; 140:15;159:2;161:13; 194:10;195:7 processing (2) 65:21;66:10 produce (1) 122:16 produces (2) 153:8,9 product (22) 12:7;19:19;20:19; 21:13;24:21;25:1; 28:22;30:7;32:8; 33:17;34:5;40:9,10; 43:16,19;44:4,6,14, 17;90:15;146:2;169:5 production (1) 27:15</p>	<p>productive (1) 106:1 products (12) 8:13;32:5;40:17; 65:18;76:17;97:20; 99:8,8;141:10,10; 145:17;146:7 profile (5) 30:19;41:7;168:11, 22;170:5 program (13) 9:6;49:14;78:18,20, 21;99:16;122:21; 152:5;166:18;168:4; 169:1;185:15;186:6 programming (1) 84:7 programs (2) 49:4,11 progress (3) 78:9;79:17;169:2 project (1) 41:17 projects (1) 41:15 promise (2) 8:5;157:10 promising (2) 94:1;170:3 promote (1) 21:9 prompt (1) 86:5 prompted (1) 24:4 pronounced (1) 107:17 propensity (1) 31:18 proper (1) 30:5 properly (1) 117:7 prophylactic (1) 82:4 proponent (1) 23:20 proportion (1) 157:19 propose (1) 9:20 proposed (2) 6:20;37:13 pros (1) 137:7 prospect (1) 110:6 protected (1) 25:1 protective (1) 137:2 protocols (2) 179:9,11</p>
---	--	--	--	---

protracted (1) 24:12	publication (1) 196:5	quickly (4) 39:21;50:18;86:16; 194:4	12:21	24:6;28:6;39:9; 49:6;64:15;95:20; 118:17
provide (4) 5:9;29:3;102:4; 178:11	publications (2) 103:6;194:22	quit (1) 157:9	rats (1) 192:21	reasonable (4) 76:11;122:11; 188:14;189:9
provider (2) 101:7;127:11	publish (1) 194:20	quite (17) 13:22;16:12;86:11; 100:19;102:6;105:9; 134:1;135:13;137:14; 140:7;141:6;143:11; 144:11;154:6;157:16; 164:4;181:21	reach (1) 161:8	reasonably (1) 87:9
providers (2) 90:19;127:2	published (11) 48:16;60:2;78:8; 85:14;93:20;107:9; 114:3;151:10;178:19; 179:19;195:7	quote (3) 47:3,8;140:21	react (1) 139:7	reasons (5) 10:10;45:19;60:10; 120:7;133:4
provocative (1) 122:13	pull (2) 22:11;139:17		read (4) 28:5;58:13;184:2,3	Recap (1) 3:3
PSG (2) 77:7,22	pupils (2) 148:3,4	R	reading (1) 83:13	received (1) 60:10
psilocybin (11) 90:14;92:20;93:22; 99:18;100:2;102:12; 106:15;107:10; 116:16;123:18;124:7	purchased (1) 168:21	R21 (1) 172:21	ready (4) 18:22;30:20;36:12, 18	receiving (1) 48:22
psilocybins (1) 61:5	purported (1) 166:2	railroad (1) 171:6	real (15) 14:22;42:2;47:8; 67:14,17;90:5;94:16; 104:3,17;108:6; 109:18;114:22; 116:18;118:17;146:19	recent (2) 93:18;165:11
psychedelic (12) 90:14;92:1;101:10; 110:3;111:14;114:5,7; 125:5;127:12;128:5; 160:3;190:1	purpose (5) 15:13;17:3,8;32:21; 193:11	rain (1) 179:21	reality (5) 23:13;29:17;30:8,9; 43:18	recently (3) 22:19;70:8;151:10
psychedelic-assisted (1) 97:10	purposes (3) 18:14;22:4,7	raise (2) 66:16;184:9	realize (3) 28:17;135:21; 163:16	receptor (1) 188:22
psychedelics (23) 54:18;88:6,16,21; 89:14;91:6,19;92:5; 95:7;101:18;102:5,20; 105:12;106:20; 107:16;108:5;110:7, 19;112:8;117:19; 118:2,10;190:13	pursue (1) 108:4	raised (2) 4:6;75:21	really (102) 3:5;4:3,5;9:17;10:1; 11:14;12:4;19:16; 22:5;23:4;30:1,5;31:1, 10;33:5;35:15;36:4; 43:16;44:5,12;47:19; 51:22;52:14,16;58:13; 59:13;62:14;63:19; 64:11;67:12;68:9; 71:10;74:16;77:20; 86:18;91:5,20,22; 92:17;93:20;96:4,13; 97:5;100:13;102:6; 103:3;106:15,21; 109:16;110:6,11; 111:22;112:8,10; 113:17;114:3,16; 120:14,20;121:16; 123:15,17;125:4,17; 126:20;127:1;128:2, 22;129:2,12;130:13; 132:7,11;133:3;142:5; 143:18;146:15;147:4; 151:10;152:6,12,17; 156:15;161:1,18; 163:5,7;165:20;167:9; 170:20;173:17;175:2, 5,17;176:10;177:5; 178:15;182:16; 188:21;189:16;190:6; 191:1	receptors (3) 130:13;134:20; 188:1
psychiatric (4) 23:14;44:22;51:9; 57:22	pursuing (2) 104:19;110:19	raises (1) 58:9	reality (5) 23:13;29:17;30:8,9; 43:18	recess (2) 88:14;162:3
psychiatrically (1) 94:8	pushing (3) 60:8;67:16;124:20	raising (1) 34:9	realize (3) 28:17;135:21; 163:16	reciprocal (2) 64:14,18
psychiatrists (1) 123:4	put (20) 10:15;30:6;36:3; 44:5;47:5;53:8;54:15, 15,17;62:21;87:20; 89:7;97:13;121:18; 141:22;169:6;172:17, 21;188:10;194:19	RAMEY (5) 48:10;111:20; 184:11,22;185:3	really (102) 3:5;4:3,5;9:17;10:1; 11:14;12:4;19:16; 22:5;23:4;30:1,5;31:1, 10;33:5;35:15;36:4; 43:16;44:5,12;47:19; 51:22;52:14,16;58:13; 59:13;62:14;63:19; 64:11;67:12;68:9; 71:10;74:16;77:20; 86:18;91:5,20,22; 92:17;93:20;96:4,13; 97:5;100:13;102:6; 103:3;106:15,21; 109:16;110:6,11; 111:22;112:8,10; 113:17;114:3,16; 120:14,20;121:16; 123:15,17;125:4,17; 126:20;127:1;128:2, 22;129:2,12;130:13; 132:7,11;133:3;142:5; 143:18;146:15;147:4; 151:10;152:6,12,17; 156:15;161:1,18; 163:5,7;165:20;167:9; 170:20;173:17;175:2, 5,17;176:10;177:5; 178:15;182:16; 188:21;189:16;190:6; 191:1	recirculate (1) 135:9
Psychiatry (3) 46:3;65:18;76:17	putting (5) 33:12;39:6;67:17; 129:16;164:9	ran (2) 70:7;127:9	reality (5) 23:13;29:17;30:8,9; 43:18	recognize (4) 44:7;84:21;87:12, 14
psychoactive (3) 102:8;107:17;117:2	Q	randomization (1) 114:18	really (102) 3:5;4:3,5;9:17;10:1; 11:14;12:4;19:16; 22:5;23:4;30:1,5;31:1, 10;33:5;35:15;36:4; 43:16;44:5,12;47:19; 51:22;52:14,16;58:13; 59:13;62:14;63:19; 64:11;67:12;68:9; 71:10;74:16;77:20; 86:18;91:5,20,22; 92:17;93:20;96:4,13; 97:5;100:13;102:6; 103:3;106:15,21; 109:16;110:6,11; 111:22;112:8,10; 113:17;114:3,16; 120:14,20;121:16; 123:15,17;125:4,17; 126:20;127:1;128:2, 22;129:2,12;130:13; 132:7,11;133:3;142:5; 143:18;146:15;147:4; 151:10;152:6,12,17; 156:15;161:1,18; 163:5,7;165:20;167:9; 170:20;173:17;175:2, 5,17;176:10;177:5; 178:15;182:16; 188:21;189:16;190:6; 191:1	recommendation (1) 61:7
psychoeducation (1) 46:17	Quaker (1) 196:8	randomized (1) 19:15	reality (5) 23:13;29:17;30:8,9; 43:18	recommendations (1) 186:19
psychology (2) 109:1,3	qualitatively (1) 70:13	randomly (1) 40:8	reality (5) 23:13;29:17;30:8,9; 43:18	record (2) 125:17;176:6
psychosis (1) 45:3	qualities (1) 185:19	Randy (1) 93:5	reality (5) 23:13;29:17;30:8,9; 43:18	recorder (1) 69:4
psychotherapists (1) 101:8	quality (3) 60:6;119:10;176:18	range (1) 17:19	reality (5) 23:13;29:17;30:8,9; 43:18	recruit (1) 150:6
psychotherapy (5) 46:5;73:19;105:4; 110:2;111:6	quantification (1) 180:11	ranging (1) 120:15	reality (5) 23:13;29:17;30:8,9; 43:18	red (1) 194:6
PTSD (2) 45:3;46:4	quantitatively (1) 146:15	rank (1) 94:5	reality (5) 23:13;29:17;30:8,9; 43:18	reduce (14) 16:13;17:15;18:4; 26:12;53:5,7;60:5; 72:3,9;79:2,3,6;124:7; 135:3
public (7) 15:22;39:20;78:11; 100:20;138:18; 145:14;157:15	quantities (1) 168:21	rapidly (1) 151:10	reality (5) 23:13;29:17;30:8,9; 43:18	reduced (2) 53:1;69:2
	quarter (1) 114:9	rappporteur (1) 192:12	reality (5) 23:13;29:17;30:8,9; 43:18	reduces (4) 15:20;24:19;62:19; 171:4
	quasi (1) 13:11	rate (4) 82:21;86:12; 123:20;138:15	reality (5) 23:13;29:17;30:8,9; 43:18	reducing (3) 59:18;62:17;169:19
	quick (2) 83:17;155:13	rates (2) 12:2;47:10	reality (5) 23:13;29:17;30:8,9; 43:18	reduction (5) 30:19;68:5,6;69:9; 71:21
		rather (4) 25:4;67:15;72:10; 122:13	real-world (2) 36:5,19	reductions (1)
		rational (1)	reason (7)	

59:7 redundant (1) 186:22 refer (1) 93:18 refine (2) 192:17;193:6 reflect (1) 77:17 reflects (1) 83:15 refused (1) 46:18 refusing (1) 92:18 regard (2) 64:6,17 Regarding (2) 93:14;150:17 regardless (3) 56:14;128:4;142:3 regards (2) 134:16;174:22 regimen (1) 11:12 register (1) 165:5 registration (1) 182:20 regularly (1) 176:15 regulate (2) 27:17;96:7 regulating (1) 96:9 regulation (2) 27:12;141:9 regulations (2) 39:22;40:2 regulator (1) 117:10 regulatory (2) 33:3;193:4 reimbursement (1) 45:17 reinforce (1) 110:5 reinforcing (1) 89:10 relapse (15) 12:2,4;16:20;38:2, 9;52:15;80:17; 122:10;123:19;124:3, 7,8;131:11,11;137:6 relapsing (1) 131:12 relate (1) 85:21 related (12) 6:8;28:8,20;76:22; 80:12;150:2;161:6,21; 176:14,19;191:12; 195:16	relation (1) 69:15 relationship (4) 63:19;64:14,18; 73:12 relationships (1) 110:9 relative (1) 56:8 relatively (7) 28:13;107:19; 109:12,17;137:14; 155:2;157:15 release (1) 178:20 releases (1) 67:6 relevant (7) 16:16;18:10;43:7; 106:18;145:10; 163:12;190:3 reliable (1) 168:19 relieve (1) 61:15 relieving (1) 128:7 remain (1) 80:13 remarkably (1) 167:3 remember (4) 8:8;14:3;58:19; 167:6 remifentanil (1) 157:5 reminded (1) 132:12 remission (1) 180:9 removal (1) 98:4 remove (1) 5:4 REMS (29) 90:17;91:1;96:6,8, 13;97:5;98:1,18;99:1, 3,8,11;100:9;109:18; 115:20,22;120:19,21; 121:11;122:19,20,20; 123:6,7;125:10,11,22; 126:4;191:8 renal (1) 135:8 renowned (1) 195:19 reorient (1) 120:14 repeat (1) 188:11 repeated (1) 159:15 repeatedly (1)	57:2 replacement (2) 13:12;25:5 report (6) 55:13,15;69:14; 75:18;170:4;191:22 reported (1) 21:1 reporting (4) 55:19;74:12;109:3; 170:17 reports (1) 74:6 representatives (2) 29:21,22 represented (1) 25:21 require (3) 52:8;91:1;100:11 requirement (3) 98:2,20;108:18 requires (2) 101:15;183:18 research (38) 8:4;14:15;19:3,11, 18;30:3,5;32:4,9,12; 35:16;39:17;40:20; 41:2,12,21;49:10; 58:15;60:9;63:14; 75:4;81:14;89:13,18, 18,22;90:2;102:21; 106:1,22;111:22; 113:8;118:20;119:13, 21;120:5;185:16; 189:3 researchers (2) 68:4;95:12 residual (2) 66:22;87:3 resistant (1) 148:11 resources (1) 139:17 respect (4) 125:10;126:15; 176:13;177:6 respiratory (7) 134:7,13;135:5; 138:15;153:10;154:2, 3 respond (5) 62:10;73:11;95:4; 97:1;156:3 responders (1) 132:20 response (10) 6:5;56:18;62:13; 71:20;129:18;130:8; 137:3;154:1;180:4; 192:2 responsible (1) 152:2 rest (4)	5:16;56:16;157:6; 159:18 restricted (1) 143:2 restrictions (1) 125:21 result (2) 103:22;129:16 results (2) 84:13;148:16 retained (2) 46:6;47:22 retaining (1) 24:9 retention (4) 8:16;47:2;49:7;53:1 rethink (1) 58:15 return (2) 4:7;120:18 revaccinate (1) 159:7 revealed (1) 120:1 revealing (1) 93:20 reverse (1) 134:13 review (9) 59:21;177:14; 178:6,11,22;186:15; 189:4;192:13,19 reviewed (1) 179:9 reviewers (1) 193:17 reviews (2) 177:2,4 revisions (2) 194:5,6 revisit (1) 165:16 reward (4) 13:13;154:2,4; 185:3 rewarding (2) 155:3,6 right (32) 5:4;11:11,11;21:5; 23:16;27:11;29:16; 30:2;43:8,18;44:1; 47:9;69:8;72:14;76:7, 13;90:1;104:12; 119:5;120:8;125:8; 138:11,16;141:7; 142:10;158:8;165:12; 167:21;186:3,3; 195:16;196:10 rights (1) 139:1 rigorous (4) 40:7,11,15;42:2 rings (1)	82:21 risk (24) 3:19;15:20;24:16, 19;30:18;33:13; 47:14;52:15;53:8,9; 104:15;115:21;116:5; 124:5,7;126:19; 128:20;129:3;137:15; 142:9,11;144:12; 147:3;165:12 risk-benefit (2) 38:18;187:10 risks (21) 3:18;6:11;89:17; 90:21;91:2,9;93:14, 21;94:16,21,22;103:2; 104:3;112:22;113:1,3; 129:11;133:9;135:20; 187:19,21 ritualized (1) 102:14 road (1) 113:2 Rob (10) 93:13;95:2;99:13; 106:12;108:12;113:4, 22;115:5;133:6; 135:18 Rochester (1) 59:20 rodent (1) 148:12 rodents (2) 148:11,14 Roger (9) 46:9;104:10; 106:12;108:11;113:4; 153:2,3;155:11; 190:18 Roland (2) 93:19;114:3 role (2) 97:3;131:15 roll (3) 100:13;106:6; 190:14 rolled (1) 100:7 rolled-back (1) 116:17 Ron (1) 97:2 room (8) 8:2;73:6;78:2; 101:8;108:19;109:11; 118:11;178:5 rooms (2) 95:21;147:20 roughly (1) 160:12 route (8) 44:17;47:2;66:3; 111:21;135:21;136:1;
--	--	--	--	--

<p>164:6;171:12 routes (1) 19:20 rubella (1) 159:17 rule (1) 141:12 rules (1) 83:9 run (5) 21:12;126:7; 145:19;174:3;195:9 running (4) 28:1;114:12;167:2; 176:4 Russia (1) 150:9 Russians (1) 139:19 Ryan (12) 7:6;10:5;12:8;33:5; 39:12;15:42:5;54:15; 61:4;67:21;70:5; 75:21</p>	<p>121:13;123:13; 128:11;153:2;154:5 Sativex (5) 20:14,19;32:6; 43:17;44:6 save (2) 93:11;194:8 saw (2) 50:8;154:12 saying (30) 7:2;9:14;15:17; 35:17;42:20,21;43:7; 55:2,15;79:19;90:8; 108:12;112:22; 113:18;119:11; 123:14;147:21; 151:18;154:5,13; 159:8;163:22;175:20; 176:20;183:6,15,17, 20;186:13;195:5 scaffolds (2) 110:8;157:4 scalability (1) 116:13 scalable (1) 116:19 scale (4) 100:17,22;156:20; 157:2 scenario (4) 11:22;81:22;131:4; 182:15 Schedule (3) 141:11,14;182:6 scheduled (2) 173:1;183:3 science (3) 39:20;119:10;168:3 Sciences (1) 142:19 scientific (1) 42:3 Scientists (1) 31:17 scope (1) 106:14 scoping (1) 59:21 Scottish (1) 195:19 se (2) 40:1;82:20 season (1) 21:17 second (7) 40:19;63:11;65:13; 81:13;92:9;161:5; 174:15 secondary (4) 8:19;56:13;175:14; 184:18 section (2) 66:1;195:21</p>	<p>secure (1) 100:8 seeing (9) 53:20;110:12,22; 127:21;154:8;166:16, 17,19;183:3 seeking (2) 94:7;156:14 seem (6) 25:22;84:21;90:14; 101:12;102:14;148:18 seemed (2) 70:16;133:11 seems (20) 6:16;10:19;17:4; 21:20;27:5,15;60:17; 64:18,21;65:4;75:16; 102:22;104:4;122:5; 124:10;125:8;155:6; 157:9;163:18;176:4 select (1) 80:19 self-administering (1) 154:17 self-administration (6) 57:4;107:8;138:12; 154:16;174:6;180:12 self-control (1) 31:18 self-report (1) 85:5 self-serving (1) 185:11 selling (1) 55:7 send (1) 193:22 sensation (1) 79:7 sense (10) 5:12;21:13,21;34:8; 69:22;71:12;75:13; 100:19;104:3;157:2 sensitive (3) 86:11;132:22;185:4 separate (4) 61:7;63:20;99:7; 133:15 sequence (2) 18:12;96:22 serious (1) 91:2 serum (1) 134:21 serve (1) 57:18 session (2) 101:9;159:21 sessions (2) 114:6,7 set (6) 4:3;55:8;95:10; 107:15;116:2;187:19</p>	<p>setting (6) 29:12;36:19;52:2; 57:11;95:10;116:3 settings (2) 90:19,22 several (5) 13:6;105:21;111:9; 123:20;193:2 severe (1) 153:9 sexual (1) 117:5 sexually (2) 142:4,5 sexy (1) 37:14 shared (1) 191:14 sharing (1) 77:2 shift (2) 48:8;54:13 shifting (2) 151:11;154:1 ship (1) 156:18 shooting (3) 108:15;146:20; 151:5 short (6) 17:16;76:8,12; 112:14;137:14;155:2 shorter (1) 181:16 short-term (1) 79:20 shot (1) 57:15 show (8) 29:10;48:19;66:6; 117:11;134:14,17; 165:4;166:20 showed (1) 134:5 showing (5) 20:14;21:1;28:4; 95:21;119:20 shown (2) 21:8;57:2 shows (1) 49:4 SHURTLEFF (17) 20:7,10;27:22; 39:16;50:18;51:2,10; 78:15;104:11;145:8; 147:8;168:3,9,16; 169:8;170:19;185:11 sick (2) 167:14;196:2 side (9) 35:1;46:22;48:4,5, 20;49:13;104:5; 115:11;182:22</p>	<p>sides (2) 91:5;93:15 sight (1) 44:20 signal (5) 8:21;9:10;10:20; 49:3;54:10 significant (1) 101:6 signing (1) 195:12 similar (7) 10:4;78:21;88:22; 89:1;108:16;129:5; 171:15 similarly (2) 14:9;20:21 simple (2) 17:6;26:20 simply (1) 128:6 simultaneously (1) 181:15 single (5) 23:22;33:21;34:4; 129:22;177:7 sip (1) 170:22 sirens (1) 156:19 sit (2) 16:5;72:21 sitting (1) 160:22 situation (13) 22:1,4;23:16;53:9; 74:11;90:16;97:9; 123:21;124:9;132:21; 147:15;148:9;152:14 six (1) 194:1 skeptical (1) 73:21 sky (1) 141:6 sleep (89) 14:21;53:15;54:14; 55:4,12,15;56:4,6,8,9, 13,14;57:3,14;58:3; 59:14,15;60:4,17; 63:13,13,15,19,21; 64:17,19,20;65:1,2, 11;66:10;67:9,16; 68:14;69:22;70:15,20; 71:1,4,6,12,16;72:4,7, 19,20;73:22;74:13,15, 17,21,22;75:3,12,13, 13;76:14,19;77:5,22; 80:4,6,11;81:1,2,8,10, 15,20,21;82:3,7,16,20; 83:2,10,16;84:19; 85:2,22;86:8,12,16; 87:20,21;185:8;190:4;</p>
S				
<p>safe (9) 91:2;107:19; 116:20;118:4;149:4; 156:4,5,8;196:16 safely (2) 116:17;126:5 safest (1) 53:13 safety (10) 31:10;34:8;36:12; 41:7;48:20,21;77:17; 89:17;96:10;153:11 same (20) 3:11;38:20;59:16; 91:18;94:13;102:17; 110:14;117:13; 135:22;144:1,2; 145:20;146:3;148:16, 17;150:21;151:21; 155:14;183:6,17 SAMHSA's (1) 152:5 sample (3) 183:12,16,19 samples (1) 146:20 Sandoz (1) 119:6 sandwich (1) 88:10 sandwiches (2) 88:7;160:9 Sandy (14) 10:3;32:19;36:11; 48:9;51:16;54:19; 58:8;68:21;91:15;</p>				

<p>191:18,19 sleepiness (1) 85:5 sleeping (3) 20:3;58:7;83:14 slides (6) 4:17,19;5:3,8,16,22 slowing (1) 134:1 small (4) 86:18;107:2; 131:21;145:22 smiling (1) 161:20 Smith (1) 71:3 smoke (6) 12:10;21:13; 143:17,18,19;144:2 smoked (2) 10:9;11:5 smokes (1) 79:4 smoking (2) 79:3;114:15 snacks (1) 88:4 snapshot (1) 186:17 snarky (1) 33:2 sniffable (1) 170:12 soak (1) 135:11 social (7) 23:16;28:11;54:2; 55:9;112:7,11;127:10 sodium (1) 125:18 solutions (1) 40:3 somebody (26) 9:9;11:1;52:5,11, 15;53:7;54:4;55:8; 68:15;69:4;73:15; 74:5,11;75:22;77:14; 91:3;105:17;121:17; 123:18;129:16; 132:21;153:13;172:1, 15;187:11;192:12 somehow (2) 9:14;27:15 someone (7) 65:17;105:15; 109:5,8;125:5;153:5; 163:21 someplace (1) 158:4 Sometimes (6) 37:20;78:1;91:4; 94:11;175:11;196:6 somewhat (6)</p>	<p>6:16;39:19;64:6; 88:19;138:16;148:16 soon (2) 75:11;137:18 sooner (1) 148:7 soporific (1) 56:20 sorry (6) 25:11;50:22;62:12; 83:18;142:16;153:2 sort (33) 8:21;9:9;12:8; 14:17;15:9;31:17; 39:17;40:15;47:18; 54:15;55:2;64:8;65:3; 83:11;85:17;86:7; 88:22;96:9;97:8; 103:8;106:8;108:17; 122:18;130:16; 138:21;142:12; 143:19;152:4;159:16; 161:13;165:20;171:2; 175:10 sound (3) 171:11;185:11; 189:9 sounds (5) 18:19;30:21;36:17; 89:9;96:9 source (1) 168:19 space (3) 76:21;79:9;136:7 spaced (1) 183:12 sparing (4) 12:15;14:18;16:18; 38:3 speak (6) 40:21,22;86:1; 93:15;96:5,17 speaking (7) 15:18;85:19;93:9, 15;104:18;109:17; 137:15 spearheaded (1) 165:8 special (3) 62:20,22;170:7 specialty (1) 166:18 specific (15) 14:8;20:12;21:7; 65:16,20;66:5;90:18; 98:8,9,11;121:10; 147:13;179:2;184:17; 191:19 specifically (6) 18:9;22:21;135:5; 175:22;190:10;194:5 specificity (1) 27:1</p>	<p>specifics (1) 20:11 specified (1) 44:13 spectrum (1) 112:13 speed (2) 65:21;66:10 spend (2) 4:8;131:3 spending (1) 94:15 spent (1) 41:15 split (1) 16:8 sponge (1) 135:11 sponsors (1) 37:20 spot (5) 54:15,16,17;89:7; 188:10 Spravato (1) 125:11 spray (1) 140:9 spread (4) 157:21;158:20; 159:1;163:20 spreads (1) 158:4 square (1) 54:7 SSRIs (2) 67:9;117:5 stabilized (2) 55:16;122:6 stable (1) 123:18 staff (1) 148:3 stage (2) 4:4;174:8 stamina (1) 171:3 stamping (1) 195:12 stand (2) 37:10;57:20 stand-alone (5) 6:22;24:15;33:12; 59:1;129:4 standard (6) 36:7;45:21;48:1; 77:8;78:17;116:20 standardize (1) 78:2 standardized (2) 77:11;169:3 standardizing (1) 21:12 standards (1)</p>	<p>14:9 standpoint (3) 78:10;134:4;144:9 start (14) 6:7;11:8,9,10;20:5; 36:4;68:4;88:12; 108:12;154:18; 158:18;162:1;166:5; 188:22 started (12) 77:15;79:15; 105:21;120:6;126:8; 127:18;142:21;154:6, 7,11;163:4;169:16 starting (2) 149:20;191:3 starts (1) 17:21 statements (1) 178:17 states (3) 28:2;30:9;32:11 statistician (1) 195:19 stay (2) 58:1;74:3 stayed (1) 8:20 staying (1) 196:16 stays (2) 124:1;133:21 steal (1) 5:21 step (10) 4:8;15:1;28:15; 32:3;42:21;47:17; 97:3;114:16,20; 168:22 stepping (1) 28:18 steps (4) 4:10;83:22;84:4; 161:21 sticks (1) 155:4 still (18) 9:4;46:18;57:14; 64:3;72:13;73:18; 108:16;116:20; 117:16;122:9;125:3; 130:16;137:21;164:7; 167:10;183:10,15; 192:3 stimulant (1) 171:6 stimulants (8) 133:10;145:13; 161:10;163:16;164:1, 15;165:17,22 stimulant-use (3) 164:10,12;165:9 stipulations (1)</p>	<p>55:9 stockpile (1) 136:20 stood (1) 140:18 stop (5) 47:14;124:6; 148:13;182:10;183:20 stopped (3) 49:4;73:6;148:1 stops (1) 157:21 story (6) 72:16;83:17;97:11; 104:13;140:4,4 straight (1) 110:1 Strain (164) 3:3,4;4:21;5:12,18; 6:2,4,7;7:12,22;10:3; 14:2,12;15:6,10,13, 18;16:3;18:21;20:8; 21:22;23:8;25:11,14, 18;27:21;29:14;30:12, 14;31:13;32:19;33:1; 34:11,18,22;35:6,10, 13;37:3;39:12,15; 42:5;45:6;48:6;49:15; 51:16;53:16;56:20; 58:8;61:9;62:11;63:8; 64:2;65:7;66:14; 67:20;68:18;70:5; 71:19;72:15;73:3,13; 74:5,9;75:16;76:7,15; 78:5,13;80:1,8;81:4, 16;82:10;83:17;84:2, 6,12,14;86:21;87:17; 88:2,17;89:19;90:2,7, 10;91:11;93:12;95:2; 96:21;99:12;101:22; 104:9;106:11;108:11; 111:19;113:4,21; 115:5;116:21;120:11; 123:13;124:12;126:6, 13;127:7;131:5; 133:5;135:18;137:9; 141:18;145:7;146:9, 12;147:16;149:11; 150:15;152:21; 155:11,17;156:1,10; 157:11;159:20;160:2; 163:4;164:16,20; 165:5,14,16;166:15; 168:8;170:1;171:8,18; 172:1,4,6,13,21;173:2, 7,11,13;174:12; 175:15,20;176:2,14; 177:14,18;184:9,20; 185:2,10;186:9;188:6; 191:16;192:3,6;196:7, 12 strains (1) 19:21</p>
--	--	---	---	---

<p>strategies (2) 117:12,17</p> <p>strategy (1) 70:3</p> <p>streamer (1) 90:7</p> <p>streamlined (1) 186:17</p> <p>street (7) 22:20;31:3;146:8; 147:10,10;149:4; 153:15</p> <p>stress (1) 83:2</p> <p>stretch (1) 128:9</p> <p>strip (1) 34:1</p> <p>strive (1) 128:3</p> <p>strong (2) 23:20;89:12</p> <p>stronger (1) 127:19</p> <p>strongly (1) 13:8</p> <p>struck (2) 20:4;126:15</p> <p>structural (1) 107:16</p> <p>structure (1) 110:9</p> <p>structures (1) 157:7</p> <p>struggling (3) 53:22;60:1;130:16</p> <p>stuck (2) 191:21;196:14</p> <p>student (1) 109:3</p> <p>studied (3) 24:15;81:1;107:22</p> <p>studies (37) 4:11;28:10,12; 31:11;34:6;40:6; 42:15;49:17;51:6,11; 54:9;75:2;99:21; 107:3,9;114:12;118:7; 119:8;120:8;127:12; 134:8;141:2;154:17; 165:15;169:11,14; 171:20;172:15; 173:16;174:5;177:11; 178:8,18;179:4;181:5, 8;182:1</p> <p>study (44) 3:17;7:3,3;8:10,15; 14:5;17:7;18:5;28:15; 34:10,12;36:5,6,19; 38:6,16;39:22;42:22; 43:4;47:7,18,19; 50:10;52:10;53:12; 58:15;61:13;70:1;</p>	<p>80:17;82:1,6,20; 85:14;87:6;107:8; 114:3;117:14;167:2,4; 174:3;179:3;181:11, 16;182:15</p> <p>studying (7) 28:9,19;29:4,9; 37:18;115:16;188:22</p> <p>stuff (15) 9:19;11:18;27:11; 32:14;68:20;69:15; 88:1;97:19;124:15; 138:12;149:20; 150:13;152:4;177:6; 189:17</p> <p>stupid (1) 144:7</p> <p>subjective (6) 77:4,5,9;81:7; 111:2;170:5</p> <p>subjects (2) 41:17;169:1</p> <p>submit (1) 183:11</p> <p>submitted (2) 193:16;196:4</p> <p>subsequently (1) 65:15</p> <p>substance (7) 3:9;31:5;143:7; 149:21;161:6;177:20; 189:10</p> <p>substances (7) 26:4,19;64:14; 102:8,11;103:11; 104:6</p> <p>substance-use (8) 67:19;69:20;76:21; 132:1;136:6;175:6; 176:19;177:15</p> <p>substitution (6) 13:16;19:7,12;24:5, 15,20</p> <p>successful (2) 94:19;101:18</p> <p>suffering (1) 61:14</p> <p>suggest (3) 28:10;129:15; 184:11</p> <p>suggesting (2) 22:11;64:13</p> <p>suggestion (4) 81:14;111:4,21; 122:13</p> <p>suggests (5) 12:20;78:22;79:2,5; 111:1</p> <p>suicidal (1) 49:2</p> <p>summary (1) 192:14</p> <p>super (2)</p>	<p>91:7,7</p> <p>support (5) 61:16;62:4;86:17; 91:10;178:11</p> <p>supportive (1) 125:1</p> <p>supposed (5) 89:21;90:3;98:18; 121:2;142:5</p> <p>sure (29) 3:10;4:2;5:2,19; 11:2;18:15;20:8;45:3; 61:6;62:11;64:16; 73:13;80:2,9,22; 83:15;85:13;87:1; 95:8;96:18;98:6; 103:7;147:7;164:2; 167:10;169:20;173:3; 178:21;192:11</p> <p>surgeon (1) 109:12</p> <p>surgeons (1) 97:22</p> <p>surgery (1) 97:14</p> <p>surgical (1) 97:13</p> <p>surprise (2) 46:4;133:17</p> <p>surprised (1) 80:21</p> <p>surprisingly (1) 63:17</p> <p>surrounding (3) 47:11;124:15; 158:20</p> <p>sustained (1) 136:12</p> <p>suvorexant (1) 69:12</p> <p>switch (3) 128:8;130:1;156:7</p> <p>sympathize (1) 39:18</p> <p>symposium (1) 133:8</p> <p>symptom (7) 14:21;61:14,15,19; 68:5;80:15;128:7</p> <p>symptoms (14) 13:17;17:15;50:6,8, 9,17;51:3,9;55:18; 58:18,22;59:1,10,12</p> <p>system (5) 12:20;67:6;100:13; 101:12;119:3</p> <p>systematic (7) 53:21;177:2,4,14; 178:6,11;189:4</p> <p>systematically (2) 171:21;178:10</p> <p>systems (3) 13:13;29:19;98:12</p>	<p>T</p> <p>table (2) 16:15;90:8</p> <p>tag (1) 128:11</p> <p>talk (38) 3:14;5:7;18:3,15; 22:5;32:22;33:6;34:5, 6;35:17;36:11;38:16; 54:14;60:22;63:5; 68:6,14;81:6,9;88:21; 89:3;94:14,18;99:20; 113:10;115:9;128:10; 144:18,18;161:2,20; 171:5;176:17;180:6; 185:12;191:7,14; 195:11</p> <p>talked (6) 13:5;53:4;74:17; 149:14;192:14,22</p> <p>talking (32) 13:9;18:1;22:9,10, 20;23:1;27:2;31:22; 46:10;51:22;58:11; 68:4,22;70:21;71:3, 11;77:20;91:4,14; 101:1;121:2;128:17; 137:15;151:15;176:3; 177:17;178:13; 180:20;185:8;187:7; 188:1;195:15</p> <p>talks (2) 161:14;195:1</p> <p>Tanya (8) 42:6;45:6;48:8; 104:10;106:12; 108:11;111:19;184:9</p> <p>tapered (1) 70:19</p> <p>tapering (1) 135:16</p> <p>target (8) 12:13;56:5;59:1; 65:13;128:7;132:9; 147:13;149:18</p> <p>targets (4) 12:14;29:2;37:17; 107:14</p> <p>Tarrowalla (1) 173:20</p> <p>task (2) 185:3,6</p> <p>tasked (2) 60:14;186:12</p> <p>taxes (1) 158:10</p> <p>TCAs (1) 117:6</p> <p>tea (1) 173:8</p> <p>team (1)</p>	<p>128:12</p> <p>techniques (1) 63:12</p> <p>technological (1) 175:9</p> <p>technologies (3) 82:18,19;148:17</p> <p>technology (5) 61:2;85:12;86:9,16; 191:18</p> <p>teenage (1) 142:2</p> <p>teeth (1) 122:21</p> <p>tempted (1) 156:19</p> <p>tend (1) 193:19</p> <p>tension (2) 181:4,14</p> <p>tent (1) 79:11</p> <p>term (8) 12:3;17:16;69:18; 70:4;75:6;76:8,12; 112:14</p> <p>terms (21) 3:6,11;10:16;26:15; 41:7;53:11;89:2;96:6; 107:22;112:15;114:9, 16,16;121:3;123:17; 125:17;131:9;156:20; 161:14;178:8;189:2</p> <p>terpenes (2) 21:15;29:9</p> <p>terrorism (1) 150:12</p> <p>terrorists (1) 140:8</p> <p>Terry (1) 169:13</p> <p>test (3) 76:8;116:15;140:18</p> <p>testable (1) 76:2</p> <p>tested (5) 26:15;116:7; 182:10,11;183:8</p> <p>testing (9) 42:10;75:8;116:2; 151:1;182:6,13,21; 183:1;191:22</p> <p>tests (2) 166:21;183:5</p> <p>Thanks (12) 27:21;33:1;56:2; 88:3,13;89:19;93:12; 116:21;141:19; 185:10;196:13,13</p> <p>THC (9) 19:21;20:2;26:8; 27:3;30:18;41:5,18; 44:21;45:1</p>
---	---	--	---	--

<p>theater (1) 139:20</p> <p>themes (2) 42:8;89:2</p> <p>therapeutic (3) 29:18;103:12;104:7</p> <p>therapeutically (2) 91:7;105:3</p> <p>therapies (1) 121:6</p> <p>therapist (2) 109:4;114:6</p> <p>therapists (1) 116:3</p> <p>therapy (12) 19:7;24:6,15;25:5, 12:56;10:70;2:76;6; 101:13;109:4;114:7; 116:11</p> <p>thereby (1) 65:1</p> <p>therefore (2) 26:11;187:20</p> <p>there'll (1) 160:9</p> <p>thinking (42) 4:8,10;6:11;7:4; 11:10;14:14;16:9,10; 17:2;24:7,13;25:3; 33:18;36:4,14;45:4; 47:19;52:3,9;59:8; 60:4;64:4;71:21; 83:14;85:6;87:19; 101:20;115:12; 116:13,14;122:8; 124:14,16;145:11; 152:10;160:15; 161:17;169:17;188:2; 189:8,21;191:17</p> <p>third (6) 41:17;56:12;92:15; 105:13;157:21;158:1</p> <p>though (14) 9:8;12:1;14:3;96:4; 103:18;122:19; 145:18,22;148:8; 156:2,5;159:3;175:18; 183:21</p> <p>thought (18) 6:12,15;7:7,19; 10:13;34:2;58:13; 87:3;106:5,9;114:15; 126:11;156:4;165:21; 172:21;173:2;174:14; 183:9</p> <p>thoughtful (1) 4:5</p> <p>thoughts (18) 4:15;7:6;53:17; 54:21;55:20;56:16; 87:2;89:6;121:7,10, 11;128:12;159:21; 163:8;165:19;174:13;</p>	<p>188:8;192:1</p> <p>thousand-fold (1) 148:12</p> <p>thousands (2) 102:13;103:10</p> <p>threads (1) 110:20</p> <p>threat (1) 150:12</p> <p>threatening (1) 91:17</p> <p>three (1) 91:22</p> <p>throughout (3) 9:16;82:22;152:3</p> <p>throw (1) 61:8</p> <p>throwing (2) 60:19;152:19</p> <p>thumbs (1) 3:8</p> <p>tie (1) 59:17</p> <p>tied (5) 59:2,7;60:5;67:10; 69:2</p> <p>tier (1) 105:13</p> <p>tightly (3) 100:7,17,21</p> <p>till (1) 171:1</p> <p>times (10) 13:6;77:14;83:11; 144:4;146:1,1;149:13; 156:17;182:17;195:18</p> <p>Tiny (1) 138:2</p> <p>titrating (1) 171:2</p> <p>today (8) 3:9,12;34:12;63:6; 151:15;152:1;186:1; 192:21</p> <p>today's (1) 4:4</p> <p>together (10) 26:12;44:5;60:14; 133:9;139:17;164:10; 176:11;177:11; 183:11,14</p> <p>told (1) 127:9</p> <p>tolerable (1) 112:15</p> <p>tolerance (3) 26:11;124:19;125:7</p> <p>tolerant (1) 52:15</p> <p>toll-like (1) 130:13</p> <p>Tom (20) 23:8;25:15,19;81:4;</p>	<p>82:10;84:17;87:2; 121:13;123:14;133:6; 135:18;137:9;141:19; 147:16;149:12; 151:15;154:12;156:4; 157:11;163:14</p> <p>tomorrow (4) 4:20,21;138:21; 141:7</p> <p>Tom's (1) 28:20</p> <p>ton (2) 44:1;177:9</p> <p>took (3) 4:4;95:15;168:17</p> <p>top (5) 13:2;44:16;146:16; 148:15;156:20</p> <p>topic (10) 14:16;16:4;37:14; 60:17;66:16;75:17; 128:13;135:21;175:4; 188:9</p> <p>topics (2) 160:16;163:12</p> <p>total (1) 77:5</p> <p>totally (1) 175:1</p> <p>touch (1) 196:17</p> <p>touching (1) 177:19</p> <p>tough (2) 93:16;113:18</p> <p>TOURE (5) 76:16;78:7;83:6; 84:10,13</p> <p>toward (2) 10:16;126:16</p> <p>towards (5) 25:4;79:17;94:5; 126:9;159:21</p> <p>tox (1) 118:6</p> <p>toxic (1) 132:22</p> <p>toxicities (1) 26:9</p> <p>toxicity (2) 131:15;136:10</p> <p>toxicology (4) 118:1;179:12,13,17</p> <p>track (3) 88:20;109:19; 125:17</p> <p>tracks (2) 30:17;31:17</p> <p>Trade (1) 27:13</p> <p>traditional (1) 67:9</p> <p>traditions (1)</p>	<p>103:13</p> <p>trained (2) 97:22;98:3</p> <p>training (8) 79:1,2,6,12,17,21; 100:13;152:2</p> <p>tramadol (1) 171:11</p> <p>transcript (2) 4:18;5:13</p> <p>transfer (1) 175:12</p> <p>transition (5) 11:15;26:17;70:2; 71:7;129:14</p> <p>translate (1) 175:13</p> <p>translates (1) 62:3</p> <p>transporters (2) 168:7,11</p> <p>travels (1) 196:16</p> <p>treat (10) 37:13;38:1;56:9; 57:9;58:17;61:13; 62:8;75:22;100:19; 195:22</p> <p>treated (2) 109:22;181:2</p> <p>treating (8) 7:20;11:17;57:22; 59:11,12,15;129:1; 187:10</p> <p>treatment (68) 6:12;7:5;8:17;9:2; 13:19;14:17;20:15; 23:18;24:10;25:4; 33:9;36:17;37:10,22; 38:8;39:8;45:21;46:6; 47:4;48:1,3;49:18; 51:20;55:14,17;58:1, 5;59:3;61:17;68:22; 70:8,22;71:16;73:18; 74:3,4;75:19;79:18; 80:13;86:3;92:2,6,10; 97:10;99:17;101:16; 105:13;106:7;121:5; 122:7,12;123:20,22; 124:6,17,18;125:13; 129:2;136:13;138:22; 149:19;156:13; 167:16;170:4,18; 175:10;180:4;182:2</p> <p>treatments (19) 6:18;10:18;19:12; 23:11;31:21;37:12; 45:14;46:16;56:11; 73:20;74:20;92:18; 93:10;107:4;122:2,5; 124:20;188:17;190:6</p> <p>treats (1) 59:10</p>	<p>tremendous (1) 26:1</p> <p>trend (1) 89:12</p> <p>trial (24) 7:14;20:18;33:7,15; 46:10;47:8;50:15; 52:4,9;53:10;56:15; 66:8;70:7;74:10;77:3, 17;81:18;176:13; 188:19;189:2;190:8, 11,15;191:4</p> <p>trialists (1) 46:13</p> <p>trials (21) 3:15;6:10;9:13; 16:1;30:21;46:8;56:5, 14;82:18;83:3; 150:18;175:6,13; 177:22;178:12; 182:20;188:16; 189:12;190:21; 191:11,14</p> <p>triangulation (1) 115:2</p> <p>tried (3) 42:9;172:11;180:5</p> <p>trip (3) 95:20;113:2;122:17</p> <p>true (11) 63:17;76:4;81:22; 94:1,3,6,8,10,12; 152:6;184:8</p> <p>truly (2) 45:20;156:13</p> <p>try (17) 17:16;25:14;28:16; 42:15;54:9;73:3,4; 76:5;78:2;93:2;113:9; 116:8;179:6;193:18; 194:3,10;196:5</p> <p>trying (11) 3:12;17:1,8;29:8; 48:14;57:12;73:18; 88:19;126:20;130:12; 175:2</p> <p>TURK (5) 5:1;16:4;89:21; 192:8;195:3</p> <p>Turk's (1) 20:10</p> <p>turn (4) 55:10;91:20; 115:10;131:5</p> <p>turns (1) 72:20</p> <p>TV (2) 72:21;73:5</p> <p>Two (17) 5:1;6:13;11:13; 30:17;41:16;56:3; 59:3;61:7;65:10; 84:15;120:16;123:12;</p>
--	---	--	---	---

<p>164:17;178:21; 190:18;191:9;195:4 tying (1) 156:18 type (8) 60:20;70:3;90:17; 91:10;113:6;135:6; 145:14;177:10 types (7) 16:6;19:18;51:11; 97:17,20;113:1;187:5 typical (2) 161:13;174:6 typically (5) 71:16;94:15;173:9; 193:19;194:6</p>	<p>132:13,15;153:8; 176:11;191:14 University (2) 59:20;168:20 unless (3) 20:1;91:19;141:15 unlike (2) 92:5;171:6 unpack (1) 186:4 unregulated (1) 174:9 unrelated (1) 166:9 up (68) 3:8;4:16;5:6;18:15; 23:18;27:22;34:15; 42:18;43:16;47:14; 51:17;66:17;68:21; 70:6,17;75:3;77:16; 86:5,21;87:2;88:11; 89:3;91:14,19;94:2; 95:21;109:15;110:1; 115:19;120:6,16; 122:4;126:7;127:4; 131:5;134:1;135:11; 138:16;143:10; 146:21;148:6;150:9; 152:17;153:7,14,17; 156:16,21,22;157:8, 12;158:15;159:13; 161:7;162:1;163:6,9, 17;165:4;166:20; 168:16;169:18; 181:16;186:11,12; 189:19;192:8,13 upon (4) 6:20;17:8;100:2; 131:11 upstanding (1) 180:15 urban (1) 157:15 urgency (1) 41:11 urinate (1) 117:6 urine (10) 166:21;179:12,13, 17;182:6,20;183:1,5, 16;191:21 use (92) 5:15;8:21;9:5;12:4, 18;13:2,3;14:16,17; 17:8,14,15;22:2,6; 24:20;25:7;28:3;30:8; 32:8;33:19;36:15; 38:9;39:20;40:10; 43:17;44:15;45:1; 50:6,7,8;52:20;53:1,5, 7;59:7,18;63:15,17, 19;64:15,15;65:2; 66:18;68:1,7,16;69:2,</p>	<p>3,10,22;71:14,15; 72:3,9;74:7;75:2; 76:11;80:20;82:17; 86:7,10,19;90:18,21; 91:2,6;94:3,20;98:7; 99:20;103:5;104:6; 108:7;109:17;114:14; 116:14;121:9,12,15; 124:8;125:10;126:18; 145:14;147:10; 156:20;169:19; 177:12;180:14; 182:12,15;190:2,5 used (20) 3:21;9:1;17:16,18; 40:18;49:20;77:21; 102:9,11;103:11; 114:3;127:17,20; 129:1;146:8;152:16; 167:16;170:19,21; 179:1 useful (10) 11:22;50:12;54:22; 66:13;89:4;168:13; 184:12,14,15,19 user (3) 72:19;121:17; 149:21 users (5) 23:22;132:2; 136:21;151:17;158:2 uses (2) 16:15;22:8 using (43) 8:18;9:4;15:2; 16:10;17:1,14;21:9; 22:21;23:2;25:5; 26:15;36:15,16;40:9, 14;42:2;43:8;44:4,18; 47:20,21;57:6;82:15; 95:8,11;99:3;102:18, 20;105:2;125:14; 126:19;136:16; 148:16;151:18; 153:14;156:5,6;171:2, 7;182:8,9,10;183:10 Usona's (1) 99:16 usual (1) 138:12 usually (4) 77:15;152:15; 154:19;158:3</p>	<p>vaccinating (1) 154:18 vaccination (1) 158:18 vaccine (40) 121:21;128:15; 129:4,6,12,15,16,22; 130:3,6,10,11,18; 131:10,13;132:5,6,20; 133:18,19;134:15; 135:20;136:1;137:1, 11,17;138:1,4,20; 140:19;141:21; 143:16,22;148:14,19; 154:1,8;156:3;159:6; 190:17 vaccines (16) 54:20;88:6;127:6; 128:10,19;130:10; 132:9;134:6;136:6; 138:10;141:11; 154:13;158:1;159:5, 11,22 valuable (4) 22:14;72:14;74:4; 186:21 value (2) 56:8;189:20 VANDREY (8) 7:9,17;8:1;10:11; 42:7;70:6,12;76:9 vanishingly (1) 107:1 variability (3) 130:8;147:10;178:8 variable (1) 179:2 variation (2) 16:20;21:16 variations (1) 21:14 variety (3) 29:11;58:2;166:1 various (5) 37:13;67:8;77:21; 87:11;104:19 vary (1) 17:7 vast (1) 45:11 versions (2) 26:2;194:1 versus (12) 12:7;43:17;44:14; 52:19;74:18;81:6; 117:1,12;135:21; 136:21;140:19;191:14 veterinary (1) 157:18 view (1) 151:20 virtually (1) 100:22</p>	<p>visits (2) 101:11;183:12 Vivitrol (8) 11:15;24:18;57:13; 92:10;123:19;124:1,2; 151:22 VOICE (20) 12:6;35:3;56:20; 131:6,6;139:1;140:3, 5;149:8;150:21;151:4, 7;153:19;164:19; 167:22;169:6;171:17, 22;183:21;184:2 Volkow (1) 61:12 volume (2) 131:5;154:15 volunteers (1) 85:15 vortioxetine (1) 65:19 vulnerability (1) 94:10</p>
U			W	
<p>UC (1) 110:10 ultimate (1) 115:1 ultimately (3) 70:17;100:14; 101:18 Ulysses (1) 156:18 unable (1) 117:6 unanswered (1) 72:14 unavoidable (1) 187:14 unbound (5) 135:2,3,9,12,13 uncomfortable (1) 122:9 unconscious (1) 134:11 under (8) 65:22;79:11;96:9; 98:1,17;101:4;115:20; 125:11 underlying (4) 24:11,12;59:11; 70:22 understood (2) 80:3;133:11 undiagnosed (1) 81:10 unexpected (1) 143:14 unfill (1) 163:15 unfortunately (3) 26:20;51:7;158:21 uninvolved (1) 165:2 unique (16) 6:16,21;9:22;17:11; 95:6,22;102:6;103:3; 107:12;129:11;130:5;</p>			<p>wait (4) 19:10,17;32:16; 37:5 waivers (1) 98:19 walk (1) 123:5 WALSH (1) 146:14 wants (5) 33:17;52:5;68:6; 122:3;192:6 watch (1) 86:13 watches (2) 82:21;83:12 watching (3) 30:16;72:21;109:16 water (1) 143:1 way (51) 9:12;15:2,18;26:12; 38:20;40:11,14,16; 42:8;46:8;47:14; 48:20;52:7;53:21,21; 58:14,15;60:3;62:21; 65:3,13;72:2,7;73:11; 74:2;79:19;91:9; 93:10;94:21;100:8,17; 102:17;109:10;116:6; 122:10,16;138:3; 141:12;145:18;147:9, 13;151:21;152:11,20; 181:22;186:14,17; 187:6;188:2;189:21; 192:10 ways (18)</p>	
		V		
		<p>vaccinate (6) 141:2;143:7,16; 144:20;157:19;158:7 vaccinated (7) 132:22;134:11; 152:12;153:6,13; 155:1;158:22</p>		

22:13;31:6;40:3; 54:8;55:17;56:3;65:4, 10;77:10;79:11; 80:11;91:22;95:14; 128:16;149:7;150:11; 159:11;191:5	whenever (1) 121:19 wherein (1) 64:15 Whereupon (3) 88:14;162:3;196:19 whichever (1) 56:11 whole (20) 18:12;19:2;29:19; 36:10;45:19;46:9; 58:2;59:9;63:8;88:1; 117:21;118:7,12; 125:22;142:18; 143:16;152:7;167:8; 178:7;187:19 who's (8) 44:2;95:19;109:4; 121:17;123:18; 124:14;132:8,22 who've (1) 196:14 widely (2) 183:12;184:5 widespread (2) 22:2;36:15 wife (1) 169:13 wild (2) 32:11;93:15 willing (3) 5:9;161:18;194:14 willingness (1) 75:22 willy-nilly (1) 180:15 WINCHELL (27) 9:11;37:5,8;39:13; 61:11;62:20;63:4; 80:2,9;90:12;96:20; 97:5;99:2,6;126:12; 133:7;164:8;165:1,4, 11;166:1;178:20; 180:3,21;183:22; 184:3;187:3 wind (2) 23:17;150:9 winding (1) 159:20 window (1) 182:7 withdrawal (28) 8:12,14;10:22;11:5, 14,17;13:17;14:18; 16:13;17:15;18:4; 24:8,12;38:1;43:3; 49:8;50:5,6,7;63:20; 82:1,3,6,8;84:19; 129:1,17;167:10 within (5) 21:15;146:1;175:3; 178:15;186:17 without (9)	7:15;12:10;27:6; 31:21;35:7;68:8; 94:15;111:13;120:2 wonder (7) 68:20;82:16;83:4; 89:5;96:5,11;113:19 wonderful (1) 119:19 wondering (8) 10:7;38:19;51:4; 88:18;106:8;145:15; 146:5;147:14 word (4) 48:9;50:11;144:22; 145:2 wording (2) 65:21;66:5 work (45) 13:1,4;19:1,1,10; 20:6,13;23:17;26:1; 40:5;47:13;49:8; 51:21;53:20;68:15; 73:18;76:13;78:9; 79:1,4,20;89:12; 92:22;93:11;101:4; 103:18;105:9;109:14; 114:15;117:14,21; 118:8;122:17;125:1; 137:12;138:2;141:16; 148:7;149:1;156:7; 159:11;167:9;171:11; 177:9;196:6 worked (5) 39:9;48:12;87:9; 160:5;192:10 worker (1) 73:5 workers (2) 170:22;171:7 working (9) 33:4;93:6,7;99:11; 136:22;141:13; 154:11;164:9;195:16 works (4) 139:2,3;141:12; 176:9 workshop (1) 164:10 world (12) 5:16;42:2,13;47:9; 62:7;71:9;103:18; 104:3,17;109:19; 116:9,19 worried (2) 140:8;149:19 worry (3) 92:3;114:19;149:2 worse (7) 49:20,22;63:16; 64:16,20;66:20;81:9 worsen (1) 64:19 worst (1)	9:8 worth (2) 28:18;77:2 wrap (4) 88:11;110:1;126:6, 11 wrapped (1) 43:16 write (4) 61:6;85:22;86:5; 177:3 writing (3) 152:6;177:2;186:12 written (1) 4:12 wrong (1) 91:3 wrote (3) 58:11;59:21;142:18 X Xyrem (1) 125:18 Y Yang (1) 79:1 Yasmin (1) 20:22 year (6) 31:21;41:18;84:15; 86:18;107:7;174:19 years (16) 19:10;27:7;31:19; 67:3;69:14;72:17; 96:15;102:13;103:10; 106:21;118:3;124:16; 142:20;154:8;167:3; 179:4 yesterday (21) 3:14;4:3,16;7:10; 8:9;32:13;33:5;35:9, 12;46:10;53:4;60:17; 64:5;89:8;90:13;93:6; 96:13;100:10;101:2; 132:12;174:17 yesterday's (2) 55:22;77:19 York (1) 150:21 1 1 (4) 3:3,8;127:22;183:8 1.5 (1) 3:4 1:01 (1) 196:19 10 (8) 70:18;71:2;143:22;	144:2,3;145:22;154:8; 162:1 10:14 (1) 88:14 102 (2) 194:22;195:6 10-minute (1) 160:7 110 (1) 21:14 12 (1) 161:22 12:00 (1) 162:3 12:10 (1) 88:12 12:15 (2) 88:12,12 12:23 (1) 163:2 120 (3) 21:14;195:2,3 12-week (1) 181:11 15 (2) 87:8;181:9 15-minute (1) 88:3 16th (2) 164:19,20 17 (1) 99:19 18-MC (2) 107:18;110:15 1962 (1) 119:1 1975 (1) 119:22 1987 (1) 120:5 1990 (1) 120:6 2 2 (8) 3:4;71:2;79:6; 112:16;115:21; 123:22;174:1;193:3 20 (3) 31:19;142:20;146:1 20-years-ago (1) 157:13 24 (3) 85:3,8;87:20 2-liter (2) 72:22;73:7 3 3 (5) 123:22;130:19; 159:7;182:17;195:18
--	---	---	---	---

<p>30 (3) 60:22;100:5;183:8 30-year (1) 23:1 33 (1) 28:2</p>	<p>78:18</p>			
<p>4</p>				
<p>4 (6) 3:13;86:8;170:14; 192:4,4;195:18 40 (2) 27:7;54:13 45 (3) 88:5,6;160:12</p>				
<p>5</p>				
<p>5 (2) 79:2;195:18 5- (1) 160:7 50 (5) 20:16;47:3;101:16; 106:21;118:3 50-60 (1) 47:8 50s (2) 105:22;118:21 58 (1) 177:22</p>				
<p>6</p>				
<p>6 (6) 47:4;130:19;159:9, 12;179:4,4 60s (9) 95:18;105:19; 106:3;114:8;118:14, 19;119:14,15;120:9 65 (1) 177:21 6-mitragynine (2) 172:2,15</p>				
<p>7</p>				
<p>7 (1) 181:10 7-hydroxymitragynine (2) 166:12;173:21</p>				
<p>8</p>				
<p>8:37 (1) 3:2 80 (1) 20:16 80-90 (2) 47:7;151:16 8-week (1)</p>				