Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest
Hybrid Public Workshop
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Morning Transcript

Opening Remarks

Susan C. Winckler, RPh, Esq, Reagan-Udall Foundation for the FDA
Marta Sokolowska, PhD, U.S. Food and Drug Administration

Susan Winckler (00:00:26):

Good morning. Welcome to those of you who are here in the room, and to those of you who are joining us virtually, I'm Susan Winckler and I serve as Chief Executive Officer at the Reagan-Udall Foundation for the FDA. We are the organization that's been bombarding you either with speaking invitations or with the invitation to please come to this meeting and learn more about ketamine today. That is our goal that we will be under specifically, trying to understand the use and emerging areas of therapeutic interest for ketamine. Before we begin, I have to do the housekeeping issues and then I promise we'll get to the substance quickly. Most of our speakers and about 50 attendees are here in the rooftop. The reason I'm looking back at the camera is because we have several hundred attendees joining us virtually, and we tape these events so that there is enduring material available after the meeting.

(00:01:21):

So we are here to enjoy the experience in the room and to assure that we are providing good information for those who are joining us virtually as well. Because of the size of the meeting, virtual participants are muted and your cameras are off. That will be in place throughout the event. Our in-person engagement is primarily through written questions and our speakers who will be up here on the dais with us, but if you'd like to engage in the meeting, if you're joining online, we will have questions submitted using the Zoom Q&A function. If you're in person, my team is going to have some index cards that they'll make available. If you want to write a note on the index card, then that will get to me so that you can submit a question. We have already gathered hundreds of questions and we do not have hundreds of hours to answer those questions, but we will get through as many as we can.

(00:02:18):

And as a reminder, as I said, we are recording the meeting and we'll post the recording along with the slide deck and transcript on the foundation website, which is reaganudall.org, later this week. I want to take a moment before we dive into the agenda for the day, but if we could move to the agenda slide, I want to thank our FDA planning team for helping to organize this discussion. We appreciate the agency's partnership and collaboration in the planning process. So here's our plan for today. In the morning, we will explore ketamine, its history, the shifting landscape of use from being a schedule three controlled substance approved by the FDA as an anesthetic agent, which it is, but we want to learn more about its emerging off-label use for the treatment of conditions such as depression or chronic pain. That's our morning. We'll take a break at 12:05 Eastern and return at 1:15.

(00:03:18):

For those of you nearby, there are plenty of places to eat. For those of you who are virtual, you need to handle it as you would any other day that you're working virtually. In our afternoon sessions, we will focus on policy and regulatory considerations at the federal, state, and local level, as well as online promotion and access to ketamine. We'll conclude the meeting with a forward-looking discussion that reflects on what we have heard today and explores where do we go from here? Our speakers, who are brilliant on this topic, the prep calls were just fascinating, but they include academic and clinical researchers, practitioners who oversee ketamine use, policy experts, and partners from the federal government. They will speak to current clinical uses, potential safety risks, policy and regulatory challenges, as well as the effects of rising online promotion and access to ketamine. The full agenda and biographies are available in your handouts and on the foundation's website, and the link is also posted in the chat.

(00:04:21):

For those of you who are in the room, please join us in this room and not in the Zoom room because if you all join the Zoom room, we risk the Wi-Fi connection to broadcast to said Zoom room. So enjoy the in-person experience and we will keep you up to speed with what's happening in the online interaction. I'm done with housekeeping. So let's move to substance. I am going to turn the stage over to Dr. Marta Sokolowska to provide our initial opening remarks. Dr. Sokolowska serves as the deputy center director for substance use and behavioral health in FDA Center for Drug Evaluation and Research, where she sets the strategic leadership for the center's work related to controlled substances and substance use disorder. Dr. Sokolowska, would you open us with a few remarks?

Dr. Marta Sokolowska (00:05:15):

Well, thank you very much Susan, and good morning everyone. On behalf of FDA, I would like to welcome you all, both in the room and in the virtual room all around us. I would like to start with thanking Reagan-Udall Foundation as well as the planning committee for all the efforts to convene this important meeting, to our speakers, panelists, discussions for taking your time to help us to better understand this issue and really initiate this important discussion. This meeting is about emerging areas of therapeutic interest related to ketamine. FDA does not regulate practice of medicine, however, that's why it's important that I start with noting what are the FDA approved uses for ketamine. So FDA has approved ketamine hydrochloride, which is a schedule three substance, as an intravenous or intramuscular injection solution for induction and maintenance of general anesthesia. We have approved esketamine, which is a product derived from ketamine, which is also a schedule three substance, and it's approved for two indication.

(00:06:31):

In 2019, we approved esketamine as a nasal spray and it's approved for treatment of treatment-resistant depression in adults in conjunction with oral antidepressants. Second, in 2020, we approved esketamine as a nasal spray to treat depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, again, in conjunction with oral antidepressants. And because of the potential risks associated with esketamine, including sedation, dissociation, potential for misuse or abuse, esketamine label contains box warning, and it's also subject to strict controls on dispensing and administration under safety program called the Risk Evaluation and Mitigation Strategy or REMS. So that's what we've approved it for. Now, let's note what we have not approved it for. We have not approved ketamine as being safe and effective for any of the mental health or pain conditions. We have not approved ketamine as nasal spray as oral formulation product, and FDA does not approve any compounded drugs, and that also includes ketamine products.

(00:07:56):

These are important points to note because we are aware that ketamine products, including compounded products, have been used in a wide variety of mental health as well as pain conditions. And in the past few years, FDA has received safety reports involving compounded intranasal as well as oral products to treat psychiatric conditions or psychiatric disorders which may have put patients at risk. And in response, we issued two compounding risk alerts in the past few years that include important safety information for patients and healthcare providers to consider when thinking about using compounded ketamine products. So more broadly, reading news or scientific literature, we recognize that there has been a growing interest in utilization of ketamine for indications for various purposes. If you look at clinicaltrials.gov, you can see that ketamine is being evaluated to use in the potential treatment of a number of conditions such as depression, chronic pain, acute pain, to name a few.

(00:09:05):

We also recognize that in the real world, many people are currently using ketamine for a variety of conditions in variety of healthcare setting, and in using variety of formulations. So given these realities, this workshop is an important opportunity for us to expand our knowledge about the currently use of these products. What evidence do we have? What are the gaps and what else do we need to address? So today, I look forward to this discussion from a variety of stakeholders committed to advancing science of understanding this emerging space. We are excited to explore this project, these topics. Because the scope of ketamine use in this emerging areas is so exploring and it's really becoming broader, we want to learn about potential safety concerns, but we also want to learn about the policy and the regulatory challenges, online promotion, and access to ketamine and the implication of it, particularly for safety.

(00:10:09):

So throughout our speaker's presentation, our panelist's reactions, and our audience members' participation, with all of that, we hope to learn also from researchers, clinicians, policymakers, professional organizations, patients, and patients' advocates, federal partners, and more, we understand that these conversation will help inform the broader context and understanding around FDA's regulatory decision making. And with that, I would like to turn the stage to Susan and start the meeting.

Session 1: Overview of the Changing Ketamine Landscape

Gerard Sanacora, MD, PhD, Yale University

Susan Winckler (00:10:40):

Fabulous, thank you Dr. Sokolowska. And it's just important for us to understand what the approved piece and then what's emerging in this space as we turn for our next approximately six, seven hours to learn about that emerging interest. So I want to turn to our first session speaker, Dr. Sanacora, if you would move to the podium. We are going to open first and here from Dr. Gerry Sanacora, associate professor in the Department of Psychiatry at Yale University, presenting the current ketamine landscape, which as you know is changing. So I'm going to walk past that way, and if you would kick off, we'd love to hear from you and you should get full 20 minutes.

Dr. Gerard Sanacora (00:11:22):

Thank you, Susan, and thank you Marta for that background. Thank you for the opportunity to talk. I understand my role here is really to give the sweeping overview of ketamine and where it's gone over

the past 25 years or so that I've been in the field. I do have several disclosures, more than glad to make those public, and I will be talking about off-label use, mainly ketamine, but also some other things. So really this is what I'm going to try to present. This is a timeline of ketamine, and granted, this is a little depression-centric. We're going to be hearing about a lot of other uses for pain, PTSD and other things today. But this is really a big picture, capturing the complexity and the highs and lows of ketamine over time. Really first synthesized back in 1962 with the goal of developing a safe, rapid-onset anesthetic that could be used in situations where you were really worried about blood pressure dropping out and respiratory rates dropping, mainly in field hospitals.

(00:12:27):

This came out a lot during the Vietnam War where it was used a lot in field hospitals, became very popular, and ketamine quickly made it to the World Health Organization list of essential medicines. But then some of the complications started to arise, and we're going to see this, some of these potential toxic effects. Originally developed as a neuroprotective, these NMDA receptor drugs, a neuroprotective mechanism, but we started to learn that they themselves have toxicity, neurotoxicity and toxicity in other body regions. And then we also started to learn a lot more about the abuse potential. And with that, the World Health Organization expert committee on drug dependence evaluated ketamine for safety versus risk several times over that period of time. And then really, it was the discovery of ketamine's effects on neuroplasticity and its potential antidepressant-like effects that really stimulated a lot of new interest back at the turn of the millennia.

(00:13:29):

And that eventually led through the APA... I'm sorry, through the FDA approval of a version of that, esketamine, and we'll go through that. So right now, let me just give you a background of why ketamine? This is really going from the work 1980s, early 1990s, especially related to depression, but most neuropsychiatric disorders, realizing that the previously held neurochemical hypothesis, chemical imbalance, really wasn't explaining the pathophysiology of these illnesses and really wasn't explaining the mechanism of action. And a lot of work from... in this case it's Steve Hyman, Eric Nestler, and others at the time, but really doing some of the basic work suggesting that it really is the drug's effects on neuroplasticity, these longer term effects, that may be generating these beneficial properties that we see with antidepressants of all types, and the idea that if you could target that a little bit more directly, you may be able to develop better antidepressants, more rapidly acting antidepressants, and possibly antidepressants with greater potential.

(00:14:34):

There was also work from the NIH at the time, Phil Skolnick and others who was doing some preclinical work also looking at the ability to change neuroplasticity in the form of LTP and how the NMDA receptor, the glutamatergic NMDA receptor, could be related. And they started to identify drugs that target the NMDA receptor as potential antidepressant-like drugs. So this is around 1990 when this started to come about. And all of this was in the context of a lot of new discoveries in the field suggesting that depression was probably more of a cortical disorder than an illness of the raphe, which is where most of your serotonergic neurogenetic neurons, the midbrain, is coming from. And it led my colleagues back at Yale, John Crystal, Dennis Charney, Rob Berman, and others to really question whether you can target the NMDA receptor, the glutamatergic NMDA receptor, to develop new treatments for depression.

(00:15:34):

And this is really their idea, which led to this now seminal and quite famous study of seven people showing that a single dose of ketamine can have this rapid onset of antidepressant effects within hours

lasting for days compared to... the blue line is when a saline control was given. Really quite amazing finding. And even the authors at the time said, "To the amazement of our patients and ourselves, we found that ketamine produced rapid, profound, and surprisingly durable antidepressant effects that were temporarily dissociated from the brief acute behavioral effects of the drug." Remember, ketamine has a very short half life. It's kind of in and out, but yet these antidepressant effects continued. That really stunned the field. People became very interested, started to do all kinds of work, but it really took six years, which is amazing, to be replicated at the NIMH. Again, Dennis Charney, Carlos Serrati at the NIMH replicated the finding now with 17 people, a larger but still small sample, but very closely replicating, showing that about 70% of the people had a response by day one.

(00:16:43):

Now that's the equivalent of six weeks of treatment with other oral antidepressants, so pretty amazing finding. That was followed up with another series of small studies, all less than 20, 30 people, but consistently showing this very large effect size right after treatment lasting for a few days and even for a week after. That generated a lot of interest. From the academic side, it generated a lot of interest in us trying to understand the neurobiology of it. At the time, most of us were saying, "Yeah, but this is ketamine. This has all this baggage. It really can't be used that much clinically, but it could give us insights into how we can develop new drugs." So we really did a lot of work trying to understand the molecular biology of it, the mechanisms, and I have to admit in retrospect, a lot of this is confirmatory.

(00:17:33):

We had the hypothesis that this was acting through the glutamatergic system, that this was inducing plasticity, that this could reverse some of the effects of stress that we thought were associated with the pathophysiology. And there was a lot of work suggesting that ketamine does in fact do that, and we tied that directly to the antidepressant effects. Now we understand there's probably other mechanisms, many other mechanisms, that also contribute, but it also stimulated tremendous interest in the clinical field. This is just a brief survey that we did. About 10 years ago we started it, but showing this very rapid increase in the use of ketamine clinically. There started to be a lot of media reports coming out... I'm sorry, a lot of media reports coming out showing this rapid onset of antidepressant effect. People got quite excited about it, and I think it really speaks to the desperation of patients suffering from severe treatment-resistant depression and the desperation of the clinicians trying to treat them.

(00:18:28):

And it really very rapidly took a lot of attention and gained a lot of attention from the media, but also clinicians starting to use this drug more and more with very little clinical evidence to support it at the time. And this is also in the face of increasing acknowledgement of the potential dangers of ketamine. So as I said, these NMDA receptor antagonist drugs were originally thought to have neuroprotective properties, but more and more work started to come out suggesting that in fact, they could have some neurotoxicity of their own, excitotoxicity it was thought to be, because of that unique mechanism that low doses of ketamine could actually stimulate more glutamate release. So this ironic thing that you're blocking one of the glutamate receptors, but you're actually increasing activity through other glutamate receptors, that could be leading to some of this toxicity. So the famous Olney lesions, these vacuolizations in specific brain regions, was demonstrated around 1990 with these NMDA antagonist drugs and ketamine.

(00:19:29):

So we started to really realize, "Well, this could be toxic." And then increasing number of papers coming out either in non-human primates, but many in cases where humans that were misusing or abusing ketamine for different reasons, showing dramatic toxic effects on the brain and that having functional

impact. So really we start to see the danger of this becoming quite real. And then it was at that time that the APA task force for research really came to me and a few others and said, "We'd like you to generate some guidelines on how to use ketamine." So this is 19... sorry, this is like 2015, 2016, and they said, "There's such excitement, enthusiasm about giving this treatment and the hope and optimism that it's offering patients and clinicians, but we're balancing that against very little data and the real risk of toxicity. How to do this?"

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So we set out to try to write guidelines, and we very quickly realized that we couldn't write guidelines because there wasn't enough data to really write guidelines. To make meaningful guidelines you have to base it on real data, and at the time, there just wasn't that much there. So we at least set out to make a consensus statement that would draw boundaries about what we know and what we don't know and what the risks are. And really we identified several major questions at the time. What is the optimal dosing strategy? We really didn't know at the time. In fact, we had no clue at the time back then. What are the longer term effectiveness of the treatment? Again, most of these studies were single dose at the time. What was long-term safety? That, we had almost no data. And I'll argue we still have almost no data for many versions of the treatment. What are the critical moderators of the response? So we really didn't know what diagnosis was going to be optimal. We didn't know if there's drug-drug interactions.

(00:21:19):

We didn't know if there were genetics that could put people at risk at either increased benefit or harm. So there were so many questions that we didn't know. And then came the idea that, how do we scale this up? Remember, ketamine is a drug that is approved by the FDA in 1970 as an anesthetic. It was really hard to get protection of intellectual property around it. So who is going to do these multimillion dollar studies, hundred million dollar studies, to really get this information? That became incredibly complicated and really hard to solve. But then there was the idea of using esketamine. So esketamine... ketamine is a racemic mixture of having two enantiomers, the S and the R. Esketamine is just the S enantiomer. It's just half of what's in normal racemic ketamine. And it was the esketamine, the S enantiomer, that has a higher affinity for the NMDA receptor and therefore is more potent at the NMDA receptor and having these effects.

(00:22:22):

And that's been shown in anesthesia that you can use lower doses of esketamine and get the same anesthetic-type effects. So the idea that Janssen Pharmaceuticals had was, "Well, maybe we can make esketamine and turn it into a nasal spray, which allows reduced volume that could be absorbed much better," and they could show that lower doses of esketamine seem to be quite potent in their original studies. They then set out to really run these large studies. So this is the portfolio that was put together for the FDA. Now you see studies with several thousand, a couple of thousand people, following people out for a year with large numbers, really high data quality. So now you had a real sense of what the efficacy and longer term safety is. And that, as Marta said, led to the FDA approval in 2019 for treatment-resistant depression alongside an oral antidepressant.

(00:23:19):

And then later, about nine months later, for the approval for major depression associated with suicidal ideation. In the US and Europe, they consider it requiring hospitalization more than suicidal ideation. But you see this approval process set out. But as Marta also said, it came with a REMS, a risk evaluation mitigation strategy, that very strictly limited the dosing: 56 milligrams twice a week, going up to 84 milligrams twice a week for one month, then going to once a week, and then trying to space out from that. It also very tightly regulated how it was administered. Pharmacies had to have special approval for

it. It had to be given in a healthcare facility under the supervision of a healthcare provider who followed them for at least two hours under observation. And importantly, it also came with this registry, which allows us to continue to collect data. So every time you see a patient, you have to fill this registry out asking about some of the key adverse events of interest, but also more than anything, tracking how frequently the dose and other characteristics that are given.

(00:24:27):

With that, I don't expect anybody to read this slide, but now we have data on well over 58,000 patients with over 800,000 administrations, and this is a poster recently presented by Janssen. So now we have data, really strong data on huge numbers of people because of this registry. So that's something that we have. Where does it stand with ketamine? Not quite the same. This is probably the largest study done with ketamine to date that's under that really tight follow up, and this was 195 people. This was a recent PCORI-sponsored study where we saw antidepressant response with ketamine non-inferior to ECT. Actually, probably numerically looking better than ECT, which is pretty good. We also get a real sense of some of the risk, but again, this was using 0.5 milligrams per kilogram IV for 40 minutes and only giving six treatments here, so really limited. Most recently, I was just talking to one of my colleagues, Alison McInnes from Osmind, and they have data from several thousand people suggesting that the average dose now being used in the community by the end of treatment is over 0.85 milligrams per kilogram.

(00:25:46):

And in fact, she would say that it's probably closer to one or over one milligram per kilogram, so much higher than where we have real safety data in this sense or high quality safety data. So the community is using doses much higher, and in many cases, giving many more treatments than were given here in that one study. The last thing, I didn't really know how else to include this, but I think it was such an important point to make, and I think we're going to hear from Boris Heifets later today, but we are also understanding that besides the NMDA risk mechanism, there are other mechanisms that the drug could be working through. And one of the big ones that I think we're going to need to talk about to some extent, and it really is rearing its head even with the most recent MDA cases, is this idea of expectation and the idea of contextual effects.

(00:26:34):

How big are all these other effects beyond the specific effect of the drug? I just want to raise that because I think it's such an important thing that we need to consider in how are we going to deal with this moving forward. But regardless of the mechanism, we know that the landscape is changing so rapidly. It's changed how people are using ketamine. They're rapidly shifting, and you're going to hear from Joey Palamar later today too, talking about how things have changed. And just within the past two weeks, there've been two major papers coming out looking at oral IV ketamine being given in studies of varying degrees of rigor. And we have to be really careful how we're evaluating this data, both for the safety and efficacy, but it's happening. It's happening fast and in large numbers, so we really have to stay on top of it.

(00:27:26):

So where do we stand today? I think we're really stuck between this balance of trying to make what I would consider a lifesaving treatment for many people available, but doing it in a way that's safe and responsible. We can't deny the fact that there's real toxicity associated with the use of ketamine, and there's real risk for drug diversion if it's not done carefully. So I think we really need to balance those two. And this is just the last slide saying that we tried to convene an expert panel international looking at this, and there are certain principles I think that we could take from it that we have some good ideas about, especially esketamine, the approved version. I think now we have really good data for that, but

for IV ketamine or for other routes of administration, we still have a lot to learn. So I'm just going to leave it at that. It's kind of a broad overview. Thank you.

Session 2: Scope of Ketamine Use in Clinical Practice

Presentations:
Steven P. Cohen, MD, Northwestern University Feinberg School of Medicine, Uniformed Services University School of Medicine
Eric Hermes, MD, Veterans Health Administration
Panel Discussion:
Mikhail Kogan, MD, George Washington University Center for Integrative Medicine
Brittany O'Brien, PhD, Baylor College of Medicine
Jessica Poole, DNAP, CRNA, Pennsylvania Association of Nurse Anesthetists
Sandhya Prashad, Md, American Society of Ketamine Physicians, Psychotherapists, and Practitioners

Susan Winckler (00:28:24):

So thanks so much Dr. Sanacora. That [inaudible 00:28:29] what [inaudible 00:28:33] us move into our additional sessions. So let me give you a little framing for our second session. In the second session, we'll start our format of having two shorter presentations and then be joined by a couple of additional folks to help us have a rich discussion. So this is the first time that you will be seeing that. So let's prepare to turn to our first speaker for session two, which is Dr. Steven Cohen. Dr. Cohen is Professor of Anesthesiology and Vice Chair of Research and Pain Medicine at Northwestern University. I think if we tick forward, we would get to Dr. Cohen's slides. There we go. Are you ready?

Dr. Steven Cohen (00:29:14):

Sure.

Susan Winckler (00:29:14):

Take it.

Dr. Steven Cohen (00:29:15):

So I guess the disclosure is, I'm still at Johns Hopkins. There was some legal issues with transferring grants without halting studies, so both institutions asked me to extend. So I was asked to speak on our guidelines that we published in 2018, and I asked for permission to update because there's obviously a lot of information that's come out since 2016. So just one slide on development. So we use the USPSTF guidelines, which were used for preventative services task force, but they're the most commonly used means for guidelines in pain medicine. So all these pain organizations use them. So ASRA, which I'm president elective of, but American Academy of Pain Medicine, ASIP, they use it in the poly analgesic consensus guidelines. Aspen uses them, and because it offers more flexibility than, let's say grade. And we were asked to put together guidelines for pain medicine. We quickly realized that you can't include chronic and acute pain together. And we had modules of four to five people, and they came out with recommendations and then it went to committee. So kind of like a hierarchical thing.

(00:30:53):

And like I said, the reason why I think people use USPSTF guidelines rather than grade is because it allows for more flexibility. I am an anesthesiologist by trade, but I wouldn't be surprised that if you used grade guidelines you might not be able to make a grade A recommendation for using pulse oximetry, because you probably have no huge randomized trials.

(00:31:19):

And so this is basically what it is, and it is modified for pain. This is a summary slide. So these were published, like I say, the organizations that sponsored this were the American Site of Anesthesiologist, ASRA, and the American Academy of Pain Medicine. This is the full list of guidelines. It's a reference, and I'll go over some specific things.

(00:31:42):

So who can give ketamine? And the practice statement for depression had come out a few years earlier in JAMA Psychiatry. And we looked at this, and we looked at protocols from maybe 15 or 16 different hospitals. And many hospitals said only a physician can give ketamine. And we did not agree with that. So the FDA, as was noted earlier, says ketamine is an anesthetic induction agent, but the doses that are used were one to 4.5 milligram. The doses that are used to treat, well psychiatric disorders and pain are much lower. And that's not really what was being used in clinical practice.

(00:32:40):

However, we did say that a physician really needs to be available. I think one of the first lines on the FDA monograph for ketamine is that 12% of people will have emergent reactions With ketamine, things can be very bad. But that the person, because the doses are higher than for psychiatric indication should also be ACLS certified. What are the indications? Like I say, the absence of evidence is not evidence of absence. And in our guidelines we found, because there are two papers in the same edition of pain from 2009 that looked at CRPS and showed some evidence of efficacy, that the evidence was strongest for CRPS for spinal cord injury in the short term. For headache, I would update this and I would say it's pretty mixed. The studies are kind of equally divided.

(00:33:47):

Ketamine of course, is very difficult to do great studies because the reasons that were mentioned earlier with funding for IV ketamine, and because it's incredibly difficult to blind. In one of those early studies, I think only 28 out of 30 people were able to guess the group that they were in.

(00:34:15):

Contraindications. I'm just going over some of the key points. A lot of these are derived from the higher doses used for anesthesia. Ketamine can cause cardiac complications. They're pretty uncommon. It can trigger psychosis. We've had a lot of issues with current grants and things like this. Is a psychiatrist going to be immediately available if there's anything for a DOD study that we're doing?

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It can cause liver toxicity. These are dose dependent. There's a lot of controversy around intracranial pressure, intra intraocular pressure, probably not at very low doses. It may not be relevant. The American Society of Anesthesiologists does not even require labs or EKG in healthy people for most surgeries. So it's hard to justify requiring everyone to get labs and an EKG when they're getting much lower doses of ketamine. And this is really patient dependent. And we also recommended, again, this is 2018, using higher doses for chronic pain than for acute pain.

(00:35:39):

That's kind of because people thought that ketamine, because central sensitization wind up is mediated through the NMDA receptor, that if you antagonize it, you might be able to possibly reverse that, but it would require higher doses. Is there role for oral ketamine or other NMDA receptor antagonists as follow-up treatment? A lot of this is in the psychiatric indications. I would say that most trials for oral ketamine are not positive. Oral ketamine has very low bioavailability.

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Also, there are a lot of risks with oral ketamine. So I know that one big hospital in Boston, this went through legal department because people were prescribing oral ketamine and they said they recommended stopping. And I was an expert in a case with a really brilliant MD PhD who gave ketamine on the outside. These things you can find on Google. And there were huge lawsuits for this. So there's just some legal issues if you do it.

(00:36:50):

Intra nasal Ketamine has higher bioavailability. There's a little bit more data, including for headaches, probably a reasonable option. But again, it's the same legal issues. We've done a lot of studies looking at very low dose, very, very low dose ketamine, so 0.1 milligram per kilogram blinded and then giving people dextromethorphan. And you can see the sensitivities and specificities when these different studies for neuropathic pain and opioid tolerant people and for fibromyalgia were all combined. I will say as the author of these studies, that if you responded to placebo ketamine, you also responded to dextromethorphan, right? That's not surprising.

(00:37:44):

These are some oral NMDA receptor antagonists. There's a few studies for dextromethorphan. It's pretty mixed. There's two very small double blind studies in phantom limb pain that are positive, for memantine, it's negative. Magnesium is also often listed as an NMDA receptor antagonist, actually stabilizes membranes and there's a magnesium block for the ion channel. And magnesium has side effects, but the evidence seems to be positive. Again, not strong.

(00:38:18):

And carbamazepine is also listed sometimes, but probably carbamazepine is a sodium channel blocker. It's the only FDA drug that's approved for trigeminal neuralgia. Really classic neuropathic pain condition. So we said, considering the costs and the resources involved that it was reasonable to provide a trial with follow-up oral or intra nasal ketamine, or dextromethorphan in lieu of serial treatments. Of course the landscape has changed. Now there are ketamine clinics all over the place. Higher dose repeat infusions should be provided to non- responders.

(00:39:01):

And this was kind of a negotiation with the American Society of Anesthesiologists, like how often we should recommend it. And I guess they used to be called the impact. And then it transitioned to action guidelines. So the impact guidelines for pain, and I was the first author on the interventional ones. And so every treatment for pain, there has to be an endpoint. Like having six months benefit for spine surgery is not going to be a good outcome. Having one month benefit with radiofrequency ablation is not a good outcome.

(00:39:35):

And so we had decided on six weeks for multi-day infusions or four weeks. Well, is there any evidence for dose response? And I think the first lecture probably answered this for psychiatry. Of course, all medications have a dose response. It's a big red flag if you're doing studies in animals and there's no dose response. And this has been shown in many different review articles.

(00:40:04):

There are different centers in Mexico and in Germany where studies were stopped where they were using basically anesthetic doses of ketamine. And I know that there were two cases, at least at Walter Reed, we had to get separate IRB ethical approval to do that because there were risks. They were stopped in Germany because someone died. We did a meta-analysis, [inaudible 00:40:30] is the first author. It was I think the cover of July, 2019, where we looked at all of the studies for pain, the placebo

control trials for pain. And we found that higher doses, and with a receiver's operating characteristic curve that was 400, higher doses had better outcomes.

(00:40:53):

But of course these doses were given in different ways. Some people did infusions every single day of low doses for five days, inpatient infusions. There were lots of different ways that they were given. And so it's not just really the cumulative dose, but probably the peak blood levels. And I would say the rate of rise to peak blood level, which kind of correlates with some of the psycho mimetic effects.

(00:41:21):

And in the psychiatric literature, there is a correlation, I think it was something like 37% of studies, psycho mimetic effects were correlated with antidepressant effects. So we concluded there was moderate evidence to support higher doses of ketamine over long time periods, and more frequent administration for chronic pain. Probably similar to psychiatric indications. Side effects are also dose related.

(00:41:58):

And, as I mentioned for a single inpatient infusion, we had determined that multi-day infusion, six weeks. For single infusions, usually much higher doses for chronic pain, four weeks was a positive outcome. A positive outcome is basically a lot dependent on patients personalized medicine. So what constitutes a positive response to treatment? So for people who don't do pain here, those impact guidelines, and this is based on studies for both acute and chronic pain, have said 30%.

(00:42:46):

We've even done our studies for spinal pain where it's even a little bit lower, like 23, 24%, which correlates for patients saying, "Yes, I'm satisfied with this treatment, I will repeat it." And you have these different things, the minimal clinically important difference, you have them for almost everything. You have them for depression, you have them for oswestry disability, for back pain, for neck depression, neck disability index. So almost everything that you can have them, for back pain, it's between 10 and probably 13% improvement.

(00:43:25):

So you have to consider these things also for pain, per the impact guidelines. These things include function, emotional wellbeing, sleep, medication, outcome predictors. When you look at the trials, the randomized trials for ketamine, they're not great studies. They're small, they're underpowered, right? Blinding is usually not assessed. When blinding is assessed, it's not really successful. Four of the studies use 50% pain relief, which would be considered in most European medicines agency and FDA studies to be a substantial responder. One used 30% pain relief for cancer pain. Some didn't mention it, no studies designated that there was a primary endpoint either.

(00:44:16):

So we considered, like I say, 30% or greater decrease in pain or a comparable improvement in function, coupled with patient satisfaction to be a positive outcome. And again, I was saying single outpatient improvements, probably pain relief of more than three weeks. For multi-day infusions, probably six weeks. So in the pain world, it used to be people would just get rote infusion, so people would be referred for a series of three epidural steroid injections no matter what. You didn't get better with the first two, you got your third. You got 100% relief with the first one, you still got two more. Nobody does this, right? This is silly. It doesn't make any sense.

(00:45:04):

And so it's really the same thing with ketamine. It should be personalized. Chronic pain is associated with almost every type of psychiatric morbidity that there is. Even personality disorders, I won't go into this in detail, but even in the psychiatric literature, higher doses seem to work better. IV ketamine probably works better. And as I mentioned before, there is a correlation between psycho mimetic effects and antidepressant effects.

(00:45:40):

We have a $2 million study. Captain Gelfand is helping out with this study for PTSD and traumatic brain associated headaches. So along with chronic pain, these are often considered the polytrauma triad. But like I say, there's a growing rate of abuse, and there's a lot of legal issues. So in like Hong Kong, I think almost 50% in one study of people who got involved in motor vehicle collisions, ketamine was found. And there's definitely legal issues in this country as well.

(00:46:22):

This is kind of interesting. So Melzack... If people did pain, they know like Melzack and Wall, the gait control theory of pain. Well, he also said that there's more than one dimension of pain. You have a sensory discriminative dimension, which is how much does it hurt, where does it hurt, what does it feel like? But you have affective motivational, the emotional component of pain and you have cognitive evaluative components.

(00:46:50):

So the FDA has said repeatedly, there's no fundamental physiological difference between cancer pain and non-cancer pain. There's no cancer pain pathways or parts of the brain that are unique to cancer pain. The difference is these affective motivational and cognitive evaluative components. So there are many studies which look at quantitative sensory testing, right? Where you test pain thresholds, pain tolerance to all different stimuli. And after two days, you almost never see a difference in pain threshold or pain tolerance with ketamine, right?

(00:47:29):

So people aren't feeling less pain, they're not more tolerant to pain, but they feel better. They report lower pain scores. So why would this be? And my argument is that this is probably from this affective motivational component of pain. Schwartzman, who used to be up in Philadelphia, I think he still is, but he's retired, actually looked at this. You can measure these components, and found that there was a 50% greater reduction in the affective motivational than the sensory discriminative component of pain. And then in our own work, one study we found that obese patients responded better to ketamine than non-obese patients. And you could say, well big deal. But obesity is a huge risk factor for pain and obese patients, they just don't respond to anything. You can look at the surgical data, you can look at medication data.

(00:48:24):

And I said, "Well, this is probably just an aberration." And I looked at data from George Washington, and I saw something online, it wasn't peer reviewed and they found exactly the same thing. And if you look deeper into this, obese patients have very strong affective component of pain. There's a few different papers on this. So this is the last slide to wrap it up, I think Eric Schwank, my colleague is going to go over this.

(00:48:52):

We have acute pain indications, so moderate to severe postoperative pain, people who are refractory to opioids, people who are opioid tolerant. There is data from the VA that if you are in remission for substance use and you have surgery, that you're going to overdose and die. It's not amazing. So we had

recommended sickle cell anemia, people who are going to have specific issues with opioids, like obstructive sleep apnea. And we gave it a grade C evidence for ketamine. PCA as a solo analgesic, grade B for an adjunct to opioids.

(00:49:27):

And most of the data for acute pain is actually done now in emergency departments. That's not surprising. And this is a meta analysis. Three studies, 251 patients, mean difference was not statistically significant. It favored ketamine. But people who got ketamine required more dosing and they had more side effects. So in summary, the skyrocketing use of ketamine warrants the development or really the update in this case of consensus guidelines, which can improve patient care. They can inform regulatory decisions and enhance safety, because now it's the wild west.

(00:50:09):

Considering the risks and the resources of IV ketamine and the lack of strong evidence for long-term benefit, it's reasonable to try oral and NMDA receptor antagonists. Probably the best evidence is dextromethorphan. Like I say, indirect and some direct evidence now support a dose response relationship for sub anesthetic doses. Of course, higher doses are also associated with more side effects. Per the impact guidelines, this has kind of become, everyone does this now, right? 30% or greater pain relief coupled with similar improvements in other important domains like function, quality of life.

(00:50:57):

There's growing evidence for use of ketamine in acute pain, and compared to the use for anesthesia and even depression, and I used to have slides that went over the number of studies published for psychiatric indications in pain, and psychiatric indications dwarfs pain. We have a lot of work to do. So thank you very much.

Susan Winckler (00:51:17):

Thank you Dr. Cohen. We'll... In a little bit with our other panelists, but we have one more presentation to get through before we start our discussion. The framework and better understanding the broader clinical space. Walk to the stage and we'll begin his slides. Dr. Hermes, thank you for joining us, as you serve as the national director for psychopharmacology and somatic treatments from the VA's Office of Mental Health. And I think we already heard mention of some things in the VA, so take it away.

Dr. Eric Hermes (00:51:56):

Great, thank you. Appreciate it. So I don't have any financial disclosures to make. I am a federal employee, and I was looking forward to coming down here and sort of commiserating with other federal employees in the FDA, but clearly we're not in a federal institution here. It's beautiful up here.

(00:52:19):

I think if VA and the FDA were kids in high school, they'd certainly be friends, but I think we could all agree that they wouldn't be sitting at the cool kids table at the lunch table. So I'll start with that. Great. Our last talk was sort of focused on ketamine for pain. I'm going to talk about VA's sort of national rollout of ketamine and S ketamine. That is primarily focused on the treatment of treatment resistant depression and acute suicidality. So I'm going to sort of focus in that realm.

(00:52:58):

I'm also going to use the term somatic treatments quite a bit. And so we tend to lump ketamine as ketamine with other complex interventions for mental health disorders, such as ECT and TMS. And so I'll show some data, some comparison data on that for the VA as well.

(00:53:17):

Great. So this is sort of my favorite slide here because it really shows the extent of our system and we're really proud of this. So the VA has over 1300 individual clinics across the country. These are divided into 139 individual facilities or systems. And those facilities of systems take care of over nine million veterans across the system. So we're a big program here, and we're really proud of obviously helping veterans.

(00:53:48):

The other thing I want to say here is just kind of how the system works. And Marta alluded to this with the FDA. So the FDA makes hot policy, the VA central office, which is just down the road here, makes policy and creates guidance for how care is done. But of course care is done by individual providers at individual facilities making decisions with patients on the care that's provided. So the responsibility for care here is at the facility. And you can kind of see that in my job, my main job is to sort of develop programs and policy for VA central office, but I also have a ketamine clinic up at VA Connecticut where there I'm responsible for actually the care of patients.

(00:54:30):

And so this has sort of broad implications on how our guidance interacts with what providers and patients actually do in terms of care. And so I like to make that distinction. Great. And so this is an example of some of the guidance here. And so this is a guidance developed by the Office of Pharmacy Benefits Management. We have Dr. Fran Cunningham come and talk later about some of the programs they do. And so this is national protocol guidance for S ketamine and IV ketamine. So this is sort of produced and approved by the National Formulary Committee for VA. And within this guidance it talks about inclusion criteria, dosing, dose scheduling, safety precautions, all the things.

(00:55:23):

And so this gets pushed out and individual programs review that and create their own SOPs at the facility level. Great. Yeah. So this is another example of VA national guidelines. So these are the VA DOD clinical practice guidelines for the treatment of major depressive disorder. So these were sort of recently updated. Ketamine and S ketamine appear in these guidelines for the treatment of treatment resistant depression.

(00:55:56):

And so also in these guidelines are other somatic treatments for treatment resistant depression, ECT, for severe depression and treatment resistant depression and RTMS as well for treatment resistant depression. So another example of the guidelines that are produced centrally that sort of guide what facilities and providers do.

(00:56:19):

Great. So other than producing guidelines, what has VA done to sort of roll out programs across the system to disseminate ketamine and S ketamine across our large system? So one of the big things we've done is we have a really strong community of practice for somatic treatment providers. So we have a group of over 600 providers across the system. We have an email group, and then we have monthly meetings where we'll talk about clinical cases and have some CME work as well. Those individual meetings, we will probably get 200 providers on each of those. So that's really a strong thing we do.

(00:56:59):

We also have a special interest group of ketamine S, ketamine providers that have particular expertise in the delivery of these two interventions. And I'll talk in a sec about some of the things that this group has done here. In the middle there you see, we have a national training program, training providers and

provider teams in the delivery of ketamine, S ketamine. And so that gets into the clinical delivery as well as sort of the administrative things, personnel, facilities restructuring, stuff like that.

(00:57:34):

And so those other issues tend to be big barriers to the dissemination of these programs. And so we have a training program that helps providers through that. We do have an information hub for policy and data and stuff like that. And we do some technical support over email and meetings, as well as we do some program evaluation. But the big thing to note here is kind of the things that are missing. And so I might characterize this dissemination strategy as kind of light touch, primarily because what you don't see up here is specialized funding.

(00:58:11):

And so these programs have been rolled out without specialized central funding. And so it is up to individual facility leaderships and mental health leadership at individual facilities to decide if it's worth starting a program or not. And so that's an important comment to make. Great. And so this is data on VA facilities. And so the counts here are VA facilities. Again, we have 139 total facilities here. Over on the right you can see the ketamines. We have IV ketamine on the left in the red box and S ketamine on the right. In the blue bars, these are facilities that have a program at the facility. And then the orange bars are VA facilities that refer to community care for the delivery. And so as you can see over time, this is FY 15 to 22, you can see over time these are increasing.

(00:59:07):

Interesting comparison here is over on the left, that's ECT. So obviously we have a lot more facilities that provide ECT, but you can see that trend has actually gone down a little bit over time. And this is obviously happening in the VA, but happening outside the VA. ECT is used a little bit less, and there's a lot of sort of hypotheses floating out there that the two trends might be related. So we might see a trade-off of ketamine for ECT and these other interventions.

(00:59:35):

Certainly in my ketamine clinic, one of the important things we do clinically is help patients through the decision making process on, what is the best treatment for your treatment resistant depression? And I think we can sort of see this in the data. So this is data on veteran utilization. So these are veteran counts, and you can see ketamine and S ketamine over here on the bottom. As you can see over time, they're increasing. The important comparator here is TMS, transcranial magnetic stimulation. You can see as of right now, we're treating about half as many patients with ketamine or esketamine, or excuse me, we are treating about as many patients with ketamine and esketamine as we are for TMS, and so that's an interesting trend. I had an additional thought here, but it'll probably come to me here in the end.

(01:00:34):

Great. So this is actually data from currently as of June of this year. This is the distribution of ketamine and esketamine facilities across our system, and so we have currently 39 facilities that provide either one of these interventions at the facility. We have 13 facilities that provide both. What I like to point out here is the empty space, and so you can see some empty space in the upper Midwest and in the west, and so it has been very difficult to implement complex mental health interventions in this area. Obviously we have the VA's Office of Rural Health is specifically tasked for managing this type of issue, and this is not a VA issue alone. It is difficult to provide complex care in these areas in general. I will say we are currently working with facilities in Minnesota and South Dakota and Wyoming to start programs. Actually, I think just a couple of weeks ago we had some veterans treated in Spokane, so there probably should be a circle there. So that's some of the issues. Great.

(01:01:52):

So now I want to turn to questions of who in the VA we're actually treating and what those outcomes look like. And so this is a publication that came out about a year ago from our ketamine special interest group, and so these are the providers in our system that have particular expertise. This is a study of veterans who entered treatment with IV ketamine in 2020, and so one thing to point out early on is just some data issues here. And so this group back in 2020, actually we have a difficult problem separating IV ketamine for mental health indications and IV ketamine for other indications like corneal transplant or whatever, chronic pain. So that group actually had to dive into the medical record and figure out who was getting ketamine for what. And so thankfully I think in the last year we solved that problem and are able to use data methods to understand who's getting what going forward in time, and so that's been I think a big win for us.

(01:02:59):

So in this publication in 2020, we had 215 patients treated with IV ketamine for mental health indications, right? So some important things to note here, this was primarily for treatment resistant depression, and we can see here that this was a group with a lot of severe treatment resistant depression. So they had a mean of 39 mental health visits in the last six months. 22% had inpatient stay in the prior six months prior to going to treatment. 13% had TMS in the past and 18% had ECT in the past. So this is really a highly treatment resistant population that was treated in 2020, all right?

(01:03:45):

Second thing to note here is that it was also a population with high comorbidity, and I've circled there the primary comorbidity, which is PTSD, and so we had 70% of those veterans with a PTSD diagnosis. And certainly clinically what I see in our clinic is that really the comorbidity between TRD and PTSD is really pretty strong and probably predicts outcomes as well, meaning that it seems like patients with PTSD may not do as well. And so obviously this is a huge area of research going forward and it will take time to figure this out. Great.

(01:04:31):

So last thing I want to talk about is the mean infusion. So this group got a mean of 18 infusions over their period of treatment. That works out, depending on the protocol that you used, probably about a mean of three months of treatment, so that was interesting. 50% of these patients improved and a little over a quarter of the patients responded. So that's really pretty good for a highly treatment resistant population. Great, great.

(01:05:03):

So what are some findings and issues going forward? Overall, we've had increasing availability and utilization of these two interventions for treatment resistant depression across the system. This is really pretty good because these interventions are complex. They're difficult to develop. These clinics, they require a lot of care coordination between work streams at the facility and also they require people to actually come in and get physically treated at a facility, right? And so this is in a day and age where we're increasingly using virtual care for treatment, especially mental health disorders, right?

(01:05:46):

We do have some challenges going forward. Many challenges, I've highlighted two here. One is the issue of our dissemination and it's where it's taken place, right? And so what we've seen is that rich facilities really have gotten richer and the bulk of our expansion has been in facilities that already have some other somatic treatment program, ECT, TMS, something else, right? And so it's been very difficult to get

programs into facilities that don't have anything, and so that's really been something that we've started to focus our work on.

(01:06:26):

Secondly is this persistent undertreatment of veterans with treatment resistant depression, and so we have data showing that we're really maybe only treating 2% of patients who may have treatment-resistant depression. Now remember, TRD isn't a diagnosis, you can't code it, but we have some sort of data ways to try to figure out who might have treatment-resistant depression, and when we use that we can see that we're not getting a major percentage of those individuals in for treatment. So that's a way forward. Great.

(01:07:02):

I want to talk about a couple next steps here. So first is to improve our data capture and the standardization of delivery. I talked about one way we're doing that, which is now being able to finally figure out who's getting IV ketamine for a mental health indication and who's not, right? We also want to standardize the delivery of care. We'll do that through note template so we can really know what patients are getting the treatment, at what dose and over what period of time, and so that'll be important going forward.

(01:07:37):

Second is to explore this under the utilization of treatment for patients with TRD in general, and so we really want to understand what's going on and then try to mitigate that issue. Lastly, we want to look forward to the future, and so there may be new sematic treatments on the horizon for treatment resistant depression. So excited about that. Obviously nothing's been approved yet and obviously I'm referring to psychedelic medicine here. And so right now we have nine facilities who do some version of pairing psychotherapy with their ketamine delivery, right? We also have a lot of VA facilities engaged in research on psychedelics in some form or another. So we want to use the experience from these facilities to help in our potential future rollout of these new interventions for TRD. So that's what I had to say. I guess we'll go to panel now.

Susan Winckler (01:08:40):

We will.

Dr. Eric Hermes (01:08:41):

Thank you.

Susan Winckler (01:08:48):

Thanks Dr. [inaudible 01:08:44] All right, so it's time for the cool kids club. Let's have our panelists come on up, and you can adjust the chairs. It doesn't need to be the lineup that it looks like. Adjust it to become comfortable, and as you do that, I will introduce you and we'll put that next slide up. So [inaudible 01:09:13] second half of this [inaudible 01:09:16] we are going to have a conversation. And in fact, once you're all settled, I'll climb up here. But joining us for the conversation, we have Dr. Sandhya Prashad, who's founder and president of the American Society of Ketamine physicians, psychotherapist and practitioners. Thank you for joining us. Then next to Dr. Prashad is Dr. Brittany O'Brian, who is associate professor in the Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine, and then in the middle we have Dr. Mikhail Kogan, Medical Director of the George Washington University Center for Integrative Medicine.

(01:09:54):

And then we should have one virtual panelist. Is Dr. Jessica Poole available and can we show her on the video? Dr. Poole is director of State government Affairs for the Pennsylvania Association of Nurse Anesthetists. So while we pull that up and switch over, I want to turn first, there we go, to our new voices. Do you have any questions or things that you want to call out for Dr. Hermes or Dr. Cohen? Any questions or things that you want to underscore of what you heard? Go ahead, Dr. O'Brian. I was going to call on you anyway, so it works great.

Dr. Brittany O'Brian (01:10:34):

Okay. Thank you. And thank you so much Dr. Kogan and Dr. Hermes for your presentations. They're really wonderful. So first off, I just wanted to start by saying that we've done a lot of research and we're doing our best to really look to and apply the evidence base, but we still have a really long way to go. And there seemed to be a lot of unanswered questions and a lot of gaps that we're going to need to do more research in order to better address. So one of those questions for me is dose and the dose response curve that Dr. Cohen brought up, and the other one relates to maintenance treatment, the phase of treatment that follows the acute course.

(01:11:24):

So in terms of dose, and Dr. [inaudible 01:11:27] brought up a survey that they conducted back in 2017, there was a follow-up survey to that in 2020, and it was a nationally representative survey and it was an anonymous survey completed by IV clinic providers in the community. And I stole one of Dr. [inaudible 01:11:45] co-authors for that. And what we learned was that the majority of IV ketamine providers were initiating an acute course of treatment at 0.5 milligrams per kilogram that aligns with and follows the evidence base. That was good news. What we also learned is that the vast majority of providers were titrating up from 0.5 throughout the acute course of treatment, and this was really in order to optimize patient response during the acute course.

(01:12:17):

So unfortunately, at least as far as I'm aware, we do not have any trials that are prospectively testing and evaluating repeated doses that are titrating above 0.5, and this is what a substantial proportion of folks in the community are doing. And these are folks who are really trying to follow the evidence base, but also balance optimizing and personalizing their care for their patients. And while we've done and are continuing to do some retrospective studies looking at the relationship between dose and patient outcomes, without a planned controlled randomized trial design, we're really not answering that question as best that we can. And therefore there's going to likely remain a pretty large gap between what the clinical trial evidence protocols are and what's being rolled out at places like VA and the actual real world practice of ketamine.

Susan Winckler (01:13:20):

Which Dr. O'Brian, I'm struck, as you were speaking to the evolving evidence landscape, it's clear I think when we heard in each of the presentations that we need to do more to help that evolve. So one more thought and then I want to make sure that we turn to Dr. Prashad.

Dr. Brittany O'Brian (01:13:35):

Yes, of course. I'll make this brief. This is just in regards to the maintenance phase of treatment, and I was really glad that Dr. Hermes, you brought up where are we going now in the integration of psychedelic assisted therapy in VAs. I was actually at a ketamine assisted psychotherapy training recently, and I met a therapist from VA and I was just thrilled to learn from her that she was there because her VA was formally integrating psychotherapy as part of their ketamine and esketamine

service. And so I'm just really hopeful that there will be more studies to evaluate the benefit of potentially integrating psychotherapy or including psychotherapy in ketamine treatment, not only to potentially enhance the effects in the acute course, but also extend the benefits, extend the duration of effects so that we may not need as much medicine.

(01:14:23):

And just to wrap up, I just think it's really important we focus on the maintenance phase. Depression is not something like an infection we clear with an antibiotic. It comes back, we need maintenance treatment strategies. And so exploring alternatives like the oral and MDA antagonist that Dr. Cohen mentioned, psychotherapy, TMS, maybe esketamine, I think will be really valuable. Yeah.

Susan Winckler (01:14:44):

So you set us off great in setting a great model in the reaction and then contributing, so let's continue that conversation. Thank you Dr. O'Brian. Jessica Poole, we can see you on screen. So Dr. Poole, do you want to ask any questions or reflect in a manner similar to the way that Dr. O'Brian just did?

Dr. Jessica Poole (01:15:06):

Sure. Thank you for the opportunity to be here and the invitation, and listening to Dr. Cohen and Dr. Hermes, I think that a lot of us were doing work that dovetailed very nicely off of one another. I agree with the comments that have been made that it certainly seems when I'm reflecting on the work that we did in 2017 to 2020 surrounding guidelines was subbing aesthetic dosing of ketamine, that we're definitely at a point where we may need to be revisiting the evidence and updating some of the guidelines that currently exist, but that essentially was my role.

(01:15:45):

I was fortunate to be on a task force at the national level with the American Association of Nursing Anesthesiology and also at the Pennsylvania state level with our Department of Health. We really started to have conversations surrounding this in the 2016, 2017 timeframe, and we wanted to just be able to support positive patient outcomes and enhance patient safety as Dr. Cohen stressed. And I agree that although side effects for subbing anesthetic and low dose ketamine is rare, it still happens. And so for us at the state level, we realized within Pennsylvania that we had a need for alternative treatment passed for our patients, but that we really didn't have a foundation and we didn't have any language within our regulations or statute that would help guide those decision makings. And so the Pennsylvania Department of Health originated some guidelines to help providers develop these types of practices.

(01:16:51):

We wanted to focus mostly on having the appropriate multidisciplinary members available to make sure that we were addressing any side effects that could come up and also address prescribing and diagnosis, and we also wanted to make sure that we were taking into account appropriate patient selection. I think that this was mentioned before that some of our patients are certainly candidates to have these alternative treatment paths for psychiatric disorders, chronic pain management in office or clinic-based settings, but based off of comorbidities and other co-founding factors. Some require a higher level of care, so we really wanted to develop guidelines around safe practices.

(01:17:37):

I think that the guidelines that we were able to establish in Pennsylvania really served as a foundation for a lot of practitioners, anesthesia providers, certified registered nurse anesthetists that were really able to utilize the data and increase access, especially in parts of our state that are underserved and those patient populations needed the healthcare services the most. But I would agree that what we

seem to have done in 2020 and then listening to everyone's presentations today that we're probably at a point this space is evolving and it's something that we should consider. So thank you.

Susan Winckler (01:18:19):

Thanks, Jessica, and as I think we told you in the prep call, feel free to just jump in because I can see you and hopefully you can see us, but just pretend you're sitting here on the stage. Dr. Prashad, do you want to chime in here? Join the conversation please.

Dr. Sandhya Prashad (01:18:35):

Thank you so much for inviting me. I think it's so important with where we are in the space right now that we are meeting in this way. Something that really I think stood out to me in Dr. Hermes's talk was just a persistent undertreatment of TRD. Despite the fact that we have some of these treatments, we're still not necessarily using them, and a lot of patients still do not really achieve remission. So we've had data for a very long time, large scale data that showed with just using oral antidepressants, only about a third of patients will achieve remission. And so like Dr. O'Brian mentioned, there's still a lot of work to do and that we should see these as chronic conditions.

(01:19:15):

For the most part, many patients, the treatments are still just treatments, not cures, and so that long-term ongoing treatment is needed. But part of that under utilization probably has to do also with the lack of consensus, the lack of guidelines, the lack of really having a clear picture of what best practices are, and then that leads to not having payers to pay for treatment. And without that, that continues to drive this under utilization of treatment. So I echo a lot of what everybody else has said, but I just wanted to add that piece.

Susan Winckler (01:19:49):

Yeah. Well, and that ties in one of the questions that had come in on the chat and beforehand is this question of why. What's been the draw to use ketamine? And I think you've just mentioned, right, it's in components in treatment resistant depression where we don't have treatments. What are other reasons? Again, you touched on some of these, but let's just underscore, let's answer that question of why.

Dr. Sandhya Prashad (01:20:13):

Yeah, so-

Susan Winckler (01:20:14):

And Dr. Kogan, if you want to jump in after Dr. Prashad.

Dr. Sandhya Prashad (01:20:17):

I mean for me, in my practice, so I primarily focus on treatment resistant depression. I've been in private practice since 2011, but you get a lot of patients who either don't get better, we don't have great treatments for patients who continue to struggle with suicidality, more complex patients. Those are really big areas where we need more treatments.

Susan Winckler (01:20:38):

Dr. Kogan?

Dr. Mikhail Kogan (01:20:39):

Thank you for inviting me. So our practice is just a couple of blocks, literally. I walked from the office. So we're at an tertiary center. We see about a million patients a year, and then only most complex patients refer to us an integrative medicine center. And we have seen ketamine due to the need, basically, due to the failure of a standard of care being used for probably less of a half a dozen conditions, and the pain and depression already been described quite in detail. I will add to this, any autonomic instability conditions, whether it's a long COVID, whether it's a chronic Lyme, whether it's things related to POTS and Parkinson and other conditions, there seems to be some signal of benefit, and I think I'm going to swing it into a very different direction altogether.

(01:21:31):

We only used the word psychedelic once. You used it, and I think that's not right. I think we have to be open. Yes, it's scary to say word psychedelic and scientific meeting, but we have to. The ketamine is a classic psychedelic, the dissociation is very dose dependent. It's best with IV or IM. It's the weakest with oral and nasal, but you can get there if the dose is high enough. And I think what we've observed after thousands of treatments is that really the psychedelic effect is where the magic happens here and why and how, very non-linear, very unpredictable, not clear what happens, but it's very typical. We would see a patient come out of the trip, that's what it's called, and they will have aha. They'll wake up from the short experience and they say, I see it differently now. And if you have a very gifted therapist in there, that therapist will flush it out to the point where you know where you're going next with a therapeutic journey. And that's where I've seen stuff that if I'm ... and I have fellows and residents writing up reports and for example, we're writing a long COVID report right now because we've seen about 30% cure from a couple of treatments. Now is that going to translate to real evidence? Who knows, right? I mean, that's when we really need doctors like O'Brian and Cohen to do this because what happens off label in a clinical practice, but that leads me to a question. Are we going to be actually studying psychedelic experiences just like Hopkins did with psilocybin? Where are we with that?

Dr. Steven Cohen (01:23:16):

I would agree with you. I think I probably said twice because you don't have this information for pain, that the psychiatric benefit seems to correlate with psycho-mimetic effects. And that's probably why high doses of IV ketamine works better, right? Because it's not just the peak, but it's the rate of rise to the peak blood level. I thought of something, I'm sorry for thinking out loud, but this is-

Dr. Mikhail Kogan (01:23:51):

Oh, that's what we're doing. Please.

Dr. Steven Cohen (01:23:53):

But it's really interesting, and I think there's a lot of psychiatrists in the room here, but for almost all psychiatric treatments like SNRIs and tricyclic antidepressants and probably ECT, which might show some kind of signal, and even RTMS for pain, the psychiatric doses are higher, right? They're always higher and it takes longer. So you can look at the FDA indication for duloxetine. It says there's just no benefit for going over 60 milligrams and it's 60 to 120 milligrams, right? So for almost all psychiatric treatments, you need higher doses, but for ketamine, people use higher doses for chronic pain than for all the psychiatric indications.

(01:24:46):

And this is interesting, but I remember chairing a session on this at, I think it might've been the American Academy of Pain Medicine. And there was a guy who is speaking, and he was at Walter Reed, and he's based here, and I know I work at Walter Reed and everybody got 500 milligrams and they got it as fast as they could. And somebody asked a question, how do you give it? His name is Aubrey, and he says, we give 500 milligrams because that's what comes in a vial. If 1,000 milligrams came in a vial, we'd give 1,000 milligrams.

Susan Winckler (01:25:25):

So perhaps not an art there?

Dr. Steven Cohen (01:25:27):

Yeah, but this is like what you would bring up with a dose response. I mean, it seems counterintuitive that ... Either people with psychiatric indications should be getting higher doses or people with pain, we might be exceeding the healing effect for doses unless ketamine happens to be an outlier. But like I say, every other treatment and everything that works for depression seems to work for pain. NICE says that antidepressants are the most effective treatments in the world. They don't recommend to anything else. This is why we have to figure out, we're either underdosing for psychiatric or maybe we're overdosing people for pain. And part of it is also who's giving it, right, because who's in pain clinics? Well, anesthesiologists and they're giving people thousands of milligrams if you're getting ketamine infusion, right? Because the induction dose is up to 4.5 milligrams per kilogram. So there's no problem just bolusing someone 200, but a psychiatrist is not going to do that where we are, and I work very closely with psychiatry. You can't have an IV on the psychiatric ward.

Susan Winckler (01:26:57):

Yeah. Well, so Dr. Hermes, I want to go to you and then I want to have this conversation about setting and where ketamine is administered and how does that change our clinical considerations and approach and experience.

Dr. Eric Hermes (01:27:09):

Yeah, well, thanks. So what I heard was dose, maintenance treatment and psychedelics, and so I think I can talk to all three real quick. One is the dose. So in VA, our guidelines are limited to 0.5 mgs per kg. And my feeling is that we'd have to look at the data, but my thought is that in giving IV ketamine for mental health indications in VA, most facilities are sticking to that 0.5 mgs per kg, so that's dose. The other thing is maintenance treatment. I think that is the single most important clinical issue. And so we have residents in our clinic, and the one thing I tell them that ketamine, esketamine clinics are boring because you give the drug and then you watch people sleep or listen to their radio for two hours.

(01:27:59):

So the real key to the clinic is understanding who should come in to get treatment, and then once you've gone through an induction period, who should maintain treatment and then who's good enough to leave, right? And so that is usually a discussion of the risks and benefits of ketamine and alternative treatments for TRD, which are difficult to have, but we don't have a lot of data informed discussion because we don't have a lot of data on that. So I think that's where we really need a lot of data.

(01:28:38):

And then lastly, psychedelics. I will just mention that VA is moving forward in sponsoring psychedelic research. So later last year, VA came out with an RFA for research projects focused on psychedelic

medicine, so that's an area we're pushing into. We've also developed a work group to think about the planning for clinical implementation of psychedelic medicine if these are approved in the future. So we're working toward that, looking to the horizon for that.

Susan Winckler (01:29:14):

You did tick off each of the things. Dr. Prashad.

Dr. Sandhya Prashad (01:29:17):

Can I just add one more thing? You mentioned the word art, and I think there's some importance in that. What we are calling depression is probably many different things that people get to that point from very different places. And I think there are actually several studies that show that more isn't always better, that it really is this art. There's a lot of U-shaped dose response curves that show that there is a sweet spot, patients that have anxiety along with their depression, that may play a role, and they may not necessarily tolerate higher doses, and they may do worse with higher doses. So there really is this art. Jerry, I know you kept wanting to ... Okay, I didn't know if you had something to say. Okay. Yeah, but there's some published data that shows that more isn't always better. So I think it's, again, why it's so hard to create these sort of guidelines and specific protocols because it is so nuanced. That's what I wanted to add.

Susan Winckler (01:30:11):

And Dr. Senacore, you're welcome to come and stay. I just don't have a seat and a mic for you and they can't hear you if we do the audience piece, but you can continue to channel or just come on up. So let's talk about settings. So we got a description of, I think I got a pretty good visual what happens in the VA when we have the administration, you just did the, it's boring, but let's talk about other settings. What are other settings where ketamine is used? And I'm happy to, Dr. O'Brien and then Dr. Kogan. And then again Dr. Poole, just jump on in.

Dr. Mikhail Kogan (01:30:54):

Yeah, sure.

Susan Winckler (01:30:56):

Yeah.

Dr. Mikhail Kogan (01:30:56):

So we have actually two ways that this is done. And actually the reason it's very practical, it's a cost. So if you're not doing a ketamine, if you're doing inject, and not to say anything bad about the drug, but in our experience, 90% of patients will not peak nasal because it just doesn't get you to psychedelic at the doses that are prescribed as much. I mean, you can probably get there, but so my bias is more that we get sent patients who have failed as ketamine in the standard psychiatric clinics, and so we do more of an injectable. And so we have two models. So we have an actual coach, it's a yoga therapist with about 2000 hours of psychedelic training or psychedelic sitting we call it. So it's their coach really. So it's not really a therapist by training officially, but that's more for patients who really wanted to have repetitive sessions and they're really coming specifically for just the being a mirror and it's not necessarily a deep psychiatric need. So this would be more of a chronic pain. This could be more of, I mentioned some other non-pain related conditions.

(01:32:03):

And then there's also a psychotherapist who's trained in psychedelic assisted therapy or KAP in this case, is a ketamine assisted therapy. And so she would be doing an actual counseling with the patients when they started coming out of the deep state. So we will never think that ketamine administered without that would have any benefit whatsoever in my opinion. There may be some superficial benefit of doing this, but really the meat of benefit is in the counseling. It's not in an actual drug. The drug induces the state, the state of openness, the state of potential information sinking in and doing something there. Of course, there's dissociative component I mentioned, and it's profound, but we don't really know the research behind what happened. So if you want to follow the clear evidence, you have to use a lot of counseling in there.

(01:32:56):

And so this would be the psychologist or social worker in our case would really be there as a therapist. And then often the sessions are followed by multiple after sessions. So the effect may be acute, it may last, as Dr. Cohen mentioned, just minutes. But then you have profound shift that occurs for the weeks after, especially if the dose was good enough or deep enough. And then often that counseling has to continue. And often sometimes we even do it daily for a couple of days in a row after because there's still this aftermath that continues and there's a very kind of fertile ground to do this kind of counseling to continue shift. We had one patient said that after a trip said, this is like 10 years of psychotherapy combined in two hours, literally. And we hear this repetitively, that patients get the depth of insight in there, but it has to be guided. If it's not guided, I think effect is a fractionally as good. There probably is some benefit, but you can dramatically enhance it by having a therapist.

Susan Winckler (01:33:58):

So that's a description of your approach in the broader piece, but in seeing some of the discussion there, very different models. Yeah, go ahead.

Dr. Brittany O'Brian (01:34:09):

So full disclosure, I'm a psychologist and a psychotherapist, and so my biases are probably going to come through here. And so I really appreciate you being such a proponent and champion, sorry, of the psychedelic psychotherapy movement. But what I also really want to point out is that the evidence speaks for itself. There are plenty of trials where there is no psychotherapy component where patients get better. And I've done retrospective studies where there may be actually psychotherapy going on in addition to or in conjunction with the ketamine treatment that patients are receiving, but it's not, sorry, formally integrated as part of the treatment protocol.

(01:34:52):

So there was a wonderful presentation actually at ASKP III maybe last conference, where we had a ketamine clinic provider who did a study and an analysis of his own data where he compared the patients that had ketamine alone with the patients that had ketamine plus psychotherapy. And the outcomes were identical, which I think pissed off a lot of people. We all have our opinions-

Susan Winckler (01:35:19):

At least they looked at it cynically.

Dr. Brittany O'Brian (01:35:20):

And we want a winner. But what I think that we need to keep reminding ourselves that there isn't a one size fit all here, different patients need different things. I believe that having psychotherapy as part of the process adds an enormous benefit, if not preventive value, because these medicines do produce psychedelic effects. They're not always fun and pleasant, they're very hard. And so having some psychotherapy support around that and to work through that can take a bad experience and produce a good outcome.

(01:35:54):

And other times the psychedelic are really powerful and meaningful and they benefit from having some psychotherapy support around it to better process it and integrate it for that person to then, again, sustain the benefits of the treatment. So last thing I'll say is just there are different settings. I think we're going to have to get comfortable that there will be different settings, and we just want to better understand what we call the set of each patient is going into the treatment and what kind of setting they need to best optimize their experience and outcomes.

Dr. Mikhail Kogan (01:36:34):

I think we need some kind of a data collection that is not controlled, necessarily. Because in this kind of, you see how we have very different voices and it's actually because of the bias of referral. I'm strongly believing this. The types of patients we're getting, they already failed in standard processes, and so they end up in our clinic as a lost resort. I think if we try to capture the data by cases, the N of one is a powerful stories. We just think that this is situation where you have to have controlled trial. Of course you have to have controlled trial, but we missing tremendous amount of data that can be gathered. And I think if we have a system for that, and maybe there will be some infrastructure to do that, I think we can capture this sort of degree and breadth of experience as clinicians are seeing in real practices.

Dr. Sandhya Prashad (01:37:25):

I agree. I mean, I feel like I'm saying the same thing with regards to the nuance, but I think to echo what Brittany said, and I think it's very important, we do psychotherapy in our clinic as well, but for some patients, they're not necessarily at a place where psychotherapy is something that they'll be able to engage in right in that moment and ketamine can be very useful in just managing acute suicidality. And we should think of it as a life-saving treatment in that regard. So I wanted to make sure that point didn't get missed today. I feel very passionate about that.

Susan Winckler (01:37:57):

Do either of you want to jump in? I'd love to hear more about set and setting as it relates to pain, if we have any conversation about that.

Dr. Steven Cohen (01:38:05):

Sure, I can do that.

Susan Winckler (01:38:09):

Well, and I used set and setting, sorry. Route of administration and how you use it.

Dr. Steven Cohen (01:38:15):

So like I say, people who live in pain clinics are anesthesiologists. We like IV medication, it seems to work better. And like I said, we got about 16 protocols from all over the country in different areas. So in pain

clinics, much higher doses are given, often hundreds of milligrams. There's anesthesiologists. The way it works at Johns Hopkins is there could be two patients, one nurse at Walter Reed, there's one nurse, one patient. I can tell you how everything it is. Both of those venues used to have also inpatient infusions, which are much lower, right? Because you don't have a doctor sitting by the bedside.

(01:39:08):

Anyone who thinks that you can't get tolerant to ketamine doesn't use ketamine. It's not a G protein coupled receptor like opioids. But there are many different ways to get tolerant. You can have behavioral tolerance, you can have changes in sensitization, internalization of receptor. There's lots of different ways. And so having a relatively low dose at 20 milligrams when we have sickle cell patients from Baltimore coming in and they're 23 years old, and ketamine used to work really well, and then it doesn't work well for very brittle patients. And so I think there should be some flexibility. I wanted to say one other thing because at Johns Hopkins, we stopped actually doing ketamine infusions in the pain clinic. So there's two issues. I'm not going to get into money, but there's no CPT codes for ketamine.

(01:40:12):

It was a service. Nobody cares. People make very little money compared to our peers. But what ended up happening is there were so many regulatory issues that kind of confronted so that when we were doing these ketamine infusions, the fellows couldn't do other things. It basically took about three hours of their time every time a dose, we stopped doing them. But of course there were patients that needed to still come in for the infusions and there were no restrictions. There were no restrictions on giving sedation or anesthesia during procedures, so we started to bypass it.

(01:40:59):

People would come in. If they needed ketamine, we would do basically as an anesthetic. And we started to do this. This is, I think, kind of interesting, and I think it was published just like as a brief report in JAMA Dermatology, but there are some patients, dermatology, I would say mistakenly calls them neuropathic itch. The worst thing that you can have. I mean, they rip their faces out itching. It's really not neuropathic itch. Probably the correct term is nosoplastic itch. So in 2016, the ISP they classified, they developed, or they categorized a new type of pain that's associated with no biomarkers. There's no pathology. Like fibromyalgia is classic irritable bowel syndrome, and they call it nosoplastic pain.

(01:41:54):

So dermatologists are not pain doctors, they still call it neuropathic itch, even though in some cases there's just no pathology, they itch. And so we started to use ketamine because it's from central sensitization, we think. And we would've been able to get more answers, but because we couldn't do infusions for these people, we had to do nerve blocks and then nobody could complain. So we took the most itchy area, and these people were coming in from all over the world and their lives were just destroyed. And then we did kind of a field block, but the treatment really was ketamine, and it changed a lot of these people's lives. But of course, it's how do you know what's really working when you're doing a field block? Although these people had itch all over their body, and this is kind of one of the things in the job of dermatology.

Dr. Mikhail Kogan (01:42:53):

You're hearing continuous trend of signal. No matter where we look, if it's a condition that has a complex neurologic underpinnings, there seems to be a benefit, and we just don't know exactly what's happening. Ido want to add, so for chronic pain, what we started doing, and we're seeing good success with this mostly just cost and basically pragmatic, doing small groups, IM shots, usually two shots about 20, 30 minutes apart. And the sitter would just be there to observe. And if something comes up, sitter

can talk, but you can do several patients. We have a physician on staff, but the nurse can administer the shots, and it cuts cost dramatically. It gets access increased, and it is potentially even a billable model. Theoretically, if you can figure out how, if the physician is on staff. Of course probably institutions are going to be quite resistant to the billing until FDA approves this. But nonetheless, we're already doing this just because of the demand.

Susan Winckler (01:43:53):

None of you have talked about a home setting administration, or I happen to see on a trip last week, the clinic, it was actually in a strip mall, which was, it was just an outpost of ketamine administration. Does anybody have any experience in what is the environment in those situations? And if you don't, that's okay.

Dr. Mikhail Kogan (01:44:25):

Yeah, well, we've done it. We've done it. It would be the best, but it's obviously the most expensive. You have to transport the practitioner, multiple, two practitioners potentially to the patient's house. There's CPT code for home visit for physician. You can bill that, but then how do you bill for other practitioners like a sitter to be in there? Most sophisticated, most complicated, but probably from patient's perspective, potentially really good because they're in their own safe environment. But you can emulate the safety of environment in the clinic too.

Susan Winckler (01:44:57):

So that would be accompanied by a practitioner for that administration?

Dr. Brittany O'Brian (01:45:02):

Yeah, I mean, thank you for starting there. I think it's a really controversial and hot and problematic topic right now. It's the safety issue, right? Doing this unsupervised at home, you're increasing the risk. And as safe as ketamine is, and as long as it's been around and for the many ways in which we've been using it, it's still a medicine that requires some supervision. And doing that at home makes that more complicated. And so we have a lot of work to figure out how we're going to be able to do this safely and effectively in the home if that's really where it's best for the patient to be doing it.

Dr. Sandhya Prashad (01:45:43):

Yeah, I don't use it personally in my patients for home use. Since what happened with Matthew Perry, there's been a lot of pressure. I say us, American Society Academy physicians, to put out some sort of guidelines, thoughts on it. And our thoughts on, we actually just released this has to do with that there probably very few situations in which it's appropriate, and it might be, but it's really in the context of a really strong patient provider relationship and very strong expectations. Because one of the problems I think they've seen in studies when they look at it is if you prescribe it and you tell patients how to take it, they don't take it the way you tell them to take it a lot of times. If you're given several doses, it becomes this, I'm having a bad day and taking it, which is very different than depression, suicidality, maintenance treatment. And that's where that kind of abuse and stuff becomes problematic.

Dr. Brittany O'Brian (01:46:42):

And I mean from people I know in the community that do prescribe or allow for, or I don't want to say advocate, but believe there's a place at the table for at-home use, almost always, it's only after it's been

done in office and we've established safety and have some idea. Every experience of ketamine is different, but being able to have some data in which to make a good clinical decision.

Dr. Sandhya Prashad (01:47:16):

And that's those mentioned in our guidelines too, because you'll have patients that get an incredibly small amount of ketamine, and it's a very big response with a big jump in blood pressure. And then you'll have patients that get that same dose and they're totally just staring at you and no jump in blood pressure. So this is again, that nuance. So having that context of treating them in the clinic, seeing how they tolerate it, I think is probably prudent.

Susan Winckler (01:47:42):

Dr. Cohen.

Dr. Steven Cohen (01:47:43):

Yeah. I don't mean to offend my hosts, you know, the FDA, but-

Susan Winckler (01:47:52):

That's okay. We're the foundation that supports the FDA, so it's okay.

Dr. Steven Cohen (01:47:57):

You look at a nerve growth factor inhibitors, and like I say, I realize a lot of people are not pain, but nerve growth factor inhibitors, you had these huge companies, right? Pfizer, Regeneron, these definitely work. These are new drugs, osteoarthritis, they work really, really well. The problem is that a small percentage of people would get rapidly progressive osteoarthritis. So this was very concerning to people, but it was learned that if you limited the dose, it still worked. And if you didn't give NSAIDs, you could really completely reduce the risk. So this should be approved. You have a completely new drug, you have something that people are getting knee replacements, hip replacements, hip replacements work pretty well. Knee replacements, they work okay in some people, but not everyone is a candidate.

(01:48:56):

But the FDA doesn't approve it because basically what they say is you can't stop people from taking NSAIDs. You can go get it in a supermarket if you have a headache. People don't know. But we do this for opioids, we do this for ketamine. You can tell someone to take 1 5, 3 25 Percocet one once every six hours for pain, but that doesn't stop them from taking 15 at a time. But we allow this for certain things. And it's the same thing for ketamine in some way. I feel that there is just, there's a contradiction, and I'm not getting into this nerve growth factor inhibitor things, but I think that there should be some consistency. And for pain, it's very hard because a lot of these things, maybe ketamine, there might not be alternatives.

Susan Winckler (01:49:57):

And I think that's part of why the agency wanted to partner in hosting these meetings to explore and learn more and say, where do we need to learn more? And there are limits in what the agency can require and expect, but we can learn more and improve and then have the agency review whatever might be presented. But Dr. Hermes, you were moving your microphone which might've been an indication.

Dr. Eric Hermes (01:50:28):

I was bouncing my head on the learn more. And again, I think one of the places we need to go is understanding sort of maintenance treatment, how to provide maintenance treatment, who needs it, and how to better inform these risk-benefit discussions of other potential treatments for TRD. And so that's where I think one of the things I think we need to go to next.

Susan Winckler (01:50:55):

Yeah. And I want to turn to Dr. Poole. I know you had done work on some of the guidelines in those discussions. Did you tell us a little bit about how that group might've talked about maintenance versus kind of initial use? Was that a component of the work that you did?

Dr. Jessica Poole (01:51:19):

I think that there were some prescribing guidelines as part of the overall guidelines. But from our perspective, our goal at that time was we understood that there were a lot of clinics that were opening, again, without really having any guidance from our state to follow. We had a lot of scenarios where it was a solo provider administering the IV ketamine. So our focus and our priority was really just developing guidelines around the safety protocols that we should be following and making sure that we had adequate amount of professionals available to monitor the patient and treat any type of adverse events. But as far as prescribing maintenance, that wasn't really something that we got into with the Department of Health guidelines.

Susan Winckler (01:52:14):

That's really helpful though. Tell us a little bit more about the thought process there and then the results of that. Maybe just to give us a thumbnail sketch of the resulting guidelines in the structure that was provided to those who want to practice in Pennsylvania.

Dr. Jessica Poole (01:52:32):

Sure. It was truly a multidisciplinary team. We all came with different backgrounds and experiences, and I think ultimately we talked a great deal about the potential for the adverse effects with the sub anesthetic dosing. I know that I've mentioned, and we're all aware that the side effects and adverse effects are quite minimal, but they can still occur. And we wanted to make sure that we had a provider that was ACLS certified along with another practitioner that could manage any type of advanced airway situations that could arise, or administer subsequent medication if there were any ketamine complications.

(01:53:16):

So we just had some general guidelines surrounding proper monitors to have in a clinical type of setting. If you were an office-based scenario, what type of provider should be physically present and how many patients would be safe to treat at one time? I think all of which we have heard from different versions from the panel here, but our consensus was the same, that you need to have at least two providers that can manage any type of complications that can occur and monitor the patient throughout their infusion. In many instances, we have some patients that can be with us for anywhere from four to eight hours and up to four rooms at once, but all dependent on the patient selection.

Susan Winckler (01:54:02):

Okay. Really helpful. Dr. Prashad, did you want to add any?

Dr. Sandhya Prashad (01:54:08):

The only thing I was going to, Dr. keeps saying this, and I think this is a piece that we haven't talked a whole lot about. We've talked a lot about efficacy and acute treatment setting, but getting data for longer-term safety and with regards to maintenance. And then I think when we're talking about dosing, when we're talking about repeat dosing, so what does the safety look like there? I don't know that we have a whole lot of data in that regard, and that's really important additional research that we need.

Dr. Brittany O'Brian (01:54:34):

This on. And just circling back to what Dr. Cohen said, developing a registry would be enormously helpful in collecting some of that data. So to design a trial that lasts five years to track these longer-term outcomes is an undertaking I'm willing to engage in. But it's hard to do. It's hard to get funded, it's hard to do that trial attrition, all the things. But by being able to partner with places that are already seeing these patients and are tracking their outcomes and are carefully collecting data and putting things into a system like a REMS, but being able to actually really critically evaluate that information, I think will really serve us and serve the patients and give us a better understanding of what we should be doing proactively in the maintenance phase rather than just waiting for the relapse.

Dr. Sandhya Prashad (01:55:26):

Right, absolutely. And gathering that data so that we can maybe better predict outcomes. But I think also getting people together that are doing this so that we can also decide what do we need to track long-term, right? Should it be cognitive testing and what kind of cognitive testing? What exactly do we need to be tracking?

Susan Winckler (01:55:45):

So maybe even something along the line of a model structure for that.

Dr. Sandhya Prashad (01:55:50):

And we may not know really exactly what that should look like.

Dr. Steven Cohen (01:55:55):

So I do clinical trials. So if you look at pain, this is not even really a disputable statement. The placebo effect for almost everything is higher than the intrinsic effect. For gabapentin, for almost everything, the only thing that might have a higher placebo effect than pain, because it's subjective outcome, might be some psychiatric conditions. And there's a high co-prevalence. When you look at pain, the placebo effect for a procedural intervention is greater than a medication. So there's a bunch of different trials. They've looked at sham acupuncture versus placebo medication. You could see this in the migraine literature. And it's very strong when a treatment has very obvious physical effects like ketamine, right? It's just the placebo.

(01:57:05):

And this is kind of an ethical question, but like I said, for pain, you can't blind these studies. I think that the study where people are blinded by getting anesthesia for depression, and this would be a great thing for pain. So there's certain things that you can get out of registries. Registries are really, really important. But there's a lot of limitations on looking at this data.

(01:57:35):

So for example, the, I'm sorry, I'm a pain doctor. You look at sport trials for pain. If you're just looking at a registry, you'll see that people on opioids fail everything. They might be three times more likely to fail surgery. And this is a fact, if you're on opioids, everything, you fail. But if you did a randomized trial, and this has been done, and you randomize people to get surgery and then to get conventional, people who are on opioids might be three times more likely to fail surgery, but they might be seven times more likely to fail non-surgical treatments. And so if you're looking at this in the context of a randomized trial, you're coming to a completely different conclusion. So registries I think are really important. I like registries, but I think that we also need high-quality randomized trials

Susan Winckler (01:58:31):

That would help us address these piece. Well, so let me say to each of you, I came into this session and I was challenged to get you to share information about when ketamine might be used, which you covered in the various indications. I think as we've said, places where there's unmet need. That how it's used, we talked somewhat about the induction in the various settings, and then what are the needs in this space? And I think you've teed up that we wanted to know more about dose, certainly the focus on maintenance and better understanding what is the long-term use and how do you decide that? And then this discussion on where it relates to registry and guidelines for research.

(01:59:20):

So it went through all of the things that I was told we needed to talk about. So thank you for being brilliant enough to talk through all of those things and for giving us this first panel in the Cool Kids Club. So everyone, let's thank our panelists.

(01:59:43):

If you tracked the time, you've already spent two hours learning about ketamine, so it's time to take a break. We're going to take a 10-minute break, which will be much faster for those of you who are physically in the room than those who are joining us virtually. So we really are going to start again in 10 minutes, but you can trickle in as that works for you. Thank you.

Session 3: Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products

Presentations:
Joseph Palamar, PhD, MPH, New York University Langone Health
Megan Ehret, PharmD, MS, BCPP, University of Maryland Baltimore School of Pharmacy
Panel Discussion:
Francesca Cunningham, PharmD, U.S. Department of Veteran Affairs
Mark Rogge, PhD, University of Florida College of Pharmacy
Eric Schwenk, MD, Thomas Jefferson University

Susan Winckler (02:00:03):

All right, we are at 10 minutes after the hour and we said we'd give you a 10-minute break, so we need to kick off and head into our next session. I will note, I know that was a short break, but we have one more session and then we will have a longer break at lunch. But let's turn to our second session.

(02:00:22):

If you remember when we started the day we did kind of our tour of what it is that we want to discuss. I should also underscore, as we go to the next slide, underscore that the reason we want to talk today is

to be thinking about how do we generate the evidence base so that we could learn more in the drug development space as it relates to ketamine. So we can keep that in mind that we're looking at what else ... How do we need to advance that evidence base and continue to learn more and deliver on what we're seeing is at least an emerging area of use.

(02:00:59):

So, let's talk. We're going to turn now. We heard about the clinical component and now we want to turn to identifying safety concerns and the potential risks associated with the broader use of ketamine products. And to do that, we have our first session from Dr. Joseph Palamar, who is Associate Professor of Population Health at NYU Langone Health and Deputy Director of the National Drug Early Warning System.

(02:01:24):

So, Dr. Palamar, come on up. But you have a number of slides that are going to run the team through. I'll step forward [inaudible 02:01:34] when you have a minute left.

Dr. Joseph Palamar (02:01:34):

All right. Thanks for having me. Okay, it's working. So, today I'm going to talk about recreational ketamine use, misuse of prescribed ketamine and associated adverse effects. Really quickly here, my conflicts really just want to mention, I'm funded by the National Institute of Drug Abuse. They actually just funded a new ketamine study of mine, which I'm very happy about.

(02:01:59):

So, a lot of people aren't aware of the history of abuse and misuse of ketamine, so I want to cover that for a couple of minutes first. So, with respect to early use, misuse might've occurred as early as 1967. If you think back to the summer of love, 1967, people use an LSD, psilocybin, and there was actually a little bit of ketamine use in the mix it seems like. Some reports suggest that ketamine recreationally was available in both powder and pill form as early as the 1970s and abuse was first reported to the FDA as early as 1979. A long time ago.

(02:02:38):

So, by the mid 1980s, there were instances of addiction reported in journal articles, and ketamine appeared in the night cub scene as early as the 1990s, early '90s. It first appeared in ecstasy, MDMA, which a lot of the young people might know as Molly today. Ecstasy was always adulterated with one drug or another, but ketamine was a primary adulterant. And within a few years, by the early to late 1990s, ketamine emerged as a drug that was used on its own.

(02:03:10):

I remember I was a club kid back in the 1990s. Everybody was using white powder. I thought it was cocaine at first and then I found out it was actually ketamine. So, yes, people were using ketamine all over, especially where I'm from in New York City, in the nightclubs, anyway. So, where did this ketamine come from? This was diverted ketamine, usually stolen from veterinary clinics. I'll get back to that in a minute. But it was pharmaceutical grade at the very least. People would cook it up, sell it at the nightclubs to people.

(02:03:43):

Within the 1990s, the DEA received roughly 800 reports of sales and possession. So this really put up like a red flag for the DEA. They came down on it and in 1999 they made it a schedule three drug and that's when things changed at least on the recreational or black market as we might call it. I want to talk about law enforcement seizures a little bit because I want to talk about the illicit ketamine.

(02:04:10):

So, decades ago, as I said, most of it was legitimate ketamine. It was typically stolen from veterinary clinics. Now, this is what it would look like. We used to call these yellow labels in the club scene, like the Ketaset. This is what people would actually steal up through about 1999. But when the DEA controlled it more tightly, that's when veterinary clinics had to start locking it up and they had to be a lot more careful about it.

(02:04:37):

So then people moved on to Mexican ketamine. That's what we called the blue label back in the day. That was around 2000, 2001, and then that supply got cut off. People moved on to all other sorts of ketamine from other countries. And then within the early 2000s things started changing. Then clandestine laboratories started coming into the picture, primarily in Asia. And if you look over here, this is what the ketamine seized looks like today, typically. It's not the little pharmaceutical vials. It's typically already in powder form. Sometimes it's in massive amounts of just straight out powder. You never know what's in it. It's not pharmaceutical grade. It's typically smuggled in through Mexico. Sometimes there are seizures of it in airports, but typically through Mexico.

(02:05:26):

And, again, I want to point out that it's not pharmaceutical grade. You never know what's in it. Not you. I don't mean everyone here is going to be going out and buying it. Maybe some. But my concern is that people are going to think it's a good idea to mix fentanyl in it before selling it because fentanyl's popping up in cocaine as well. So, I'm worried about that.

(02:05:48):

My colleagues and I recently published a paper in JAMA Psychiatry about law enforcement seizures of ketamine. And as you can see, on the left, that's the number of ketamine seizures. It increased a lot by roughly 350% within a couple of years. And the weight of ketamine seized increased a lot. In fact, between 2017 and 2022, roughly 4,000 pounds of illicit ketamine were seized. And that's just by police officers. That's not including customs or the DEA or anything like that. 99% of this was in powder form. And that's concerning to me, because, again, this is not like your parents' recreational ketamine. This is sold in powder form already. This is not people obtaining the stolen liquid and cooking it up.

(02:06:42):

Preliminary data suggests that these numbers are actually increasing quite a bit. As an epidemiologist, I feel I have to cover the population level, the estimates of use. So, Monitoring the Future, it's a national survey of high school seniors. They survey a bunch of young people every year. This is the prevalence of ketamine use over time. You could see it has actually decreased quite a bit. It was most prevalent among high school seniors in the early 2000s, around two and a half percent or so. That goes hand in hand with the popularity of ecstasy and house music.

(02:07:17):

But the popularity fell because the popularity of house music decreased and the popularity of ecstasy decreased. But then there was a rebranding of something ... I don't like when people call it EDM, electronic dance music. That and they rebranded ecstasy into a drug called Molly. So then ecstasy rebounded as did ketamine a little bit, but it never really came back like it did years ago. It's hovering around 1% right now among the adolescence.

(02:07:49):

These are estimates among the adult population in the full US and it is increasing a little bit, but if you look at the Y axis over here, it's well below 1% within the full US population. But it's increasing a little

bit, but it's still pretty rare. Now, what's concerning me a little bit, this is the UK and they have newer statistics that came out a couple of months ago for 2023. You could see use is starting to skyrocket in the young adult population in England and Wales. It's now over 3%, I think close to 4%. It might be as prevalent if not more prevalent than ecstasy.

(02:08:29):

So is this becoming the new official club drug and ecstasy is not going to be as popular anymore? It appears that way. I don't know if the UK is going to be a bellwether for the United States and I focus primarily on the nightclub scene. That's where most of my grants have funded me to focus on. And I have recent data from early 2024. And as you can see, there's a pretty big jump between 2022 and 2024. Now close to a third of my nightclub attendees that I survey in New York City have used ketamine in the past year. It's right up there with ecstasy and cocaine.

(02:09:11):

So, again, it might dethrone those as the most popular club drugs. Ketamine is coming back. With respect to my nightclub attendees that I survey, past month use, which some agencies refer to as current use, is close to 15%. So that's pretty high. And 8% of the people we surveyed entering nightclubs said they used in the past 24 hours. And that's not including the people who have not even entered the club and started using that day yet. And we've been saliva testing people and 12% have been testing positive for that.

(02:09:47):

So, yes, use is coming back recreationally. With respect to effects, people ask why would somebody use something like this in a nightclub? Because of this. You take a bunch of ketamine and with the lights and the music, you might see and feel something like this. A lot of people find it enjoyable. You might not be able to talk very well or move that much, but when you see that, you might enjoy it.

(02:10:16):

A lot of people have tried to describe what the ketamine high feels like. It's very difficult. It's not like a traditional psychedelic. This was a popular book from a club kid back in the nineties. He says, "It pretzels your thoughts into Mobius strips. There's a lot of curling and unfolding." That's more of what we call the K-hole. I'll get back to that in a minute. But, again, very popular club drug.

(02:10:39):

With respect to general effects of ketamine: numbness, passiveness, there's a perception that the world is not real. It's very hard to explain what a dissociative feels like, I guess, unless you've done it. And change perception of body consistency or distortion of body parts. People use a decent amount of ketamine might say that their arms feel like wood. People might feel like a weightlessness or a floating sensation. I think that's part of the reason a lot of people like dancing on it. And there's an absence or distortion of time, but that's common with hallucinogens and psychedelics.

(02:11:18):

And even small doses could lead to dissociation or hallucination. You don't need a lot for these effects to kick in, especially if you're not experienced with the drug. Larger doses could lead to something we call a K-hole. And I didn't know that clinicians were referring to this as well. I thought it was just the epidemiologist. But it's an out of body experience. Some people call it a near death experience where you almost can't explain it. Someone attempted to draw a K-hole in artwork and it's almost creepy. It's kind of the opposite of what you would see regarding psychedelic artwork. If you've seen Alex Gray's beautiful artwork about DMT and LSD, it's beautiful colors. This is a little bit more creepy.

(02:12:07):

So that is closer to depicting what the K-hole is like and the effects can be pleasurable, but a lot of people feel that they're absolutely horrific. And as you could imagine, this impedes your judgment and your functioning. With respect to adverse effects, we found that a fifth of my nightclub attendees have reported a harmful or adverse effect in the past year, and 13% who have used in the past month. And a lot of these people said they asked somebody for help. Some of them even went to an emergency department. Confusion and vomiting were pretty common symptoms reported by these people. Something I want to mention is that an older survey by the Dawn Network, a lot of these people who were hospitalized involving ketamine, the majority involved alcohol. And I'll get back to that in a minute, but alcohol is a problem. You shouldn't be mixing ketamine with anything.

(02:13:01):

And there are actually some deaths reported within Chicago and California recently. They're probably involving other deaths, but we're trying to investigate them as part of my end use group. So, with respect to adverse effects, impaired consciousness is one of the big ones. That's kind of vague, in my opinion. Impaired consciousness, ketamine. It doesn't give you a lot of information, but there's acute risk of physical harm. What if you walked outside, get hit by a car or you drown? There's a Matthew Perry situation which is still being investigated. Physical and sexual assaults are big problems. I don't like calling it a date rape drug, but if your guard is down, you don't know what's happening, things could happen. You could get mugged, you could get beat up, you could get raped. And on top of that, you might not even really remember what happened. It's a problem.

(02:13:52):

Use disorder is an issue if you're using it pretty frequently. I've known people like this. K-cramps. That's when you're using it, your stomach starts aching. It's pretty painful for a lot of people. And I'm sure people are going to talk more about the bladder issues today, but the people who use ketamine frequently, bladder issues seem pretty common. It's a major adverse event. And with respect to poisonings in the US, my colleagues and I looked at this through 2019. It kind of fluctuated. Roughly one in a million reported to Poison Control. But what I want to point out is that about 5% of cases were child exposures. So that worries me of the pediatric exposures or people leaving their ketamine around and then their kids pick it up.

(02:14:36):

My colleagues and I at a group called Radars, we've been analyzing more recent data from 2019 through 2023 and the number of poisonings reported have essentially doubled. About 400 last year. Misuse or abuse is the most common reason associated with the poisonings in about 36% of the cases, followed by suspected suicide attempts, and again, something that worries me, unintentional exposure. With respect to the severity of cases. These next few slides are only focusing on the cases of misuse and abuse. So, most cases are moderate, which are severe enough for someone to call poison centers, but not that severe. 20% were major events which were considered life-threatening. And there were a couple of deaths in the mix, but there was a lot of co-drug use. That's something that complicates the situation.

(02:15:34):

Now, 41% of these cases reported co-drug use. Most of them alcohol. Alcohol keeps making its way back into the situation. You do not mix ketamine without alcohol. One thing I worry about, you prescribe it to somebody at home. What if they think it's a good idea to drink some wine with it, for example? I don't have enough time to cover all the details of the others, but alcohol is the biggest problem. With respect to root of administration, ingestion by far is the most common situation followed by inhalation, which largely means sniffing powder form. Ingestion, it could be liquid, it could be powder, it could be

lozenges. We're not completely sure. We're looking through the data now, but this right here presents shifts in time. Injection has actually decreased quite a bit significantly over the years while ingestion and inhalation are pretty stable. Injection has decreased.

(02:16:36):

And what form of ketamine are they using? Liquid for the most part. 31% in these misuse cases said that. 22.7% said they used powder, which, again, powder is the big recreational way of using. But then there's solid. What is solid? It could be powder, it could be a lozenge. It depends how the data recorded. So we need a lot more information on what's going on with this. But again, the liquid use, just like injection, is decreasing and the non-liquid use is increasing.

(02:17:13):

So, at-home psychiatric treatment, that's my big concern because I'm thinking about more recreational use, unsupervised use. So, virtual prescribing, we've already been discussing it today, some great discussions, but the lozenges that people prescribe from the compounding pharmacies, sometimes a quote un-quote month supply is prescribed, I think, and they might look something like this. Now, there have been studies where very large doses are mailed to people in multiple doses. You don't really know what the patients are doing with them necessarily. And there was an infamous case where a doctor prescribes ketamine at home to over 3000 patients, I think during COVID and the DEA came and shut down his clinic.

(02:17:58):

But I worry about the at-home use, so I want to talk for just a couple of minutes about what I think the risks are of the at-home unsupervised use. And I have seven specific concerns I want to get into. So dysphoric reactions with no supervision. If someone is at home by themselves, what if they have major anxiety? What if they don't understand what's happening? What if they have a panic attack? Yes, you as a clinician, you might've had an initial meeting with them, but it doesn't guarantee they're going to have the same reaction when they take it at home alone, especially when they're taking it on their own. You don't know what they're doing.

(02:18:39):

Patient self-harm and harm to others is a big concern of mine because what if you're at home, you take ketamine and you left the stove on? What if you have kids to take care of? Who knows what your kid is doing? What if you leave your ketamine around and your kid picks it up and eats it? What if you think it's a good idea to drive a car or operate heavy machinery, walk in Manhattan, get hit by a car? You don't know what's going to happen.

(02:19:07):

Diversion is a big concern of mine. If you prescribe, say, a month's supply of ketamine to somebody, if that's 30 lozenges, for example, who's to say they're not leaving them around for people to take? They might be selling them. They could be leaving them around, selling them. Anything could happen with these if you give somebody a large supply, so I worry about that.

(02:19:36):

Stockpiling and large doses. That concerns me because if you already give someone multiple doses, who's to say they're not just going to keep collecting them until they have 20, 30 doses and take a whole bunch at the same time? And with respect to routes of administration, this is something I want to talk a little bit more. I see I'm running out of time here. Routes of administration. When you prescribe the lozenges for people to take at home, there are people who are actually trying to break these up and sniff them.

(02:20:10):

I've been reading online, googling it, looking on Reddit. There are people giving advice on how to extract the ketamine from them. A lot of people straight out recommending put the lozenge up your butt because it's a better high. There are a lot of people who instead of spitting out the ketamine, once it dissolves in their mouth, they actually just swallow it. So they're putting a whole bunch in their mouth and swallowing it. So, you don't know how these people are using the ketamine and there's ketamine use disorder, as I mentioned. If people are using it all the time, they can quote un-quote abuse it or become addicted.

(02:20:47):

I don't like saying that it's not classically addicting, but it can lead to problematic use. And I worry about people seeking illegal supply after being introduced to ketamine through a clinic. Because if you realize how much money you're paying, if you're paying hundreds of dollars for a session and then you learn how cheap it is on the black market, what's to stop you from just going to the kid at the corner and buying it? It's exponentially more expensive when you purchase it at a clinic and the street price is much cheaper than for other drugs.

(02:21:19):

If you buy illegal Adderall or Xanax, it's expensive on the street. Ketamine is much cheaper. So, my last few points, we need more research to understand what are the drivers of misuse and abuse and the adverse effects. We need more research to monitor the legal and illegal ketamine landscape and we need to figure out is off-label prescribed ketamine use, is the ketamine making its way to the black market? We need more information on this.

(02:21:51):

We need this information to focus on policy. For example, regulation. We need this information to focus on prevention, especially education for people at risk for misusing, treatment, and harm reduction. For people who insist on using, at least learn how to use it safely.

(02:22:13):

So, thank you again. And if you want to subscribe to our weekly briefings, please scan the QR code. We send out weekly information about drugs such as ketamine and so on, but this will all be on video. So, thank you very much.

Susan Winckler (02:22:31):

Great. Thank you, Dr. Palamar. We will see you in a bit when we come back up when we have our panel discussion. So, recognizing that there is this use and that we're gathering information about the safety effects, it's helpful to have that grounding.

(02:22:51):

And then we want to turn to Dr. Megan Ehret who has information about the safety concerns and potential risks associated with use of ketamine when it's more in that healthcare and clinical setting.

(02:23:02):

So, thank you for joining us from the University of Maryland School of Pharmacy, where you serve as Professor of Practice, Sciences, and Health Outcomes Research. I bet your slides work.

Dr. Megan Ehret (02:23:14):

Thank you so much. I am coming from a different perspective. Well, I think I'm the first pharmacist here speaking today, and we have some other great pharmacists joining today. So I'm going to be talking a lot from probably the type A personality of a pharmacist in monitoring every one of these side effects, making sure our patients are educated on that.

(02:23:37):

So I thought we would approach it very quickly from a perspective of the adverse effects that we've heard a little bit about today, but maybe think about some clinical applications or where we may need to do education for family, but also for patients, especially in light of a lot of the discussion about take-home ketamine as well.

(02:24:03):

Obviously we expect psychiatric side effects from the use of ketamine and the dissociation and the somatic kind of things that we might see from this. Some of the literature does discuss potential decreases of dissociation with subsequent administration, which is helpful when you're in a clinic setting, to think about at least seeing the patient the first time, really monitoring them a lot, and then maybe understanding how subsequent administrations may affect them.

(02:24:35):

From the literature we see peaks within 40 minutes. Typically resolves within the first hour or two. And this really mimics the REMS for S-ketamine that we see. There are some clinical rating scales which can be done, whether these are very easy to implement within clinics, can be very challenging to be trying to administer rating scales when you have a person who's dissociating and maybe the nurse or the PA or someone is watching several patients at once. This can be very challenging.

(02:25:07):

And then there's also a lot of discussion about what about patients who may have preexisting psychosis and is it okay to use some of these medications and thinking about how do we select the right patient and do they need an increased level of monitoring or are they completely absolutely contraindicated? And I think some of that is still being worked out in thinking about selecting those patients. Neurologic, cognitive. Some of that dizziness, drowsiness, lightheadedness. And the importance then of having a safe environment for where that patient's being administered the medication and making sure that there's not risks of falls, that if they need to go to the restroom, someone's there to sort of assist, especially as we're sort of getting those first bits undertaken.

(02:25:52):

And then long-term exposure. I have the question mark here because I don't know that we know the cellular or molecular evidence of neurotoxicity long-term and really points to the importance of that maintenance and knowing what's sort of happening with subsequent administrations.

(02:26:08):

Hemodynamic. This is always my biggest area of concern in thinking about potential increase in heart rate and blood pressure that you might have patients experience. Typically observed within the first 20 to 50 minutes of treatment and making sure that they're having adequate monitoring, and for what adequate monitoring is can be very different for every clinic because we don't have standardized policies with ketamine like we do with S-ketamine. So with S-ketamine in the REMS, you have very specific time points when you're monitoring that and making sure you're documenting. With ketamine, everyone is having their own policies and procedures in place.

(02:26:47):

And I did put some percentages here just so we could have an idea of what that looks like when we were saying increase in blood pressure. If we're talking 180 to a hundred milligrams of mercury increases or an increase of 110 beats per minute, that's substantial and may require to have protocols in place as to how you may treat that pharmacologically, if needed, depending on potential doses that you might be giving, especially during that titration. If you're increasing it, is there increased risk for this? And thinking about do we really need to have a protocol in place and where are my emergency services if needed?

(02:27:27):

Our clinic that is just opening in Baltimore went through a lot of discussions about this and who needed to be ACLS, who could just be BCLS. Do we need to have this available, that available or is just 911 good enough for everyone? And so there was a lot of discussion and so I think that it's helpful when there is discussion of guidelines that some of this isn't available for us to know, and I'm really appreciative of Pennsylvania trying to maybe set some standards around that sort of discussion and trying to help practitioners with some of these areas.

(02:28:07):

Okay. There was discussion of some urinary type of side effects too with longer term ketamine use. This is mostly from the recreational data that 20 to 40% may have lower urinary tract symptoms. Dysuria, nocturia, urinary urgency, incontinence. This tends to be a dose dependent relationship with ketamine exposure and the probability of experiencing these symptoms. But these are things we may need to educate patients as we're considering about dose titrations, that these are particular effects that they may see as well.

(02:28:46):

Abuse. I think we've talked quite a bit about this, but the poly drug use additionally with opioids, benzodiazepines, especially with how frequently those things are available, the increased liking then for this ketamine. And so every clinic then does also have to decide, when you're selecting patients, if they're on opioids or benzodiazepines, are you going to be administering ketamine? Is that an increased monitoring patient or is that an absolute contraindication? Even in the S-ketamine package insert, there isn't specific guidelines. It just says that these are potential drug interactions to think about and you need to decide in your own clinic how you're going to sort of manage those.

(02:29:30):

So I'll be very excited in our panel to talk about some of those interactions and then that increased reward sensation and then increasing the dose. I will bring up the elephant in the room, as the pharmacist. We've done some research at the University of Maryland inquiring with prescribers across the country, including VA prescribers, and asking them about the REMS. So we do know that S-ketamine does have the REMS. That is required, which is really designed to help reduce the recurrence and occurrence of particular adverse effects. It can either be for a single medication or a class of medications. I'm sure we're all very familiar with the REMS and esketamine when it was FDA approved came with a REMS. So it has the risk of sedation, dissociation, and respiratory depression after administration. Ketamine doesn't have a REMS, it's free to use without that. Many of the providers that we talked to said that the REMS is a barrier to the use of esketamine because of the having to register every patient, having to do all of that specific monitoring, having to then perhaps double enter it in your electronic medical record because you have to put it in there, but you also have to submit it to the REMS, the follow-up with the REMS.

(02:30:55):

There can be a lot of burden, healthcare time. And so it's important for us to think about that. I think it's important too, for the FDA. And when we think about this if you are going to get that cat back in the bag, it's going to be pretty challenging given that ketamine is already out there. I do think that's an important consideration to think about for this and perhaps that increases the hurdle and changes some of the landscape around ketamine and esketamine as well. I know I'm a little bit early, but I think that that will help us get some time with the panel discussions.

Susan Winckler (02:31:33):

Absolutely.

Dr. Megan Ehret (02:31:34):

Perfect.

Susan Winckler (02:31:35):

So we'll take it. Thank you Dr. Ehret. Dr. Ehret, I'm a pharmacist and an attorney, so I'm like double type A.

Dr. Megan Ehret (02:31:46):

Oh. [inaudible 02:31:46].

Susan Winckler (02:31:46):

So go ahead and take a seat there. We're going to have, Dr. Palamar could join us back on stage and Dr. Cunningham, please come up. So our discussion session here, we'll have three folks in the room and two joining us virtually. So headed up to the stage right now is Dr. Fran Cunningham, who serves as the director of the VA Center for Medication Safety. And then joining us on screen, so they should be coming up in just a little bit to be visually presented there, we'll have Dr. Mark Rogge, who is an adjunct professor at the Center for Pharmacometrics and Systems Pharmacology from the University of Florida and Dr. Eric Schwenk, a professor of Anesthesiology and Orthopedic Surgery at Thomas Jefferson University. Let me step up to the podium. I'll first say, Dr. Cunningham, let's start with you. Do you have any questions or reaction to what you heard from Dr. Palomar and Dr. Ehret? We won't make too many jokes about whether or not any of us have been in the clubs that Dr. Palamar was talking about.

Dr. Francesca Cunningham (02:33:01):

Thank you very much for inviting me and I do have a couple of comments. First, and it's a pleasure to be at the cool kids table. I am a self-professed nerd, let me tell you. You will hear a little bit of my nerdiness come out today. So thank you guys. It was very interesting to listen to the contrast very much between Dr. Palamar and Dr. Ehret. I really enjoyed it because I live on the very nerdy side, tracking the safety and monitoring on a day-to-day basis. I do want to say one thing, and you talked about the K hall. I called it dissociative anesthesia. How boring am I because there really was a real use for ketamine as an anesthetic. Especially back in the days when I was spending time in Chicago and the emergency departments and the trauma areas when you needed that agent as an induction agent because you didn't want the patient's blood pressure to catapult or you had certain traumas that were occurring and you used it for dissociative anesthesia. There were certain uses for that agent, so I try to keep that in mind.

(02:34:08):

Just very briefly, kind of tell you what I do on a day-to-day basis and where the monitoring comes from. Our center is really responsible for tracking the safe and appropriate use of medications, specifically newer agents as they come into the VA and/or older agents that have newer indications where we really need to look at safety, where safety really wasn't considered to be important. We do this by three different methods. We do it by our regular traditional method of tracking spontaneous reporting, MedWatch. We do it by, my favorite method is epidemiologic methods by integrated databases and looking at risks of drugs the best. We have the best data system to do that with VA, but all that glitters is not gold. Right? There's certain data that are not in a structured dataset or where you can't identify the patients that got the drug. In those instances, we have to conduct other methodologies and we typically will conduct medication use evaluations, either retrospectively doing a chart review or prospectively where we literally beg our providers to capture data as the drug is being administered.

(02:35:17):

When we do this, we do this in tandem with developing that tool with our providers. That's where esketamine comes in. Esketamine, we were voluntold to track, and so it became a mandatory processor. We had to develop a tool to do a realtime data capture for the medication. We did this in collaboration with our colleagues, Dr. Hermes, Dr. Weakers, and we developed that tool. So we collected safety information for REMS and then safety information that we needed for our veterans. Keeping in mind they're the most important to us, so everything's veteran centric, but also they have a high disease state burden. We really look at things a little differently because we're looking at patients that may be more susceptible to certain adverse events that the general population is not, but that ends up being good data for other people to use down the road. Right?

Susan Winckler (02:36:09):

Right.

Dr. Francesca Cunningham (02:36:10):

One of the things that we did, first of all, looking at cardiovascular adverse events of esketamine, and I'm looking, like 40 minutes, no, no. Looking at the dose response and the concentration, that's going to be earlier. So we set up to do a 20 minute monitoring, 20, 40, 60. And so then we evaluated over time, we collected the data, we share information with our subject matter experts, with our mental health group. We would monitor the information. We started off monthly and then decreased the quarterly as time went on. We looked to confirm that they were the typical side effects, we were seeing dissociation in 80%, well, 85% of our patients had sedation, 80% of our patients. We saw mild hypertension, an tachycardia. But as far as treatable, which we were most concerned about, the treatable hypertension was lower, it was less than 10%. But we did realize that we reached our peak effect in hypertensive potential episodes at 20 minutes, so we did the right thing. We were beginning to see a decrease at 40 minutes and return to normal at two hours. These are the good things that we're able to do.

(02:37:15):

We're able to feed that information back to our providers and say, "Hey, this is safe. Can we stop the MUE?" "No, because you guys are the only ones tracking it." So we keep going and so that's where we are with this agent. We are continuing to track it both from an adverse event standpoint and more importantly to take some information. I said we worked with our providers, to take information and take subjective information that's not easily tracked, standardize that subjective information so that we can analyze it. So now we're getting to the good stuff. Now, we're getting to the point where we're looking at some questions that we asked that looked at why did you stop esketamine? What are some of the longer term side effects that we need to begin to look at? We're now just beginning to dive into that

information and take it from there. Now I'm going to briefly talk about ketamine. Difficult to track the safety of ketamine. Why is it difficult to track? Because it's difficult to capture. It's difficult to capture-

Susan Winckler (02:38:15):

Even in your system?

Dr. Francesca Cunningham (02:38:16):

... those patients.

Susan Winckler (02:38:16):

Even in our system.

Dr. Francesca Cunningham (02:38:18):

Okay.

Susan Winckler (02:38:18):

We have to depend on our colleagues, Dr. Hermes, who will set up and help us. There are certain clinics where you know that the drug is being administered. We were able to early on, identify a few of those clinics where they were even used for pain management or for mental health and then make sure that with our medication use evaluation, that information was filled out so that we could look at the safety and also the dosing. One of the things that we had to reimagine, especially as this medication ketamine is beginning to be used IM more frequently and also in the emergency department, where what's happening to that patient? Is that patient admitted? What's happening to that patient that's walking out the door within 45 minutes or an hour, where maybe not at the VA, somewhere.

(02:39:11):

What's happening and what's happening to that patient where we don't have the ability to look at the drug-drug interactions and take the time to make sure of that. We've developed or we're in the process of rolling out a medication UC evaluation that will capture that information so we can evaluate that more extensively. That's an area that I think is going to be very important, even though it's used medically. I do not know the degree of monitoring that will ultimately occur, and we need to make sure that it's done appropriately. As Dr. Hermes said earlier, we do have standard criteria and our providers do use that so it does work for us a little bit better in the VA.

(02:39:53):

Great. Thank you. So good to know that what you've been doing, and I am intrigued by the idea of the standardizing the subjective information so that then you can standardize it to collect it more routinely. I want to make sure that we provide time for Dr. Schwenk and Rogge to respond if there's anything you want to raise with Dr. Palamar or Ehret. Dr. Schwenk, do you want to jump in and add your voice first?

Dr. Eric Schwenk (02:40:23):

Sure. Yeah. I really appreciate the opportunity to comment here with a really talented group of people from around the country on this topic. One thing that strikes me listening to Dr. Palamar present a lot of sobering data about ketamine being abused is, at least from what I've seen and from what we've published from Jefferson, is the apparent discrepancy between what we're seeing in terms of toxicities and side effects in patients who got ketamine for medical reasons versus those who are abusing it. That begs the question of why is that discrepancy there? Why are patients who are getting ketamine

infusions in our settings not having really any of these toxicities, or at least anything that's nearly as severe as what's being described. I think that's a question that we don't completely have answers to. I wonder how much of it is related to some of the adulterants that are being given with ketamine or taken with ketamine and/or maybe related to exposure. But on the other hand, for example, related to the issue of cystitis, we published a relatively small study.

(02:41:38):

We looked at 4,000 patients trying to see how many had reports either from ICD 10 codes or from visits to urologists or gynecologists within 90 days after receiving infusions. We 116 patients that were a topic of focus. And when we drilled down, there were two patients in the entire group of 4,000 who were even possibly related to ketamine and both of those were, in reality, probably related to the Foley catheter. Really, in a series of 4,000 patients across three different institutions that use ketamine at high doses, we had a patient who received over 100,000 milligrams of ketamine over a series of weeks, believe it or not and really there was no signal there. It doesn't mean there's nothing there, but it means that it doesn't appear to be rising to the level of clinical concern. At least when it comes to the bladder issue, that seems to be not really the case in medically treated patients. And then there's these topics of neurotoxicity seen in rodents, which is also not something that is really matching the clinical experience we've had of 20 plus years.

(02:42:49):

We're not seeing patients with memory deficits in some unpublished data that we're going to be publishing in the next month or two. We did MCA, the Montreal Cognitive Assessments in patients who received five day ketamine infusions for migraine, five days continuously of doses up to 0.7 or 0.8 milligrams per kilogram per hour, so they're really getting in the thousands of milligrams of ketamine. On average, the cognitive assessments did not worsen, they stayed the same or even slightly improved out to 12 months after treatment. So at least from that standpoint, the rat studies are not consistent with what we're seeing in humans. I think there's some issues there in interpreting and translating the rodent studies to humans. Those are my, I guess, initial comments. I want to leave Dr. Rogge time to comment as well.

Susan Winckler (02:43:41):

Yeah, yeah, very helpful and particularly, I think we have to look at the information we can gather from all of the use and then try to evaluate where there might be differences in the use in healthcare versus unguided uses, what I'll use there. Dr. Rogge, I know you've done some work in this space as well, would love to bring your voice to the conversation.

Dr. Mark Rogge (02:44:11):

Sure. Thank you. This is so timely, I'm glad we're having this now rather later on when we might have to take a few steps back and try to figure out what we did wrong. I'll just follow up actually on a few of the comments that have already been made because I think they've really touched on some important topics here. I've had the fortune of working on some products actually that have been on the market for decades, and in each case have realized that there's really a lot more that we don't know about them. We do know oftentimes, it's because the technology wasn't there, the ability to gather the data and interpret the data appropriately. While we think that we understand these drugs quite well, the reality is we, in fact, don't. I've heard a few comments in this session, but also in the earlier session around some of the unpredictability that can exist with ketamine.

(02:45:15):

I think, in particular, because I work more in the pharmacokinetic, pharmacodynamic, pharmacology area, what we really understand, for example, around metabolism, of course we know that ketamine is metabolized by 3A and 2B and 2C pathways. We also know there's a lot of variability in those pathways, so why can some people end up, and I think Megan had touched on this, with quite significant excursions in blood pressure or heart rate, while others won't at the same dose. Could this go back to, for example, changes in metabolism? I think we heard actually from Dr. Cohen earlier in the day around the rate of increase being very important in terms of achieving a dissociation, for example, with dissociative state. I know in my own work in CNS, where we're trying to minimize those CNS tolerability or adverse event issues, we try to slow down the rate of presentation into the brain. How does ketamine get into the brain is it simply passive or are there transporters, active transporters that move it in or out of the brain?

(02:46:32):

Which again is determined genetically and phenotypically and be it the metabolism or these transporters very susceptible to drug interactions or simply induction inhibition by other factors. I think there's probably a lot more work that really ought to be done in that area. I guess I'd like to make just a couple of other comments. We talked about one of the big elephants in the room, but I see ourselves maybe at the doorstep of what, at least has the potential to be an opioid situation, and how can we avoid that? Could ketamine be a gateway drug? What can we do to make sure that, as we saw in Dr. Palamar's presentation, hundreds and hundreds of kilograms of this virtually pure material coming in to make sure that people who are getting it legitimately and under proper conditions then do not find themselves going out on the street and buying it for pennies on the dollar and harming themselves. I think we need to understand are the poisonings that we're seeing, I think Dr. Schwenk actually brought this up. Is it due to the purity of the product? Is it more pure?

(02:48:01):

Are people using higher doses? Is it route of administration? I think we have to get a better understanding on this. There are certainly organizations and means, the Corey, whoever it might be, to really begin to understand that a bit better. My last comment, and I hope we get a chance to talk about this a little bit, is where should the boundaries be? I think this might've come up earlier, outpatient use. Are there means of safely using it in an outpatient setting through some more advanced devices that the product would be embedded or encased into to prevent an overdose, or more than a number of appropriate doses being given per day? I think there's a lot of opportunity there, but we do need to think about that now and manage it now as opposed to try to fix it later. So I'll leave it at there.

Susan Winckler (02:48:59):

And helpful in just reminding us of the things that we may know versus what we need to continue to learn. I'm intrigued on this question, particularly as it relates to safety information. We're trying to learn more where the data is and where it's not. The data that you're looking at, Dr. Palamar, is not in health records. But Dr. Cunningham, you even mentioned that it's not in the typical health record. And as we talked about the lack of coverage then it's not in our usual sources of real world data and real world evidence. Are there ways to think more about those data gaps and how we bridge those data gaps or is it more about gathering what we can and then seeing how it connects? Any thoughts? You can run at it, Dr. Palmar.

Dr. Joseph Palamar (02:50:03):

It's very difficult to harmonize data. That's something-

Susan Winckler (02:50:06):
Fair.

Dr. Joseph Palamar (02:50:06):
... I've learned over the years. You have a bunch-

Susan Winckler (02:50:09):
Well, I'm not sure we can-

Dr. Joseph Palamar (02:50:09):
... of different pieces.

Susan Winckler (02:50:09):
... harmonize your club data

Dr. Joseph Palamar (02:50:11):
Better-

Susan Winckler (02:50:12):
But can we contextualize the club data?

Dr. Joseph Palamar (02:50:15):
We could try or we could compare trends.

Susan Winckler (02:50:19):
Okay.

Dr. Joseph Palamar (02:50:20):
My new ground is to examine what's happening in the shifting ketamine landscape, medical and non-medical use. So we want to look at trends in the prescribing. We're going to talk to prescribers, we're going to talk to patients, and we're going to compare their responses to see, "Do you feel like you're over-prescribing?" And then we're going to ask the patients, "How easy was it for you to get? Did you lie about your symptoms to get it? Did you really have depression or did you just want it? Did you sell your ketamine?" And then we're-

Susan Winckler (02:50:49):
Did you want the drug, not depression?

Dr. Joseph Palamar (02:50:50):
Oh. Yeah, yeah, yeah. But then we're going to look at at-risk populations, the nightclub people, we're going to look at college students, just recreational use. We're going to look at a whole bunch of things and we're going to compare trends to see how the landscape is shifting. See is one thing, predicting the other, possibly. It's going to be difficult, but we're going to try.

Susan Winckler (02:51:10):

Yeah. And Dr. Schwenk, I see your hand raised, so I'm going to come right to you. I want to give voice to an observation that was made on the virtual meeting that some individuals when they're underserved or stigmatized in the healthcare system, will pursue the non-medical drug supply as a way to treat their symptoms. I think this comparison and connection of your work, and then I'm glad to see the convergence there, or at least the comparison and the trends. Dr. Schwenk?

Dr. Eric Schwenk (02:51:46):

Yeah, thank you. My comment's pretty brief, but I am going back to a comment Dr. Cohen made earlier about the need for randomized controlled trials to better understand. I think a registry would be complimentary to RCTs, but RCTs are still important and it would require funding and a lot of effort to study it further out. But I would really implore the FDA to consider lowering the bar in terms of doing early preliminary non-clinical work to study some of the long-term effects in humans. For example, the requirement of doing rodent studies and other things like that. Even though the indication and the dosing may be slightly different, I think we all know it's only approved for use as a general anesthetic right now.

(02:52:29):

But the percentage of use that's being used in anesthesia for ketamine is minuscule compared to pain and depression right now. In order for us to, as a community, to understand more we have to do the research. And to do the research, we have to be able to get over the hurdle of doing a lot of these very expensive animal studies that are necessary to do these sorts of things right now and that is really potentially stifling things. As a researcher, I know I've been dealing with some of that.

Susan Winckler (02:52:58):

That's a very helpful observation as we just think about how do we help advance the drug development in this space. So any other thoughts on kind of the data? Go ahead, Dr. Cunningham.

Dr. Francesca Cunningham (02:53:11):

I would just like to emphasize what was just said. I think pragmatic clinical trials is the way to go in certain instances, to optimize, looking at dosing, and looking at the different patient populations and then following out for long-term adverse events. In addition to what we're already collecting, I think we need to still do both.

Dr. Megan Ehret (02:53:30):

I was thinking if Dr. Cunningham is having as much trouble as she is in a very closed system where they know where that ketamine is being given and things of that sort, the struggles outside of the VA are massive-

Susan Winckler (02:53:43):

Correct.

Dr. Megan Ehret (02:53:43):

... in trying to get that data together to fundamentally make some decisions and provide guidance to a lot of providers who are looking for that guidance at this point.

Dr. Francesca Cunningham (02:53:57):

And just one more final point on that, listening to Dr. Hermes saying that they were able to identify ways to target those patients so that we can identify, that's like the holy grail for us to start tracking risks because now we can start looking at it more with the structural data and we can start standing up and doing standard pharmaco epi evaluations by identifying that cohort and following over time. I'm excited about doing that hopefully in the near future.

Susan Winckler (02:54:25):

So there are definitely opportunities to say how we might, and then we have to recognize the extraordinarily wide range of scope of clinical use and clinical deployment and nonclinical use and deployment as we've heard. In thinking about it, and I would pose this to you, where do we bring in the conversation with the patient about the risks and the benefits and the safety component. Dr. Ehret, have you seen any of that in the work that you described? I open it up to any of our panelists to talk a bit about that.

Dr. Megan Ehret (02:55:12):

I think this goes back to either treatment resistant or difficult to treat depression clinic where you're making these decisions. Which of these treatment modalities is going to be best for the patient? Are there comorbid disease states? Are there other medications? Accessibility? Are all of these accessible here? What does insurance pay? What does patient preference? And then ultimately, where in their life are they? Can they come in twice a week for esketamine? Can they come in for ECT? Do they have the capabilities and where does this fit within the landscape of where they are? A lot of that has to be brought to a patient level.

(02:55:53):

We can't talk at these, "Oh, we don't know the long-term neurocognitive." We can't use all of that medical jargon and bringing it down to the patient level to really talk about these risks and saying what we don't know. These are our best options at this point. But that accessibility point is very important because many people, the door is shut before it even starts, which is unfortunate because there isn't an accessibility to all of these treatment modalities, even in great places where we think we should have all of these things.

Susan Winckler (02:56:24):

Okay. If I think through what you've shared with us in this session in thinking about how we learn more on the safety concerns, there's things we can learn from both the healthcare system use and the outside use. And then to look at trends in particular, I think that that comparison was helpful. And then this observation as we look more towards learning more, that pragmatic clinical trials, randomized clinical trials will help us, but we should continue to learn along the way as well and look to some of those standardized data sets. I have to say to Dr. Rogge and Schwenk, really helpful to remind us of perhaps some of the typical structures that we have in place when dealing with completely unapproved drugs versus those where we have an approved use and a broader off-label use, should some of the structures be different as we explore further use and better understanding.

(02:57:29):

All right, which gets us to finishing the morning and having learned a lot and probably need to take a break and step away from discussing ketamine for about just over an hour. Let me say we're going to take a break now. We will reconvene at 1:15. That at least rhymed. So that's what I was going to say. I

hope that that's the right time, I'll look to my team. Reconvene at 1: 15. So we will see you back here in this room or back virtually at 1:15 and we'll pivot to talk about policy and regulatory pieces. Thank you.