Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest
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Afternoon Transcript

Session 4: Policy and Regulatory Challenges for the Medical Use of Ketamine
Presentations:
Seth Mailhot, JD, Husch Blackwell
A.J. Day, PharmD, RPh, National Community Pharmacists Association
Panel Discussion:
Gail Bormel, RPh, JD, U.S. Food and Drug Administration
Lisa Harding, MD, Yale University
Lisa Robin, Federation of State Medical Boards
Jenni Wai, RPh, MBA, Ohio Board of Pharmacy

Susan Winckler (00:00:00):

All right. It is 1:15 or wherever you might be in the country or around the world, it's either 15 minutes after the hour or quarter till the hour if you're in one of those places. But we are kicking off again.

(00:00:13):

So welcome back. I hope you had a restorative break and we will jump into the rest of our program. I did want to make one note, there was a great question that I did not ask in the safety session that related to the formulation of ketamine and the fact that sometimes you can have side effects that are coming from the things that are in the formulation of the commercial product. So we'll talk a little bit about that in a later session, but just wanted to flag, I do have that here.

(00:00:39):

So let's turn to our afternoon session where we are going to be talking through particularly here, some of the policy and regulatory dynamics. And to kick off that first session, we have Seth Mailhot, who is a food and drug regulatory attorney at Husch and Blackwell. I know that you do not have any slides about ketamine and its use in clubs.

Seth Mailhot (00:01:05):

Yes.

Susan Winkler (00:01:05):

But the policy and regulatory is going to be just as fascinating. Please pick it up.

Seth Mailhot (00:01:11):

That's right. Thanks a lot everyone. All right. So I'm just covering the state regulation. When we talk about state regulation, it falls into three categories, two general and one specific when we're talking about ketamine and its application in the US.

(00:01:33):

First that I'll cover is the corporate practice of medicine doctrine, which has an effect on how clinics and practitioners can be organized to provide ketamine therapy, supervision of advanced practice providers in prescribing drugs, which includes controlled substances, which controls who gets to prescribe and how and what requirements that might apply to practitioners that aren't doctors or physicians. And then we're going to cover some specific regulations and guidance on ketamine that have been adopted by certain states. Some of them are advisory opinions on the scope of practice. Some of them are imposed certain training requirements and others deal with patient notice.

(00:02:32):

So generally, ketamine can be administered by practitioners who are licensed to prescribe Schedule III controlled substances within medical specialties, including anesthesiology, psychiatry, emergency medicine, primary care, and internal medicine.

(00:02:53):

As we noted during the earlier sessions, esketamine is restricted to mental healthcare, primary care, and internal medicine. So the corporate practice of medicine, the main focus is it prevents corporations from practicing medicine or employing a physician to provide professional medical services, the idea being that we don't want Amazon to suddenly open up clinics where it's going to decide, "Oh, we're going to provide medical services to people for a profit."

(00:03:33):

The idea is really it should be a practitioner that provides services so they can govern who gets services, who doesn't, how those services are compensated based on the practice of medicine and not based on commercial interests. So you're not dealing with shareholders' interests, you're dealing with the practice of medicine and a medical practitioner's interest in treating patients.

(00:04:07):

So 32 states plus the District of Columbia prohibit the corporate practice of medicine. Now there are exceptions, of course. There are the ability to organize what are called professional corporations, which provide professional services and they're owned by and large by the practitioners themselves. But they can form a corporation in order to enjoy some of the protections that are given to typical corporations, the non-practitioner corporations.

(00:04:48):

States also provide exceptions for employment of physicians by certain entities. Although the scope can vary state by state. Now, 17 states do not have a corporate practice of medicine restriction. Florida's technically one of those states that does not have a corporate practice of medicine restriction, but they have in place of that special licensure requirements that actually put a lot of burdens on corporations that are trying to practice medicine. So it's not quite the same as some of the other states. So this is not my graph. This is prepared by Permit Health, but this gives you an idea of which states provide the corporate practice of medicine restrictions, which states don't, and Florida's flagged as being different.

(00:05:49):

Now, advanced practice providers are healthcare providers who are not physicians, but they perform medical activities typically performed by a physician, and that includes nurse practitioners or physician assistants. Now in some states, these advanced practice practitioners, whether they're registered nurses

or physician's assistant, may prescribe controlled substances. The requirements vary, but to some extent, they may need to have supervision or they need to have an agreement with a provider and/or training or other restrictions might apply. Some examples are given with South Carolina, Georgia and New York requiring a written collaboration agreement between a supervising physician and the advanced practice provider.

(00:06:52):

You could also have limitations on the number of advanced practice practitioners that a particular physician can supervise. And Georgia actually limits the distance, the physical distance between the practitioner and the advanced practice provider if that physician's out of state.

(00:07:18):

So those were general. Now they apply to ketamine clinics, but they apply to every type of practice of medicine. Now, there are specific state guidance and laws and regulations that are specific to ketamine. Utah in particular has two pieces of legislation. One is a whistleblower protection statute that covers requirements on sedation levels in an outpatient setting, which implicates ketamine. It requires healthcare providers' personnel to have certain training. It does require direct supervision of the patient during the administration.

(00:08:09):

And originally, the Utah statute required generally, or it still requires generally, that there be at least one individual within the procedure room who has advanced airway training, and the knowledge and skills to recognize and treat airway complications. Now because ketamine has particular applications, Utah clarified this in a subsequent legislation where they modified it to allow an anesthesia provider who is providing ketamine for a non-anesthetic purpose to have an individual with airway training on site instead of within the procedure room. So it's specific to ketamine in this application. Arizona and Florida have different advisory opinions and rulings that apply to the use of ketamine. In Arizona, their advisory opinion relates to when registered nurses are operating within their scope of practice with respect to administering ketamine. Now it's goes specific to what specific applications of ketamine are covered within the scope of practice. And pain control, depression, sedation are within determined by the advisory opinion, but not anesthesia.

(00:09:50):

In Florida, they put in place allowances that registered nurses with advanced cardiovascular life support training could administer low doses of ketamine, provided it doesn't rise to the level of sedation or analgesia. Rulings concluded that registered nurses cannot administer ketamine if the administration will result in sedation or analgesia, in contrast to the American Nurses Association procedural sedation consensus statement, just so that you know that there's a distinction between in Florida as to what the statements are.

(00:10:35):

So Oregon similarly has some opinions, advisory opinions that they've released related to certified registered nurse anesthesias, as to when ketamine can be administered for disorders of mood, anxiety, trauma and stressors resistant to medication and psychotherapy in an outpatient clinical setting.

(00:11:06):

This assumes that the CRNAs own and manage the clinic. Now, the disorder can't be determined by the CRNA, it has to be a licensed independent healthcare practitioner that makes that determination. And then in addition, Oregon's also developed a regulation that requires specific training and supervision when administering ketamine. And the training covers both pharmacology and ethics. So until you've

reached that specific training requirement and the regulations 850, 060, 0210, if you haven't have someone that's obtained that training, you can't administer.

(00:12:03):

So I will jump forward so everyone else can speak. And if you guys have any questions, we can follow up during the round table.

Susan Winckler (00:12:12):

Great. Thanks so much, Seth. And you did lead me to my, if you can't make an attorney presentation and not cite a regulation, so I'm glad that you hit that bingo card for us. And we'll have you back for the panel at the end, but thanks for covering the broad federal landscape as well as then some of the typical requirements at the state level and then the ketamine-specific. Really appreciate that.

(00:12:38):

So we'll have Seth return to the stage after we hear one more presentation. So Dr. Day, please head to the podium. Dr. AJ Day is a clinical pharmacist who also serves on the National Community Pharmacists Association Compounding Steering Committee. And he's going to talk to us about some of the policy requirements and then how the clinical community has been reacting in the compounding of ketamine. So Dr. Day, there you go.

Dr. A.J. Day (00:13:05):

Thank you. I'm really bad about standing behind podiums. I don't like it. So they were kind enough to give me a different microphone here.

Susan Winckler (00:13:11):

[inaudible 00:13:12]...

Dr. A.J. Day (00:13:12):

Yeah, yeah. Now I just got to watch my step, right? All right. So we're going to talk a bit about some of the policy issues that the pharmacy world has to deal with. Really appreciate the presentations from earlier today throughout the morning, as well as from our lawyer friend here that talked about a lot of the different state regulations, because that's what the pharmacists have to deal with, combination of state and federal.

(00:13:35):

FDA in the introductory comments talked about the practice of medicine. And FDA's goal is not to regulate the practice of medicine. However, what FDA does regulate is the medications that can be dispensed. So while the physicians aren't necessarily prohibited from prescribing for certain therapies, it's the pharmacies that might be prohibited from dispensing or even compounding those therapies for administration to the patients, right?

(00:14:01):

So I am a former board member for the Alliance of Compounding Pharmacy. I was also on their task force that helped develop some of the best practice guidelines that we're going to talk about here. A lot of this discussion with ketamine came to a head in the compounding world with the issuance of these two public compounding risk alerts from the FDA, first in February of 2022, followed with October of 2023. The impact of these public compounding risk alerts is that the industry... And when I talk about the industry, I'm not just talking about pharmacy, I'm talking about all of the stakeholders, but

particularly in the world of pharmacy, there was a lot of confusion because compounding is in the title of this, but there's not a whole lot that is specific to compounding apart from generalities that apply to all of compounding.

(00:14:48):

So what I mean by that is that the risk alert said that ketamine is not FDA approved for the treatment of any psychiatric disorder. That is correct. Compounded drugs are not FDA approved. That's not specific to ketamine. No compounded drugs are FDA approved. The use of compounded ketamine without monitoring by healthcare provider may put patients at risk for serious adverse events and known safety concerns associated with the use of ketamine products. And they expanded on what those known safety concerns are.

(00:15:14):

What the FDA risk alerts did not state is that use of compounded ketamine is illegal or inappropriate in any way. Off-label use of ketamine is not allowed, nor did it say that patient-administered ketamine is not allowed. So the issuance of these public risk alerts without specific actions or legal or regulatory implications left a lot of questions in the minds of the physicians, the patients who are receiving it, as well as the compounding pharmacist or the general pharmacist who might be dispensing this. In that February 2022 alert, there were three citations that were listed.

(00:15:48):

One of them is the REMS for Spravato. The other one, the third one is the drug approval package for Spravato. And the second one between those two was a 1989 study that looked at administering PCP and PCP-like substances including tiletamine and ketamine subcutaneously to rats. So again, looking at the industry response to these compounded risk alerts, they're saying, "What's this about? Why are we hearing about this? Does this apply to us?" Because the conclusion of the study that they've cited here was that ketamine treatment at 40 milligrams per kilogram was where they saw some of the cerebral cortical pathological changes, which equates to about a 3, 000 milligram dose for a 75 kilo human. And that's what the pharmacists are looking at. They're saying, "Is this going to impact what I'm trying to do on a day-to-day basis? Because it doesn't seem to correlate to what we're talking about. And even the intent of the study doesn't seem to be corrolatory to what we're dealing with."

(00:16:48):

And then the other aspect is how much of this is specific to compounded ketamine? Because if you just Google ketamine, and I'm from Houston, so if you just Google ketamine, this is your research results page. This is what pops up. And these are really largely about IV ketamine infusion, which is consistent with the morning presentations that we heard from. You see, some of these are private clinics, some of these are institutional facilities, right? So is the issue about compounded ketamine or is it about ketamine in general? The title of the risk alerts from the FDA's Compounded Risk Alerts.

(00:17:20):

So these are the questions that came up from APC members, NCPA members, from some of my own clients that we consult with. So then they fell back to, "Well, we've been working with ketamine in a variety of cases for over 30 years. We've been using it in combination therapies for neuropathic pain. We've been utilizing it for nasal sprays, for things like allodynia, for patients who are refractory to other types of therapy. And this really helps them going through the day. And then more recently, there's more clinical trial for at-home sublingual ketamine use from telehealth providers." This was a publication from 2022 in the Journal of Effective Disorders.

(00:18:01):

And so you see a number of clinical studies of varying strengths, the different methodological flaws in some of these studies. But this is what clinicians are utilizing to evaluate the appropriateness of ketamine for their patients. So given the risk alerts from the FDA, what do all of these national associations and support organizations recommend in terms of how we approach ketamine in a compliant way that acknowledges the concerns of your federal and state regulators while still making sure that we're providing access to the patients who rely on this therapy?

(00:18:37):

So in April of 2024, the Alliance for Pharmacy Compounding put forth a best practices document for preparing and dispensing compounded ketamine by pharmacies. This is not about in-clinic utilization where a pharmacy is not involved. This is specific to utilization of compounded ketamine by pharmacies.

(00:18:54):

Now, this is a best practices document, and throughout this process, there is a lot of discussion about the way that ketamine is determined to be appropriate for different patient situations. And because there are different indications that might be utilized, it could be utilized as a combination product in a topical cream. It could be utilized monotherapy in a lozenge or via nasal spray or other routes of administration depending on the specific patient that we're dealing with and what comorbidities they've got, what other allergies they've got. Dr. Winkler talked a little bit about being able to have good control over the ingredients that are in your formulation. So patient sensitivities and allergies is another component that compounders have to take into consideration when developing those formulas.

(00:19:36):

So because of that, we're not looking at specific dosing guidelines. These are not clinical practice guidelines. These are best practices for general preparing operational standards of how we prepare and dispense and making sure that we're taking into account the needs and the sensitivities of the regulatory apparatus. You can download a copy or view a copy of that best practice guidelines from the link that's provided on the bottom of that slide here.

(00:20:03):

So there are some key areas that this best practice guidance touches upon, the pharmacist's legal obligations. Now, notably absent from this discussion today is the DEA's perspective, which is it plays a huge role in anything involving ketamine. And this is a key part of the oversight for pharmacies because if the volume of ketamine that's being utilized and dispensed from a given pharmacy starts increasing, the first people that are going to have their eyes on that are going to be the DEA.

(00:20:31):

So utilization of ketamine really takes into account a lot of DEA's concerns, controlled substances laws, both on the federal and state level, and corresponding responsibility for the pharmacist. While the physician may have made determinations of what's appropriate for their patient, the pharmacist still has a corresponding liability, and so they need to make sure that they're doing their due diligence and documenting everything. So we get into some detail in this best practice document about what that means, and particularly addressing some diversion controls, making sure that we're checking the PDMP for every fill of the prescription for new patients or for refills for existing patients, verifying a valid patient prescriber relationship. And this can be a unique challenge, particularly in the post COVID era because of the utilization of telehealth and prescribing ketamine, compounded ketamine.

(00:21:18):

Considers of prescriber and scope of practice. Does the scope of practice for that prescriber appropriate for what they're determining the utilization is going to be for our patient? If I've got a podiatrist who's

utilizing a compound of ketamine, well, is that for a neuropathic issue or is it for treatment resistant depression? And so what is the pharmacist doing to be able to validate what the utilization is and that there is an appropriate scope of practice for the intended use?

(00:21:42):

Caution with high volumes. We just talked about some of that with the DEA. Multiple refills, early refill requests, watching for patterns. What do we see from an individual patient or from patients that are getting prescriptions from a physician or a group of physicians, that particular practice? These are all considerations that the pharmacists must be very aware of. Monitoring pharmacy inventory, because diversion is just not on the patient side, but what's happening within our own staff, right? Making sure that that raw ketamine powder, ketamine hydrochloride, USP, that the pharmacy is utilizing to make those compounds is not being diverted. Prompt and thorough investigations for any concerns and reporting any of the results or even the initiation of some of those investigations to the relevant regulatory bodies, boards of pharmacy or FDA. Now, there is not mandatory adverse event reporting to the FDA, but as it relates to the DEA, we need to make sure that there is a really robust chain of communication between any of these issues and that agency.

(00:22:36):

Dosing limits. This best practice guidance did not get into specific dosing limits or even starting doses because of the variety of types of conditions that ketamine might be prescribed for. So rather what the best practice document does is refer you to clinical literature and other best practice guidelines. As we heard this morning, you don't have a whole lot of robust clinical trial data to establish firm, set starting doses and escalation protocols. So making sure that the pharmacist is working with the physician to evaluate the needs of that patient and referring to published literature, whatever that literature might be for that given indication.

(00:23:17):

Using professional judgment, clinical literature, communicating the prescriber, this is all part of best practices for the practice of pharmacy for compounding generally, but we really made it very specific here in this best practice ketamine document and dosage forms. Most of the presentations that you heard this morning, the route of administration has been IV. There was some discussion over IM dosing, and there's been some discussion about lozenges, oral utilization.

(00:23:44):

Some of the most common requests that we see for compounded dosage forms are nasal and for lozenges. With lozenges, the principle is not to get oral absorption, but for primarily buccal absorption. So there are other ways to get it into the bloodstream that can be beneficial to the patient. And part of when they're utilizing, prescribing, dispensing these medications, making sure that we're thinking of the other potential... I thought that was a pointer, sorry about that. When they're using or they're dispensing these medications, making sure that there is a consideration for how other household members might have access to that medication. So it's child-resistant containers, considerations for household pets. How are we flavoring some of these medications if it is in a lozenge form, things like that.

(00:24:29):

And then of course, documentation being a key part. How do you know that you're compliant with all of the regulatory expectations and best practices if there's no documentation, if there's no paper trail? So we really emphasize a lot of the documentation that's needed, especially when we're talking about dose escalations for patients and making sure that we are observing for signs of abuse or for diversion.

(00:24:50):

And patient education is the cornerstone of all of this. What kind of education has the patient been getting from the physician, from the treating practitioner as well as from the pharmacist to make sure that the key prescient points are emphasized for how to safely utilize the medication, both in written and verbal... I keep doing that, not a laser pointer... both in written and verbal communication, supplying written educational materials to reinforce key points and give patients a point of reference monitoring for any signs of abuse.

(00:25:21):

That's where we recommend not necessarily dispensing in multi-months' supply so that you have another opportunity to evaluate the patient for both compliance signs of diversion and clinical outcomes. What are the safety concerns? What are the efficacy concerns? Educating the patients on the side effects and emphasizing restrictions on things like driving combination with other medications, including alcohol.

(00:25:44):

And then, as I mentioned, since DEA is not here, I didn't highlight these two specific areas, but constructive transfer discussions. There are situations where pharmacies have gotten cited by the DEA because they're providing that medication for in-office administration. So they provide it directly to the practitioner's facility. And the DEA says, "You can't do that. You need to send it directly to the patient." And so then there's a consideration about, "Well, what's the likelihood or the risk of diversion if we're providing directly to the patient?" So constructive transfer is a consideration, which is addressed in the best practice guidelines.

(00:26:16):

And another component is 503Bs. So what we typically think about with compounding is through 503A, which is traditional prescription-based compounding, based off of individual identified needs. 503B is a different scale of compounding. They're not having direct oversight primarily from your board of pharmacy. Their primary oversight mechanism is through the FDA, and they don't have to make things after receiving a prescription. So they can make manufacturing scale of the ketamine or other products and then distribute that to your clinics. For in-clinic administration, there is a new guidance for industry from the FDA that says that a 503B can furnish their product to a state-licensed pharmacy or federal facility. So doesn't mean it has to be a compounding pharmacy. What that guidance document would do is essentially enable a 503B outsourcing facility to furnish that medication to any state-licensed pharmacy. So they could be acquiring and dispensing ketamine prescriptions from a chain grocery store, if you need.

(00:27:20):

So that is outside the scope of traditional pharmacy practice, but 503B is another segment of the industry that needs to be discussed. So other common discussions that come up, and this has come up in regulatory action with the DEA and state boards of pharmacies related to compounding pharmacies and ketamine is why aren't you dispensing esketamine instead of that compounded ketamine, even if it's a compounded ketamine nasal spray?

(00:27:45):

Well, ketamine is not the same as esketamine. They have different FDA approvals. They're distinct molecules. So I think that's a key part of that. And while esketamine may be appropriate for many patients, doesn't mean it's the right therapy for the patient that the ketamine is being prescribed for. So

making sure that there is appropriate oversight from the treating physicians and that the patient has access to the right therapy, I think is a key component of the approach of the compounding pharmacists.

(00:28:10):

And then of course, operational protocols. Pharmacies, you have to have robust operational SOPs for making sure that there's not diversion and that the preparations are made in a compliant and quality manner, and physicians have treatment protocols for the patients. But some physicians, some of the clients that we've been working with, they have the patient and the pharmacy all sign off on the treatment protocol and the patient gets a copy of it, the pharmacist retains a copy of it, and the physician's file retains a copy of it as well.

(00:28:34):

So these are other mechanisms of assuring that the risks and benefits and the frequently asked questions from patients are all retained so that there's multiple points of access to really critical information.

(00:28:45):

Thank you for the opportunity to speak here. I know we've got the panel discussion coming up.

Susan Winckler (00:28:49):

We do. So thank you, Dr. Day.

(00:28:55):

We will turn to the panel. So if we'll have folks come up, and again, you can adjust the seats. They're a little bit of a lineup, and well, feel free to move things around. So in addition to hearing, having a return from our presenters who just presented, we have a few additional panelists here in the room and virtually. So joining us on the panel is Dr. Jenni Wai who is chief pharmacist with the Ohio Board of Pharmacy, Dr. Lisa Robin, chief advocacy officer at the Federation of State Medical Boards. And then virtually, we have Dr. Gail Bormel who is with US FDA, and particularly FDA's Center for Drug Evaluation and Research, and the Office of Compounding Quality and Compliance, which she leads. And finally, Dr. Lisa Harding, who is an assistant clinical professor in the Department of Psychiatry at Yale.

(00:29:52):

So welcome to everyone. This is our panel where we have double Lisas and virtual and a lot of things going on here. So we are going to start the conversation. I first want to first open it up to our new entrants to the stage. Was there anything that you wanted to underscore or ask a question of Seth and AJ before we move into the conversation? I'm not... Yeah, go ahead, Lisa.

Lisa Robin (00:30:18):

I do have a question for Seth. So I enjoyed your presentation and I love anything regulatory.

Susan Winckler (00:30:28):

Only the best of us do, Lisa.

Lisa Robin (00:30:31):

But I am finding an increasing number of states that have either position statements or are in the process of rulemaking and some that, including Georgia and Louisiana and others that seem to be pretty restrictive in some areas. And I think this is a trend probably we're going to see as well as with the

corporate practice of medicine that I know that that's of interest to a lot of our boards and looking at who's making the clinical decisions in these clinics and whatnot. So that's it.

Seth Mailhot (00:31:16):

So I guess, what was the question?

Lisa Robin (00:31:19):

Well, do you agree that there's going to be a lot more regulation?

Seth Mailhot (00:31:23):

Oh, yes. Clearly the focus is going to be on greater accountability for practitioners and further limitations on the practice, because I think you do see there are the potential for bad actors to step in and take advantage of the lax enforcement. So we see that that's a very helpful approach to make sure that only appropriate treatment is administered.

Susan Winckler (00:32:05):

Yeah. And you said the corporate practice of medicine, both in your slide, but I think Dr. Harding, I think I've seen some things you've written related to that corporate practice of medicine. Do you want to chime in here?

Dr. Lisa Harding (00:32:17):

Yes. First of all, thank you so much for having me, and Seth and AJ, amazing presentations. As the lone psychiatrist on a board talking about regulation, I'd like to reframe this. I think when we hear the word regulation, feathers tend to get hackled and people think that the rule-makers are coming in, and they tend to equate regulation with restriction. I would like to reframe your thought on this and to make regulation synonymous with safety. I would like you for my analogy to think of ketamine as an airplane, and the regulation is the FAA. I don't know how many of you know this, but the number of rotations the planes on an airplane makes when it has to land and take off is actually counted, and the FAA has very strict rules. And I make that analogy because I don't think anybody in this room virtually, present, would jump in an airplane if the FAA said, "Man, we don't know too much, but go fly the plane and then we'll see if you land safely."

(00:33:27):

And so I'd like us to reframe the thinking of regulation in that way. Growing up, our parents teach us, there's three things you don't talk about in mixed company: religion, politics, and the third being money. So now that we're all friends, we get to talk about money. I think very many things about the space of ketamine in psychiatry. There's the proliferation of these ketamine clinics makes me ask very many questions, and it comes to when I talk about the corporate practice of medicine in my article on the regulation of ketamine. I think of access to care. It is not covered by any insurance company, and I wonder why. If you read the STAR*D clinical trial, it tells us that two thirds of patients actually responded to the treatments that we have. So we're talking about this one third of patients, and the dearth actually lies in the number of properly trained people in mental health to treat the two thirds of these patients.

(00:34:31):

So where is the proliferation of the sertraline clinic, the fluoxetine clinic, and the proliferation of the ECT clinics? And also, how it is that practitioners that are not psychiatrists are fighting with me to treat my

psychiatric patients, but not also fighting me to give psychiatric patients the basic care that they actually need that's covered by insurance. And so I think the question comes down to money, and we often don't have that conversation because it's so icky. And access to care as defined by the Affordable Care Act tells us that we have to provide the same standard of care across the board. And so it isn't that because a kind of cure is inaccessible, we then provide a different kind of cure because that's easier for us to figure out, but the evidence doesn't back it up. I think the question I have for AJ, and bleeds into this access to care, is why do compounding pharmacies looking for ketamine for psychiatric indications exist?

(00:35:41):

National distributors have racemic ketamine. It's very cheap to manufacture. And the way I look at it, it bothers me because when individuals go to these distributors and say, "Hey, can I buy ketamine from you to provide psychiatric patients care?" And they get the answer no because they're not practicing to the top of their license, it's outside of their scope of practice. They can't prove collaboration. To circumvent the process, they turn to these compounding pharmacies. And the stop gap is never, "Hey, how do I go back and actually make myself compliant to get ketamine through this normal distribution chain?" But it is, "How do I then figure out how to then circumvent the process?" The last thing I'll say before I let AJ answer my question has to do with the regulation, I'd like to have everyone stop for a second and think about advocacy.

(00:36:43):

Advocacy does not equal action. Advocacy means giving an argument and listening to the adults in the room for what they say. I have so many patients that I don't know what post-pandemic did to medicine, but especially in psychiatry, I think when people advocate for themselves, they think that they can get what they want because they've sent away. My 10-year-old will be like, "Can I stay up until midnight and play Fortnite?" But as the adult, I have to say, "No, because I know what's best for your brain development." And I think that's where I see regulation in this. People can want a lot of things that they want, but if the evidence doesn't support it, it's the place for the adults in the room to pause for a cause.

Susan Winckler (00:37:28):

Yeah. Dr. Harding, thank you, and for bringing us to the component of this tension of not having the product approved for uses that it's being used for. How do we change that dynamic when, as you note, and we saw it in the VA slide of where we have the ketamine clinics and where we don't, and where the patients are not being served. But AJ, do you want to respond to the... What gap is it that the compounding pharmacies are filling?

Dr. A.J. Day (00:38:02):

A couple of comments there. I think what you said there, Dr. Harding, was wonderful. As you listened to the morning session and you heard a lot of the different prescribers talk about the utilization of ketamine and where there are gaps in published literature, what was presented in the VA slides this morning in terms of how ketamine delivery is provided, more than half of what was provided is referral out into a community setting. More than half of what they were identifying through their tracking at the VA system was a referral out to a community setting. That doesn't mean compounding, and they're still likely focused on IV, but the practitioners who are writing for compounded ketamine, for ketamine at-home use, for ketamine-assisted therapy, those are physicians with valid medical licenses. Those are physicians who have been trained, who have gone through residencies, maybe fellowships, maybe other levels of specialization, and made a determination of what they're prescribing for their physicians.

(00:39:04):

The pharmacies have some ability to verify and to question and to validate, like we just discussed in my slides with the best practices document. But because something is being prescribed off-label, if it's still legal, if it's still meeting all of the regulatory requirements, there's not a whole lot of impetus for the pharmacist, barring other identified risk factors for the patient or unusual patterns identified with the prescribing physician, from declining to fill that prescription. And that is part of a patient access issue. So I know your question was directed towards the compounding pharmacist, but keep in mind that all of this is in response to a valid prescription written by a treating physician. So the question is more about the determination from the physician's side than the compounding pharmacy.

Susan Winckler (00:39:56):

Well, and then it's a space where we don't have an approved product for use. So I think Dr. Harding, part of what I heard you advocating for, but I want to gut check, and I think this is part of what folks want to get to is, is there a way to structure and navigate the regulatory process to get to approved products that then may help with some of the, right now you don't have the coverage for the products because they aren't approved?

Dr. Lisa Harding (00:40:33):

Absolutely. I think the question is safety, and I think that's where the regulation lies, and regulation is there to keep patients safe. I think even though the phrase that we say, "Do no harm," is not explicitly written in the Hippocratic Oath, I don't think anybody wants to do something that would be harmful. But I also doing nothing is okay in the space where not enough evidence exists to proceed at the rates that we're proceeding at. So yes, thank you. Safety is my concern.

Susan Winckler (00:41:06):

And so I think it is that navigating and bridging in between. But I want to turn, Dr. Bormel, you think about pharmacy compounding a lot from a regulator perspective. What do you want to make sure that we contribute to the conversation? And then I want to turn to you, Dr. Wei, for how the Ohio State Board of Pharmacy is thinking about this. But Gail, would you go first?

Dr. Gail Bormel (00:41:31):

Oh, sure. Thank you, Susan, and thank you for inviting me on the panel. So yes, I do think about compounding a lot. And just to dovetail on what Dr. Harding said, we at FDA are tasked with in the compounding sector regulating and compounding by state licensed pharmacies and also compounding by outsourcing facilities. And so in that context, we have issued those compounding risk alerts that AJ Day described accurately. And I wanted to sort of take breath and explain that when we issue these compounding risk alerts, this is an initiative to provide information back to providers, the public, and stakeholders in general about what we're seeing at the FDA. And so compounding of ketamine is legal if it's done in accordance with the applicable sections of the act. But what happened was we started seeing, about five, six years ago, a lot of adverse events reported to us about compounded ketamine.

(00:42:47):

Whether it was for nasal inhalation or for oral dosage forms of ketamine, we just started seeing that and we wanted to alert the public that ketamine is approved. Well, actually ketamine is approved as an injection. First of all, ketamine hydrochloride. And there is esketamine that's approved in Spravato. But compounding drugs aren't approved. And just let's take a step and look at what we're seeing, and they were adverse events. And so we were trying to alert the public what we're seeing, in the name of making providers, pharmacists, physicians, the public aware of the importance of using the ketamine in

a safe manner. And I think that was the message that we were trying to get out with both publications of the compounding risk alerts, the transparency in information about what the FDA is saying.

(00:43:47):

And it's particularly important because adverse event reporting is not required in the law for state-licensed pharmacies, but it is required for the outsourcing facilities. So we tend to receive adverse event reports from state-licensed pharmacies or about state-licensed pharmacies, because usually it's patients who are reporting, or caregivers. Then we might see a signal of something happening. And that's why it's so important to provide this information to the public so they can be aware of what the FDA is seeing in this area so that they can better protect their patients, better take care of their patients. And so I wanted to just clarify that about the compounding risk alerts.

Susan Winckler (00:44:35):

Yeah. If we step back and just say, okay, the agency's hearing these things, they put out the communication, which had to clarify that they was for compounded products and not for approved products. And then the professional organizations respond with information that helps compounders do a better job, I think the math works, that the agency says, "We shared this safety information to the community," who then responded and said, "And here are things if you're working with ketamine that you need to think about." Is that fair?

Dr. A.J. Day (00:45:14):

Yes.

Susan Winckler (00:45:14):

Okay. So Dr. Wei, you regulate pharmacies. And what we heard from Seth, some of the components that are going on with the medical boards, how are pharmacy boards thinking about this space? And we know pharmacists are helping to fill the gap because we don't yet have an approved product in this space. How are pharmacy boards thinking about it?

Dr. Jenny Wei (00:45:40):

Great, and thank you for the opportunity to talk about ketamine use here. In our state we do regulate not just pharmacy, but also when it comes to prescriber compounding, so we do regulate in certain clinics when there needs to be ketamine compounded. And so I do see what is actually going on out there. So the situation is that what we have seen, and we've been trying to gather preliminary data, even from our prescription monitoring program or PMP. Because ketamine is a controlled substance, and whenever there's dispensing or sales, they need to be reported to the PMP. And so we've been gathering some initial data on this and we have definitely seen a decrease when it comes to wholesale sales and an increase in what we call patient-specific dispensing. So we have seen a shift where wholesalers are selling to prescriber clinics, and have seen more of a shift that compounding pharmacies are stepping in to fill that need.

(00:46:43):

Not to say that compounding pharmacy doesn't do a good job. They do, and there's a need for ketamine. There's only commercially available in solutions and the nasal spray. Any other form, whether it's lozenges, patches, is not commercially available, and that's where a compound pharmacy can step in when there is a need for different formulations or even different strength. But what we have seen is that the prescribers are going to issue prescription for the compound pharmacy to dispense. And I've

seen it from lozenges to transdermal to some spray to patient-specific, and the patient has this medication on hand. And now it is not being administered such as in an IV ketamine clinic. When the [inaudible 00:47:28] with IV ketamine, it's usually being administered at a monitor clinic. Now what we're seeing is that patient have access to this medication at home. And with the proliferation of telehealth medicine, these type of therapy and treatment sessions are now done by telehealth.

(00:47:46):

And some of them do a good job, but some of them may be lacking. But that's where I think the inconsistency or the need for standardization and that standard of care practice, incorporating telehealth medicine, incorporating there's some patients that may benefit from home administration, but what is that standard and where do we set that? Because after all, like Dr. Hunter said, it is about the patient's safety. So we have concerns when we're starting to see a shift in standard of care, a shift in supervision. Are the patients being counseled appropriately? The patient who's supposed to have a support at home, they're not a healthcare professional. They may not be a healthcare professional. What exactly are we counseling the patient and their support? When do they need a contact when there's emergencies and things like that? So we're starting to see more so with patient safety and that shift from the field.

(00:48:33):

And I can tell you that this is like the weight-loss clinic. This is like the med spa and the Botox that is popping up everywhere with ketamine clinic. I've had anesthesiologists, because we do license. I have anesthesiologists and CRNAs wanting to get licensed and establishing an IV clinic inside a gym, or in their own little mobile clinic. Let us do a little spa party. I recently just got a concern where they're doing a psychedelic event where they do use other therapies such as yoga or other methods, but then they incorporate, "Hey, if anybody that wants an IV ketamine infusion, we have this availability. But how's the patient supposed to know if it's safe and who's doing it? What is the monitoring? So those are things that we're seeing.

Susan Winckler (00:49:17):

Right, which is the side then to Dr. Harding's admonition that we think about the regulation as enabling, but it's enabling I think perhaps with constraints that are helpful for patient safety. And Lisa, I saw your hand go up.

Dr. Lisa Harding (00:49:33):

I did.

Susan Winckler (00:49:34):

Yes, go ahead.

Dr. Lisa Harding (00:49:36):

I think also we have to bring it back to what the indication is. Ketamine is not a panacea in psychiatry. A patient has to have, regardless whether they're lying in a bed or in a physician's office, they have to have first the appropriate psychiatric indication for the treatment. And I think that component is often lost in this online conversation. When patients don't respond to a medication, there's never a conversation or the conversation is always lacking. "Well, what is the diagnosis of the patient? Are we throwing spaghetti at a wall and seeing what sticks and this is the next treatment in that line? Or does that person have an appropriate psychiatric provider to say that, hey, this is the next treatment in line, given all of

the tools in our toolbox." It's a very interesting thing to think about, a patient in psychiatry who's treatment-resistant.

(00:50:34):

By the time you need tertiary care across any specialty in medicine, you should have a collaborative team. You should have a psychiatrist, a psychotherapist, your family support systems. And for me, the regulation, and I talk about this in my articles, I don't understand how one form of treatment that is completely FDA-approved for depression and major depressive disorder symptoms in the context of patients who are suicidal has a very strict REMS attached to it. The patient has to be monitored for two hours and cleared by a healthcare professional to go home. And this other one, the person can sit at home with a video, with a person monitoring them. The biggest risk to any psychiatric patient is completed suicide. And I don't know how many of you read the nature paper that Dr. [inaudible 00:51:26] had up on the screen from the phase-two clinical trial that was on there. It's a very interesting read.

(00:51:32):

I think models of care must keep patients safe, but those patients must first meet the appropriate diagnostic threshold. And the people that do that are psychiatrists. And I really would like someone to help me understand why is it all these other non-psychiatrists are clamoring to treat psychiatric patients, but aren't clamoring to also take insurance and make these treatments available to everybody, and also using the routes of administration that have the most efficacy and safety attached to them?

Susan Winckler (00:52:06):

There's obviously the broader components and part of why this is emerging, and we have to better understand where it fits in the healthcare system, which is not the responsibility of state medical boards. But Robin, I do have a question for you. Are the state licensing boards, and maybe this is a combination question for you and for Jenny. This seems like a space, and Dr. Harding just teed it up, where it would be helpful for the medical and the pharmacy boards to communicate. Is that happening? How do we make that happen?

Lisa Robin (00:52:45):

I do think that's happening. I think you are seeing some joint statements between pharmacy, nursing, and medicine. I had a regulator, I mentioned the other day, and for the medical boards, it is all about patient safety. They're worried about this. Their quote was from a presentation the other day. The proliferation of these business models have just outpaced what the regulatory system can support and to whether it's oversight and who is overseeing, they've gone through this during the opioid crisis as pain clinics, or pill mills as they were referred to then, were just proliferating particularly in certain areas of the country until they had to have some requirements as far as the specialty of the physician that would be involved with that, and some of these just protections. Or in outpatient surgery centers for where anesthesia is used. There's all sorts of very strict requirements around those, and this is just a space that there's just not.

(00:54:00):

And then telemedicine adds a whole nother level. And since COVID, we saw such a proliferation, and as was mentioned earlier, when all of the requirements were waived, licensing requirements for telemedicine practice, we saw, as the physician that was mentioned earlier, with thousands and thousands of prescriptions for ketamine going all over the country. So I do think that it is clearly much

more effective if pharmacy, nursing, and medicine work together, and I think you're seeing that in a number of states.

Susan Winckler (00:54:40):

So Jenny, if you want to add to that, and Seth, I don't know if you have an observation about what you're seeing from the state regulation, but let's Jenny and then Seth.

Dr. Jenny Wei (00:54:47):

Yeah, from the national level, and as Lisa said too, that sister agencies are working together. I know that in my state, we are working very closely with the medical board for both concerns. They handle the standard of care and we handle about drug security and also about the compound product. And again, like I said, it's not about so much compound because in our state we have jurisdiction over compounding. So even the prescriber who is making the ketamine infusion, it could be doing it inappropriately. So there is discussion and it is a certain increased trend.

Susan Winckler (00:55:20):

And I think what every one of you has said is that additional information about what works and how to do this well would be helpful, from what the compounders were doing to try and create that parameter to FDA sharing information. But Seth, any thoughts on the state piece? You got to hold your mic up though, or it won't catch it.

Seth Mailhot (00:55:42):

Yeah. No, thanks. But no, we are also seeing focus on telemedicine as a concern and a potential source of increased regulation. And to Dr. Harding's point, I think the advisory opinions are clearly the practitioners reaching out to the respective agencies to get that guidance and that help when it isn't currently there in actual regulations or in the laws, so they want to make sure that they are working within their scope of their practice.

Dr. A.J. Day (00:56:25):

And that scope of practice point was something that was also in the APC best practice document that was in the slides. So to Dr. Harding's concerns, and I think all of our thought processes here is what are we doing consistently throughout all of our organizations through all of our reach to build a system that tries to ensure appropriateness of the therapy for the given patient and the expertise level within the prescribing team? This doesn't often fall to an individual level. There are institutions that are involved. You look at those Google results that I showed. Are all of those meeting all of the board certifications and the specialties? I don't know. But none of those involved anything compounded. Those were all IV ketamine clinics. So whether it's compounded or not compounded, and then, again, ketamine is utilized for a lot of different things.

(00:57:20):

The psychiatric applications are one component of that. We heard a lot this morning about applications in pain methodologies. I was at a conference two weeks ago, and three different veterinary teaching hospitals were talking about the use of oral and mucosal ketamine in their oncology canine patients. So any regulatory implications that we're talking about would impact all of that type of utilization as well. And of course, we think back to the abuse and the nightclub utilization starting off with diversion of the veterinary product. This is all linked. So how do we build systems that allow patients to have access

where appropriate, yet also put sufficient guardrails to make sure that we're not having increased risks without warranted?

Susan Winckler (00:58:05):

I was about to go to a data question and then I was reminded, Dr. Wei, you mentioned the data in the prescription monitoring programs. Is that a data source that we should be thinking more about, as we heard earlier today from Dr. [inaudible 00:58:23] about watching trends. Give us 15 seconds on a prescription monitoring program, and then any thoughts on how that might be helpful on illuminating at least the current use of ketamine.

Dr. Jenny Wei (00:58:37):

I think that it is a starting point. It is certainly limited. For example, if a provider is administering that ketamine to the patient, it is not going to be on the PMP. It is only during the dispensing or wholesale sale. Now, can we see who are buying? Are they overprescribing? Are they buying a certain amount? Are certain forms questionable? We've had done other data sources before and it's like, "Hey, this is interesting. Why is veterinarian buying bulk APIs of ketamine?" It's like, "Oh, what are they actually making?" And they're not a veterinarian pharmacy. They're actually a veterinarian. And maybe there is a reason for that, but that just is a starting point of asking the valid questions like this. And we have seen the trend of out-of-state pharmacies. In 2022 and 2023, out-of-state pharmacy is implying a tenfold increase of ketamine coming into our state versus in-state. So you're thinking about compounding pharmacy.

(00:59:42):

Again, sorry, I'm not actually compounding. I'm just saying, "Hey, where there is a need," and I'm seeing this with whether it's ketamine or whether it's peptide combined, there is a need out there, but we're starting to see a shift. And when you're talking about out-of-state, whether it's telemedicine or pharmacy supplying it to your state, now we have to work with other states. So forums like this where we're bringing the attention of the appropriate use, what are the issues, is a starting point to make sure that, are we looking at the same standard of care? What can we do to provide that guidance, whether it's pharmacy, prescriber, even ultimately to our patient? Sorry.

Session 5: Online Promotion and Access to Ketamine

Presentations:
Michael DiStefano, PhD, MBE, Colorado University Anschutz, Skaggs School of Pharmacy and Pharmaceutical Sciences
Boris Heifets, MD, PhD, Stanford University School of Medicine
Panel Discussion:
Ilisa Bernstein, PharmD, JD Bernstein Rx Solutions
Richard Quaresima, Federal Trade Commission

Susan Winckler (01:00:20):

Well, Jenny, that was a fabulous last word. We could have this panel continue for another hour, but we have another panel coming on stage right now, so let's thank this group for an illuminating discussion. Thank you, Dr. Harding. Thank you, Dr. Bormell. So we are turning now to our session... Actually, we got a bit of a preview because we just started talking about cross-state. I was going to say cross-border, but I meant across state lines and the broader pieces as it relates to online promotion and accessing ketamine. So for this session, our first two presenters are remote, but our reactor panelists will be here

in the room. I want to make sure that Dr. Michael DiStefano is online and ready to go. I think, Dr. DiStefano, you're joining us from Europe, so thank you for taking time out of your vacation to join us in your day job. When you're in the States, you are at the Center for Pharmaceutical Outcomes Research in the Department of Clinical Pharmacy at the University of Colorado Anschutz Medical Center. So Dr. DiStefano, there you go. Take it away.

Dr. Michael DiStefano (01:01:37):

Today I'm presenting some findings from a collaborative project. It was led by Tom Moore and I. Matt Crane was an excellent student researcher with our group at Johns Hopkins, and he was the first author on this work. While this work was conducted while I was a faculty member at Hopkins, I am now an assistant professor at the University of Colorado, as just noted. Just a quick disclosure. Matt Crane currently does some work for the FDA, so I'm just noting here that the views discussed today are not the views of the FDA, HHS, or the US government. I also want to note that I have withheld or redacted the names of clinics from whose websites I will be sharing direct quotes or images. Because this analysis was cross-sectional and completed last year, it's possible that some of the websites have changed or been updated in that time.

(01:02:34):

Just to start out with some framing, this is an example of what an industry standard drug website should look like to fully inform consumers and patients. This is for Spravato, and it's spravato.com. Spravato is the S enantiomer of ketamine. It's a different drug from ketamine with a different regulatory environment. And just looking at this website, immediately you'll see the promotional materials at the top, which closely outline the two narrow indications for this drug, adults with treatment-resistant depression, and adults with major depressive disorder with suicidal thoughts or actions. Below that, you can see the important safety information prominently displayed on the homepage. Serious side effects are listed, including sedation and dissociation, as well as abuse and misuse. And this webpage scrolls down another four to five page links outlining a large amount of safety information. And then this is the medication guide that would be provided to all patients taking Spravato. Again, you see at the top of this first page, important safety information, including the risk of abuse or misuse, information about the REMS program, and the most concerning potential side effects, including increased risk of suicidal thoughts or actions. And so I show these just to demonstrate a contrast with the excerpts that we found in our study. So the excerpts I'll show on the following slides are from the survey we've conducted on Maryland ketamine infusion clinics. The impetus for this work was our interest in what has been referred to as a regulatory loophole in the FDA's oversight of prescription drug consumer advertising. So, the FDA oversees consumer ads by manufacturers, packers, and distributors, but the modern marketplace includes a growing number of entities that don't seem to meet these definitions, such as wellness clinics, med spas, and telehealth services that also advertise and sell prescription drugs. A few of us at Johns Hopkins had a passive interest in these clinics, and after a few innocent Google searches led to our social media platforms being overwhelmed with ads.

(01:04:46):

We took a more formal research interest. So, for this study, we collected information from six national databases of ketamine clinics and then enhanced our search using a geolocated Google search in Maryland. This yielded 17 unique websites for ketamine infusion clinics, and that corresponded to 26 physical locations in Maryland as of March 2023. We did not examine telehealth services that provide ketamine for at-home use only. We just looked at these brick and mortar clinics that had online websites. So, this slide shows some summary statistics from the study. The most advertised service was ketamine infusions followed by ketamine assisted psychotherapy.

(01:05:29):

Two clinics offered an oral formulation of ketamine, and one offered intranasal ketamine, which was distinct from esketamine or Spravato. These oral and intranasal formulations of ketamine are not FDA approved, and the FDA has actually issued warnings about their use in the recent past. While not all clinics disclose costs on their websites, these services can be expensive, and we saw costs per infusion reaching as high as $2,500 for certain conditions, but usually the per infusion cost is more like $450 and $500. Clinics will often promote multiple, perhaps even six infusions as being the most effective. Then there's often these initial consultations as well, and they're not always free and can sometimes themselves cost several hundred dollars.

(01:06:22):

So, on this slide are some of the more surprising claims we came across while analyzing the websites. At the top of the slide, you can see one website claiming a success rate of over 90% with the use of ketamine for several different conditions, including Lyme disease. It's not uncommon to see percentages on these websites assuring patients that their chances of remission or cure are very high. In the middle, you can see an example of some of the many conditions that ketamine has purportedly effective in treating, alcohol abuse, pain, anxiety, even asthma.

(01:06:53):

At the bottom of the slide, you can see an example of how websites minimize possible side effects. Instead of disclosing the most serious and common side effects, the web page assures patients they will likely not feel any side effects at all during or after treatment. On this slide, we show two examples from web pages which minimize the risk of abuse, misuse, or addiction. The example on top just states out right that ketamine is non-addictive, but this is false. Ketamine is a DEA schedule III controlled substance with moderate to low risk of psychological or physical dependence. The example on the bottom does not outright state it's non-addictive, but instead minimizes this concern, saying there's "virtually no potential for addiction or abuse".

(01:07:40):

On this slide is an excerpt from the best risk disclosure that we did see in our sample. This site discloses that misuse has been recorded and warns about the possibility of developing dependency, and this is close to the type of disclosure we hope to help consumers make an informed decision. This slide outlines the findings of our survey regarding addiction and risk disclosure. So, five sites minimize the risk of abuse, right? That language about virtually no potential for addiction. Three sites outright claim that ketamine is non-addictive, which is false, and seven sites did not disclose any risks of adverse effects or addiction or misuse. We also wanted to focus on the use of regulatory language on these websites.

(01:08:27):

So, on the left side here, you can see one website claims that ketamine is approved by the FDA to treat depression, which is false, right? It's approved as an anesthetic. It's not approved to treat any mental health condition. On the right side, at the top, you can see the website introduced Spravato by saying it is FDA approved, and then, without other clarification, they go on to discuss the benefits of other forms of ketamine, claiming immediate effects of reduced depression, of suicidal thoughts. It's possible that consumer reading this advertisement could reasonably be misled to believe that the contents of the entire paragraph are endorsed by the FDA. At the bottom, you can see another typical paragraph provided on many of these websites.

(01:09:08):

Ketamine is introduced as an anesthetic approved by the FDA. They say that it's used in emergency settings for both adults and children. The WHO endorses this medication because of how safe it is, right? Yale and the NIH are referenced as having referred to ketamine applications in mood disorders and chronic pain. So, what's missing on this web page is that the advertised use of ketamine in these settings is off label, and there is not necessarily high quality clinical trial evidence to support every one of the reported safe and effective uses of this drug. So, this was a summary of finding regarding any regulatory language we found on the websites. So, one site stated that the FDA had approved ketamine as a treatment for depression, which is false.

(01:10:02):

Ten sites did not disclose that ketamine use for mental health conditions is not approved by the FDA and is used off label instead. Finally, all three sites that offer unapproved oral or intranasal forms of ketamine did not disclose this unapproved nature. So, I'll close on just a few simple takeaways from the survey. So, for one, Maryland consumers and patients are not consistently being provided important material facts from these advertisements that are relevant to the decision to pursue ketamine treatment, and beyond this, the information that is provided can range from being false to misleading or deceptive.

(01:10:44):

While our study looked at Maryland clinics only, our preparatory work to aggregate several national databases of these ketamine clinics does suggest that there are at least 800 such businesses nationwide, and possibly more than 1,000 given that when we supplemented our search with Google searches, we found additional sites. That's all for now. Thank you. I look forward to your questions. This is the paper that you can look to for more detail.

Susan Winckler (01:11:19):

Thank you so much, Dr. DiStefano, and we'll have you back to the virtual stage after one more presentation. So, we'll see you in 10 minutes. Our second presenter of this session is Dr. Heifets, who is Associate Professor in the Department of Anesthesiology, Perioperative and Pain Medicine and Department of Psychiatry and Behavioral Sciences at Stanford University. Dr. Heifets, thank you for joining us. I'm pretty sure that I didn't have your title quite right there, but I am hoping we have your affiliation right, because we got that wrong earlier today with someone else. So, Dr. Heifets, correct anything I've said that's wrong.

Dr. Boris Heifets (01:11:56):

It's close enough.

Susan Winckler (01:11:58):

All right.

Dr. Boris Heifets (01:11:58):

Thanks. I appreciate it, and it's a pleasure to be here. Just out of curiosity, is it backwards? Is my background backwards? I don't know if that's distracting.

Susan Winckler (01:12:14):

It is, but that's okay. We know where you are.

Dr. Eric Heifets (01:12:17):

You know where I am. Wonderful. All right. So, this is a little bit different than, I think, some of the things we've heard about, but I think, hopefully, you'll find relevance to the question at hand. How should we think about off-label use of ketamine? I'm going to talk about a few projects that we've done in my research group. Again, I'm an anesthesiologist. That's my day job. I also do clinical trials with ketamine. A couple important disclosures is I do work with Osmind Mental Health and Journey Clinical. Osmind Mental Health is an electronic health records company that does specialize in ketamine clinics. Journey Clinical connects clinicians to therapists to provide access to patients seeking ketamine assisted psychotherapy.

(01:13:13):

So, I'm on both of those advisory boards, and some of this work that I'm going to show you as a result of a collaboration with those entities. I've got 10 minutes, and I want to give some overview of what some of the data we've been collecting hints at. Again, none of these is definitive but these are the questions they think are important to ask. You've already heard a lot about these today. What do we know about the expectations about ketamine therapy that patients bring with them into treatment, and how much of that influence outcome? Number two, what do we know about the kind of information patients are getting about safety and efficacy?

(01:13:57):

I think Dr. DiStefano did a wonderful job doing a very detailed look at that in one state. Finally, real world evidence. You've heard quite a bit about that today, but I want to just illustrate with some of our work how hard it is to collect the data on safety, and I think pointing to the need for registry type studies. So, the big message that I, I guess, want to impart is that potent therapy, by definition, carries risk. Regardless of the regulatory status of ketamine, there is still a public health need that is unmet.

(01:14:38):

There's a reason why we're talking about this today, that access to care is certainly a big issue, and again, given the severity of the issue, mental health, depression, suicidality, anxiety, it really does require a powerful approach potentially and acknowledging the risk is the first step to mitigating that risk. So, let's talk first about the first point, which is, what have we learned about patient expectations and the role they play in therapy? This came out of an effort. This is a small trial that we did, but it was highly informative, at least to me. Hopefully, to you as well, and trying to get at this question that one of the first presenters earlier in the day brought up this issue, Doctor Cohen, I think. It's hard to blind ketamine studies, right? So you have a whole bunch of factors that play into this.

(01:15:33):

This is also an issue more broadly inside blind studies, of course, but the question keeps being asked. Is that the drug? Is it the trip, or is it non-drug factors? By non-drug factors, I mean these things that happened before, where you set expectations and give patients some idea of what is going to happen and that may influence their outcome, and then what happens afterwards. What is the active care look like? How do they integrate the events of the treatment into their lives and make change? So we thought we could get at this question with a particular study design where we could achieve full blinding of the patients and maybe get rid of that conscious experience, right?

(01:16:16):

So that what we're aiming for is to separate out the drug from the trip, and the way we did that is administering ketamine to patients with moderate to severe depression or presenting to Stanford Hospital for non-neurological and non-cardiac surgery. So, we did everything we could to make this

study look like other single infusion studies that have been done in the psychiatric literature saying similar patient population, similar severity, elements of treatment resistance, similar doses of ketamine, same outcome measures. So, very briefly, what we found is that there we go. It was blinded study. We can see here is the guesses the patients had. They were under anesthesia, so they can't really figure out what treatment they had.

(01:17:11):

What we saw is very little separation, actually, no separation between placebo and ketamine. But the broader point, actually, that I take away, this doesn't really say much about whether ketamine "works"? Everybody got better. What it does show is that just looking at the response rates for the placebo patients, is that when patients don't know what treatment they're in and they carry expectations potentially about what what's going to happen, a big event like this, having surgery being an exciting trial, that alone can account for a large proportion of the treatment effect. So, we looked at this and a little bit more closely, where we took the same data and then reanalyze it according to what patients thought they got.

(01:17:59):

So, what's going on here is at the end of their treatment on day 14, we asked them, "What group do you think you're in?" Patients who got better thought they got ketamine, right? That patients who didn't get better thought they got placebo. Here, when we analyze the data that way, you see a nice separation. Again, we didn't ask specifically about what expectations they have going into the study, but it suggests that patients who had some preconception about how well ketamine works, and again, that may have influenced their potential outcome. So, another piece of this is, well, if we think that the kinds of information that the patients are getting is important. Well, what beliefs are being shaped by the media that patients consume?

(01:18:55):

You'd already seen some of these ads, but there's a very hyperbolic claims here. One of the, I think, most important trends here is this idea of psychedelic medicine and ketamine is being essentially lumped together with other psychedelics, especially as it comes to marketing. Some of the statements, of course, are not well-supported at all by the literature, and this is, I think, one of the causes for concern. So, working with Audrey Evers, a graduate student at Stanford, and Chris Kelly at Sinai, Shayla Love at Science Journalist, we put together psychedelic media exposure questionnaire to try and understand what beliefs patients are carrying. There are two samples for this study. One of them is discovery sample, the other validation.

(01:19:41):

Important thing here is that almost a half of the patients identified ketamine as the psychedelic. So, this is an important element in terms of branding and recognition, what patients are thinking when they hear about psychedelics in general. This is unpublished work. But these are statements that are sourced, specific media sources, advertisements, and you can see a range of claims that are being made, some of them beneficial, some of them less so. Basically go from zero to four, strongly disagree to strongly agree. On average, views are pretty moderate, extreme. Statements had lower agreement as you might expect, but I think it's illuminating. Psychedelics are cure for mental illness. Again, suggesting, with half the people lumping ketamine into that category.

(01:20:37):

In general, we find that neither agree nor disagree, and people are relatively conservative. There's a lot of hope evident here. Psychedelics have potential to help people, strong agreement there, and psychedelic therapy is far better than antidepressant medication. Psychedelics are dangerous. Again,

this is information that I think we need to understand. How is advertising impacting patient perceptions? The last thing I want to touch on briefly is this, the difficulty in actually collecting safety data from real world evidence. This is work I did in collaboration with as Osmind here. It's published last year. These are fact sizes for depression and anxiety from 10 clinics across the country. These are brick and mortar.

(01:21:29):

These are big effect sizes. Not a surprise, again, lots of folks have shown these sorts of things. We did our best to find some control groups, but there's a signal for efficacy. The hardest thing, I think, to quantify here is "How do you quantify risk?" It's easy, relatively easy, to show the patients who stay in care get some efficacy. But what about this dropout? This is the number of patients over visits that are still in the study, right? So that we're following patients in this real world study, but there's a huge attrition. Why do these patients leave care? Simply we don't have data. They're not all bad outcomes. They're not all good outcomes, but it's obviously a big chunk of missing information.

(01:22:17):

Our safety claims reliable without a clinician in the loop, unless specifically for telemedicine only providers. The safety concerns have already been, I think, discussed at some length here. There are a number of them. The last thing I want to point out is that the US is really the beginning of an upswing in ketamine use. This is just some media coverage from People's Republic of China. This is from 2015 where the Government of China notified the Secretary General, they recommend ketamine be placed on schedule I.

(01:22:58):

That speaks to potential abuse issues that they had that reached the level that they thought this was an appropriate intervention, and that should give us some pause about what the potential public health considerations are for large scale ketamine use. So, that's all I have to say. Thank you for your time. That was a little bit of a whirlwind, but I appreciate your attention.

Susan Winckler (01:23:24):

Thank you so much, Dr Heifets. So, let's have a conversation about this component as it relates to just the presence of the online sale and promotion, and then what are some of the results of that. So, if we could move to the panel slide, and I'm going to have our two reactor panelists here in person. You can pick any of the two of the four chairs that you'd like to use. All right, and then we have our speakers back with us. So, Dr. Heifets and Dr. DiStefano, meet Dr. Ilisa Bernstein, who is the founder and president of Bernstein RX solutions, but spent many years at the FDA and at the American Pharmacists Association. Thank you for joining us. Then we have Dr. Rick Quaresima.

Richard Quaresima (01:24:19):

Not a doctor.

Susan (01:24:20):

I know. That's all right. I give everybody a doctor. It's just much easier. Joining us from the Federal Trade Commission, and I'll just go there. What thoughts do you have? Well, actually tell us how FTC approaches the regulation of advertising for ketamine. What should we understand about that environment?

Richard Quaresima (01:24:41):

Sure, for those of you who don't know, the FTC enforces general truth in advertising laws, laws against deception. The Federal Trade Commission Act specifically outlaws deceptive practices in or affecting commerce. So, for ketamine, the approach is the same as for any other product or service, the analysis of whether or not a claim about it is deceptive. In the area of health products, where products are making claims about potential health benefits of certain products, generally, something could be considered deceptive under the Federal Trade Commission Act if it is either false or if it is not substantiated. Substantiation being defined generally in the case law as competent and reliable scientific evidence to support the claim.

(01:25:39):

What the claim and what that evidence is, is going to vary from product to product, and claim to claim. Each case has to be each claim, and each case is analyzed individually. What is competent, reliable scientific evidence, again, is going to vary for disease treatment claims most of the time that is going to be considered a properly conducted clinical trial of some sort, not necessarily the types of clinical trials required for FDA approval of a drug, but some rigorous clinical evidence.

Susan Winckler (01:26:16):

So it has to be accurate.

Richard Quaresima (01:26:20):

Truthful.

Susan Winckler (01:26:20):

Truthful.

Richard Quaresima (01:26:22):

It has to be, because as Dr. DiStefano was saying, things can be misleading. Even if they are technically literally true, something can be considered misleading in context.

Susan Winckler (01:26:36):

Right, right? As you know, with the stage is open if you want to ask questions of our presenters about that, just about the information that they had. I'm just going to toss one thing to Dr. Heifets, then I want to turn to you, Dr. Bernstein. But Dr. Heifets, I think one of the things that I heard in your assessment, is that some of the online, if I understood it correctly, like some of the online promotion and then the chatter about these products may also complicate our ability to further study them. Is that fair, or it might be contributing to it?

Dr. Boris Heifets (01:27:18):

Absolutely. I think what we've seen is that again, ketamine, there's a certain what we people call the Michael Pollan effect, how to open your mind or how to change your mind, about which really is revved up. A lot of expectation about putting ketamine in water class of psychedelics, not because that's necessarily where it belongs, but that's what public perception is being driven to and that those expectations of people develop clearly, it can set people up for success. They put a lot of hope in this, and it's a firm or disappointment, right? If it doesn't work, then what comes next? Both of those are, I think, are issues that make it difficult to really evaluate these compounds in controlled studies.

Susan Winckler (01:28:13):

Yeah, that's very helpful. Actually, it reminds me to say that I believe the official classification, at least from some in the regulatory space, is that ketamine is an anesthetic with dissociative properties. They do not use the P word that has four syllables. Dr. Bernstein, you come at this from a slightly different direction in having done a lot of work for a long time in the online promotion of controlled substances, where ketamine fits into that. Are there things that we can learn from what we've seen in in the broader online promotion of controlled substances? Are there things that we should be concerned about from that? Help us relate that experience, and just help us understand the reality of ketamine promotion here.

Dr. Ilisa Bernstein (01:29:08):

Yeah, sure. As Dr. Heifets was just saying, this is why I stay away from Reddit, for sure. But yeah, it's interesting, as I was listening to even to the last panel and some of this morning as well. It's not just one box where you need to be concerned about online promotion or access, because as we heard, there's all these wellness clinics and clinics and IV clinics. These are brick and mortar who are advertising online. So, that's one box is the advertising online. Then you have the telemedicine, telehealth, where they're advertising online that they're offering these services to provide, as well as often, the drug itself. So, that's another box. Then you have a box of the online pharmacies. These are bad boxes. Yeah. None of those should be legally selling products, drugs online, or ketamine online, but you see those. Mostly, for the most part that we've seen for those types of... Not necessarily, I don't know specifically for ketamine, but when I was at FDA, oftentimes those are the types of online pharmacies that just take your money and run and you'll never see the drug anyway.

Susan Winckler (01:30:32):

So that would be false according to FTC.

Dr. Ilisa Bernstein (01:30:34):

Yes.

Susan Winckler (01:30:36):

Just checking.

Dr. Ilisa Bernstein (01:30:37):

Then I think the fourth box, if you go online, are the compounding pharmacies. Those are a totally different level, because the other three are promoting directly to consumers. It's direct to consumer. The compounding pharmacies are online. So, that they're letting others know that they provide this product, but they don't sell directly to consumers. So, as we're looking at that access and promotion, we need to think of these different boxes and where the different risks are to patients and where the vulnerabilities are.

Susan Winckler (01:31:16):

That's helpful framing as we just think through. I might call them online drug sellers, rather than online-

Dr. Ilisa Bernstein (01:31:21):

Yes.

Dr. Boris Heifets (01:31:22):

Okay, if that's fair. That's a helpful architecture for the ketamine structure. Would the FTC look at those different boxes differently, or it's the truth that's required for all of us? To get a teensy bit closer than-

Richard Quaresima (01:31:42):

Sure. I mean, it would be the truth that would be required to all of them. I mean, the FTC prioritizes direct to consumer advertising. My guess is very little in the way, but I don't know this for sure, communication of claims from the compounders to the prescribing physicians about exactly what they're doing or how they're doing it or what the effectiveness of the product is, because from what I heard today, they're usually filling whatever the prescription happens to be.

(01:32:21):

Something like the online pharmacy that's just delivering, not delivering, well, that's actionable under the FTC Act, but it's a very different analysis, because it's just like failed to deliver the product. You said you were going to give it to me and you didn't. There's no scientific analysis or even a claim interpretation of what is the claim that are consumers being told specific effectiveness, outcomes for the treatment, and what is the science behind it? So it's a very different type of legal analysis, depending upon how you're doing it.

Susan Winckler (01:32:56):

Yeah. So, I was going to say one, they're both fraud. So, never mind. I won't go down.

Richard Quaresima (01:33:02):

Yeah, I mean, it's certainly a fraud to say I'm going to give you a product X and not give you product X. I mean, again, you can say product X does this. Product X does Y and Z and product X may do Y and Z, but if they don't give you product X, again, that's a different analysis.

Susan Winckler (01:33:24):

Yeah, yeah, okay.

Dr. Ilisa Bernstein (01:33:25):

Can I just say?

Susan Winckler (01:33:26):

Please.

Dr. Ilisa Bernstein (01:33:27):

Under the Food, Drug and Cosmetic Act, there are also provisions that have played here. FTC and FDA work together often on cases, depending on what the product is and what the claim is. At least when I was at FDA, there were some times that we would have taken action or sent warning letters or tried to shut down websites based on whatever the claim was, if it's false or misleading.

Richard Quaresima (01:33:58):

Yeah. That still goes on. We send out lots of joint warning letters with the FDA on certain aspects of it, because it's a slightly different regulatory take on it, whether or not something is an approved drug

versus whether or not the claim about it is deceptive and whether it's supported by competent, reliable scientific evidence. When COVID hit, there were hundreds of joint warning letters we sent with the FDA on sellers promising all sorts of treatments for COVID-19.

Susan Winckler (01:34:37):

Yeah, yeah, yeah. Dr. DiStefano, I want to turn back to you. I guess I'm intrigued in what surprised you the most in what you found. Then do you have thoughts about how is it that we might help consumers and practitioners navigate that online environment? And then I'd invite anyone else to chime in on that second question, too. So, Dr. DiStefano?

Dr. Michael DiStefano (01:35:09):

In terms of most surprising things we are finding, I think that would be just the multitudes of conditions that these various ketamine services were being provided for or at least advertised for, and that didn't make its way into the research letter because of space and because you have to have a way of clustering different ways of describing similar conditions. But in our rudimentary count, we saw as many as 30 different uses being advertised by single sites, and that covered common and potentially reasonable uses like various depression, perhaps pain disorders, but then Lyme disease, asthma, dementia, conditions where I would think that the evidence is not as strong. But again, I don't know the evidence bases well myself. So that was probably the most surprising. And then of course, I pointed to just false claims, right? It's not addictive. It's approved for something, it's not approved for... yeah. In terms of... The second question was how to help clinicians or prescribers? Sift through the-

Susan Winckler (01:36:35):

Right. Are there things that we can think about that might help patients and practitioners just be a discerning consumer of the information?

Dr. Michael DiStefano (01:36:50):

I think it's very difficult.

Susan Winckler (01:36:53):

Indeed.

Dr. Michael DiStefano (01:36:57):

We can't expect the lay person... I wouldn't expect myself to be able to sift through and engage in an evidence-based medicine analysis for any given purported use of ketamine. So this is an area where the information needs to be at least not false, ideally not misleading. And it's the sort of thing where clinicians with patients who have these conditions need to be, I think, proactively speaking with their patients about whether this is something that they've ever considered, if it's ever something they've pursued, and they can help them then do that in that safe a way as possible, ideally.

Susan Winckler (01:37:50):

And I wonder, is it a space then where... We know that one of the ways to help consumers better navigate challenging situations is to provide them what we do know. So is this a space where it might be helpful for professional associations to illuminate? We have already seen some research today about what we're learning, but what else might we do?

Dr. Ilisa Bernstein (01:38:17):

Yeah. I am on the board of an organization called the Alliance for Safe Online Pharmacies, and we do a study every year, the ASOP foundation does a study every year looking at telehealth and online pharmacies. And the results in 2023 show that as a result of the pandemic, because everything moved towards telehealth, 69% of those surveyed said that they'd be comfortable receiving a controlled substance strictly through telehealth. And so that leaves you as like, "Wow, how do you know if you can trust these entities that are online?" And so I think as you're saying, is how do you work together to educate the public and providers and what are those best practices? And I'm just going to use this as a teachable moment because there are some best practices.

(01:39:16):

One, are you talking to a real clinician? Are you talking to a real person or is it an AI computer? Can you verify the credentials of that clinician? Is the platform you're using HIPAA compliant? So you're sharing this information and making sure that your information is protected. Are there these claims that are too good to be true? That's a red flag. And there are other things. What are the reviews? What are your health provider says? So there are things that... you need to do your due diligence, and you can't just go online and look for these telehealth providers; and then just say, "Oh, because they're offering ketamine, it must be legal."

Susan Winckler (01:40:06):

Well, so I think that is helpful just from a framing of consumers and how we think through that, in arming consumers in being more savvy in what you find. I would still have brown hair if all of those things were possible.

Dr. Ilisa Bernstein (01:40:23):

Can I just add one more statistic?

Susan Winckler (01:40:24):

Yes.

Dr. Ilisa Bernstein (01:40:25):

Because in that same study, what the data showed, I think it was somewhere around 50% of the people believed that if you're doing a search and it shows up on the first page, then that's legal and it's okay. And that's scary.

Susan Winckler (01:40:44):

Fascinating. That's right. That I don't think passes the FTC fact test-

Richard Quaresima (01:40:51):

Well, again-

Susan Winckler (01:40:51):

It's a belief. I'm putting you on the spot, yes.

Richard Quaresima (01:40:52):

There's no specific claim on that.

Susan Winckler (01:40:52):

Yes.

Richard Quaresima (01:40:54):

But yeah, again, one issue, instead of going back to I think one of the previous panelists, is the opportunity to make money from something like this. There's some parallels here to the proliferation of clinics that offer stem cell therapy, and this again, just ballooned, exploded, for a while. And we've taken a few enforcement actions against them, but there are hundreds and hundreds of these clinics here. And a lot of them are to the extent that there needs to be some medical person there prescribing a lot of times, that in some of these places might not be very well supervised or somebody's being paid to write prescriptions without having really providing clinical evaluations.

(01:42:04):

So these are things that you don't know. And I think there's just inherent danger in going online and searching for a place, for a particular therapy that you've read about [inaudible 01:42:16] and just let me get the therapy. Because you're already predisposed to want the therapy because you're looking at it, rather than through the normal course of consultation with your physicians. And I think that just increases the likelihood that you're going to be drawn to potentially deceptive claims.

Susan Winckler (01:42:34):

Yeah. And I think we had a great question that was where are the state regulators? Because if it's outside the scope of practice of the prescriber or outside the practice of what the pharmacists should be doing - I think that was last panel - that's a part of what state boards are grappling with. But in an area where we're still building the clinical evidence exactly what's in-bounds and out of bounds is evolving, although there are some bright lines that can be followed.

(01:43:06):

I also want to give voice, we should acknowledge that sometimes those who are searching for a treatment online are searching online because they don't have access to healthcare services and have not been treated well in the system, and are looking for an alternative. So we should just recognize there's that component as well.

(01:43:29):

We have one minute and 30 seconds before our break, which allows me to say to one of you, who would like the last word and what do you want to say? Your time's ticking. All right Ilisa, it's yours because nobody else jumped in.

Dr. Ilisa Bernstein (01:43:44):

Susan knows me.

Susan Winckler (01:43:45):

I do.

Dr. Ilisa Bernstein (01:43:47):

I think this is an area where, and Jenny in the last panel talked about this, that this is very similar to what we've seen in med spas and for Botox and for GLP-1s and for stem cells, and where there's an opportunity and someone will take that opportunity. But as we heard this morning, there are some very beneficial treatment here.

Susan Winckler (01:44:13):

Right. Certainly emerging clinical uses, yeah.

Dr. Ilisa Bernstein (01:44:17):

It's where all of these players, all these stakeholders really need to get together and figure out how are we going to approach this? They talked about guardrails and I think having guardrails are good, but you can't put that out there as a roadmap that creates the way for more.

Susan Winckler (01:44:37):

How to get around them.

Dr. Ilisa Bernstein (01:44:39):

Yeah. And bringing the regulators, the state, the federal, the clinicians and the researchers together and really figuring out that game plan for providing access to treatment, but also making sure that those bad actors are not available and providing products.

Susan Winckler (01:44:59):

Right. Including those who are developing drugs in this space, who are trying to pursue those indications so that we have the factual basis. All right, Dr. Heifets, Dr. DiStefano and our doctors on the stage. Thank you so much.

Session 6: Potential Future Use of Ketamine

Panel Discussion:
Eric Hermes, MD, Veterans Health Administration
Caroline Huang, PhD, U.S. Food and Drug Administration
Michelle Kim Leff, MD, MBA, Substance Abuse and Mental Health Services Administration
Lisa Robin, Federation of State Medical Boards
Gerard Sanacora, MD, PhD, Yale University
Gerald Gelfand, Captain, U.S. Navy

Susan Winckler (01:45:19):

We have another quick break and then we'll come back for our last panel where we will say, what is it that we do next? So we will see you at 3:10 PM. Let's go ahead and get started with our final session. Thank you for returning to join us. We have a great discussion to help us close off the meeting. So we have a few folks who are rejoining us, you've seen them before, and then a few new faces on the stage. So if I go across the stage, a reminder, you've already met Dr. Eric Hermes from the VA, and then next to him new face, Dr. Caroline Huang, who is a senior science policy advisor at FDA in CDER's controlled substances program. Second new face, next to Caroline, Captain Harold Gelfand, a physician at the US Navy, Executive Director of the Defense and Veterans Center for Integrative Pain Management.

Captain Gerald Gelfand (01:46:18):

[inaudible 01:46:20].

Susan Winckler (01:46:19):

Yes. All right. But I got it.

(01:46:21):

Third new face, Dr. Michelle Kim Leff, who is a senior advisor and acting deputy director at SAMHSA, the Substance Abuse and Mental Health Services Administration. And then back to faces that we have seen before and voices that we will hear again, Dr. Gerry Sanacora and Dr. Lisa Robin.

Lisa Robin (01:46:41):

No doctor.

Susan (01:46:41):

I know, but it's just easier. I get in the mode and it's easier. So let's start this conversation. And I am not going to go in order of the row, but I am going to start at that end because Dr. Hermes needs to catch a train. So you said you wanted to go first, what do you want to say? And then we'll talk about what's next in this space.

Dr. Eric Hermes (01:47:05):

Yeah. Well, I appreciate it. I have to catch a train so I got to get it going. But what I think we focus on the afternoon a little bit is understanding what's happening with ketamine for mental health in the community. VA often divides care that it does at VA facilities differently from the care it pays for in the community. And one of the panelists accurately identified the fact that the ketamine that VA delivers, over half of that ketamine is from community providers. And so we as a institution run into the same issues with understanding the quality of that care that we've talked about today. And so we are limited by law on the type of data we can ask from our community providers on how they're delivering the care and the outcomes of that care. And so we have really a dark spot in terms of understanding the quality of the care for half of the ketamine that we deliver to our veterans. So it's an issue that we're working on as well.

(01:48:14):

And so I just wanted to put that out there, that we run into some of the same issues as an integrated health system that the wider community is running into. So I appreciate that.

Susan Winckler (01:48:27):

Yeah. So as we think about that potential future use of ketamine, I think earlier we're thinking, "Oh, the VA is going to be this great place to study." It is. And then there's a reality that you've just helped us understand the context, and some of the dynamics that there's in facility and more broadly.

Dr. Eric Hermes (01:48:47):

So it's the classic story of the VA. The VA is a great place, but then there are aspects of the VA that are a little bit less than that. But I do appreciate the time. I do have to go, so thank you.

Susan Winckler (01:49:02):

Yes. All right.

(01:49:02):

So then I do want to... Let me turn first to Dr. Leff. SAMHSA looks at a number of different things, but as you've been sitting here today, what are you thinking about in the emerging use of ketamine and what it might mean to the work that SAMHSA does?

Dr. Michelle Kim Leff (01:49:22):

Thank you. Yes. So first I just want to do a little table setting and talk about SAMHSA and our mission. We are an agency within HHS and when you think about HHS and improving the lives and health of anyone and everyone living in the US, that is our mission in the area of behavioral health. And that includes substance use prevention, substance use treatment and mental health services. So when I think about today, SAMHSA is very interested in the developments in both looking at what is going on in terms of recreational use and misuse. So what Dr. Palomar had mentioned, and we are actively looking at that because there definitely is a place for us in terms of prevention and substance use treatment.

(01:50:18):

But we're also very interested in looking at ketamine as an emerging therapeutic too. At this point, well, not at this... Well, we do follow, we always follow, the policy set forth by HHS. And at this point, ketamine treatment is not considered an allowable expense for SAMHSA grant funds. And so therefore at this point we are not monitoring or collecting any ketamine clinical data.

(01:50:51):

And then the other thing I just want to say. So we try to make sure that we can provide people more access to treatments. So I think, when in this conversation, we really have to think about access and affordability and equity in terms of who gets these treatments.

Susan Winckler (01:51:18):

Yes. And what's driving some of that need and that whole holistic question.

Dr. Michelle Kim Leff (01:51:25):

Absolutely.

Susan Winckler (01:51:27):

That's really helpful and we'll come back as we talk about it and just think through what are things that each of us heard and where do we think there is an opportunity to improve just what we're seeing and have better use of ketamine.

(01:51:46):

So I want to turn, Captain Gelfand, to you, because the Department of Defense has some experience here that might be helpful just to help us further round out this conversation.

Captain Gerald Gelfand (01:52:00):

Certainly. So thank you for having me, I do appreciate the opportunity to speak on behalf of the DOD. So one thing that struck me in the talks we've had with regard to ketamine were two big things. Firstly, ketamine is very much an orphan drug with evolving indications that will have impacts on a large segment of our population. So the issue we run into is because truly being a 50-year-old drug, there is no fiscal incentive to seek those regulatory approval processes to the extent that we would normally

pursue for a new or novel drug. When the Esketamine enantiomer was developed, that was developed as a new patentable drug and it pursued all of the FDA regulatory affairs requirements for a very narrow indication. So we now are looking at a drug through these conversations that have at least five potential indications.

Susan Winckler (01:53:02):

Or 30 depending on what's online [inaudible 01:53:05] but that's okay-

Captain Gerald Gelfand (01:53:04):

On rights. Whether you believe those all or not, but at least-

Susan Winckler (01:53:07):

Narrow back, I think five fits with what we heard.

Captain Gerald Gelfand (01:53:09):

Five legitimate, two of which are FDA approved; anesthesia and sedation. So we need to potentially start divorcing each of these pillars from each other because what the regulatory requirements may be for each of them, could very well be different. So by way of example, and our particular interest, is the acute pain indication. There's at least 40 years of evidence in the literature and in military experience and use, demonstrating the safety and the efficacy of low dose ketamine for analgesia in the trauma environment, particularly in the downrange environment. And this has been echoed in at least a half dozen major societies in the surgical anesthesia and supportive medical spheres in trauma care, that say... and have supported and have consensus and often joint consensus statements. Imagine that, getting six societies to all agree on a consensus that ketamine, and with prescription recommendations and uses of recommendations, for ketamine as the preferred trauma drug for moderate to severe pain in the potentially unstable patients. The issue we run into on our side of the house, and this has been without effort on the part of the DOD, in fact certainly fiscal effort as well, is because of the narrow FDA classification for ketamine, we have been unable to develop delivery systems that can be used in the trauma and downrange environments. So the only delivery system that any of our medics or your pre-hospital administration personnel can do, is through drawing from a bottle and administering it - either IM or if they have an atomizer, potentially intranasal - but they have to actually draw that medication in a combat environment where it's fraught with error. Now certainly there is now evidence that we have, through its use in the battlefield, that even when given at exceeding doses, the side effects and the complications are virtually non-existent. Unlike what would've happened if this was fentanyl or morphine and the same was done. So that's an important point with respect to safety. And that this maintains the patients hemodynamic stability, unlike the opiate drugs do.

(01:55:45):

The only option that is metered and pre-drawn and ready to administer in that medics kit is morphine. So there's morphine autoinjector, and that's the only FDA approved analgesic autoinjector system that is available. So we're very much locked in a very difficult situation. All of the evidence would have us use ketamine as our principle analgesic choice for moderate to severe pain in the trauma patient, but we have no way of safely administering it in the pre-hospital environment. And that is really where this issue as far as how the FDA moves forward, and what evidence from 50 years of work is sufficient to permit reclassification or the additional classification of low dose ketamine for analgesic use, and potential even in the trauma scenario.

(01:56:50):

So that's really what we are striving to accomplish. And it's been... I would say we've incorporated ketamine in the TCCC guidelines since 2012. That's when it was first incorporated as the preferred analgesic for trauma pain management. Since that time, we have been unable to move forward with any of these initiatives to actually be able to create a delivery system that could be fielded by medics in the combat environment. And this is also very telling in that when you compare types of medical resources, so if you look at your special forces operator medics compared to your regular line medics, you find there's a difference in ketamine use. Those operators with special forces, given the additional training they have with respect to resuscitative care for the types of submissions and expectations they have, use ketamine to a far larger extent than does your rank and file line medic. And that has to do with that needing to draw the medication and administering it using those tools.

(01:57:54):

So that's really where, from the military's point of view, we need to move forward. And where we see the future is in the low dose analgesic use for trauma, pre-hospital care.

Susan Winckler (01:58:08):

And what's helpful in that example is it allows us to unpack a few different things, but also put this... I think the phrasing that would be used in the world of food and drug law, is that it's actually a repurposed drug. So it's a drug that's already approved for one use and now we have these other indications. And I think what we've exposed through today is that in some places getting that information and collected, and navigating the FDA process to end up on a label, it doesn't really matter. There's broad appropriate use even for those unapproved indications as part of the practice of medicine. My sense that I've heard from today is that this might be a space where in fact would be great to have additional understanding of the safety and efficacy such as would be navigated through an FDA process, and in particular, as you point out, to meet the DOD guidelines.

(01:59:13):

So Caroline, Dr. Huang, I'll turn to you to say, when we're thinking about it from the FDA perspective, the agency can only evaluate applications that are submitted to it. And so what are your thoughts as you reflect on the day and in just learning more about this space?

Dr. Caroline Huang (01:59:39):

Yeah, thanks so much Susan. And I wanted to say thank you to the Reagan-Udall Foundation and all the speakers, all the presenters and all the audience members, virtually and in the room. We've certainly learned a lot and I think we'll be unpacking this discussion for a long time to come.

(01:59:54):

I think I actually want to start a little bit further back, which is that I think one of the things that we've heard today is that there is really a gap in the accessibility and also the acceptability and the effectiveness of different kinds of approved medications from the perspective of patients and providers. And so that's really made it not surprising then that you have people that are looking to use something like a ketamine for these emerging areas of therapeutic interest. And I think you teed me up very nicely because we do have an established pathway for looking at how we are going to evaluate whether something is safe and effective for a given indication there.

(02:00:31):

And certainly you have heard different perspectives today on ways in which some of the regulatory barriers and whatnot might be challenging. I think I would actually go to Lisa Harding's framing of that in saying that it's really for safety reasons. We really want to make sure that we can stand behind the

safety and efficacy of a drug once we've approved it for a particular indication. All that said, I think that FDA has really leaned into looking at the modernization of clinical trials. We recently launched our CDER Center for Clinical Trial Innovation. I had to look that one up because it's C3TI, and that's the only way that I know-

Susan Winckler (02:01:07):

Yeah, I was going to say it's C3TI, I can't tell you what it means.

Dr. Caroline Huang (02:01:09):

Federal means we only do acronyms and I don't know the full names of anything. But I'd say that, and also I think in the last couple of years we've really issued some guidances on things like real-world data and real-world evidence and also on how we modernize clinical trials. So I think there is a recognition that there are different kinds of emerging evidence that are also important there. So I don't think that's going to solve your problem tomorrow, but I think the other piece of the day is that I think we've really talked a lot about the need for better data collection. A lot of the challenges in looking at different aspects of ketamine and especially the long-term effects there and the need for blending better clinical trials along with things like registries.

(02:01:49):

And so I think I'll just closed by saying that I think this is hopefully the start of our collaboration with everyone on the stage and on our audience and whatnot, and not the end of it. I think that certainly our federal partners certainly know where to find us. And I think it's certainly an ongoing conversation where we need a lot of different voices here because there is a lot of need, and we want to make sure that we do it in a responsible way.

Susan Winckler (02:02:14):

Well, and I'm struck too, and the mention of real-world evidence, I think the real-world evidence that Captain Gelfand just mentioned is very different from the real-world evidence that we have seen in some other places, and also in an indication where it may be easier to assess impact than in some of the psychiatric indications that we're talking about, where still important. But I think that will be perhaps something that the agency would... there are mechanisms for that to be presented to the agency. That's the way I should say that.

(02:02:55):

So let me turn, Lisa, to you and then I'll turn to you, Dr. Sanacora, and let's turn this into a conversation. But Lisa, we heard a lot about the policy and regulatory issues and things that are happening at the state and the federal level. What might you want to highlight? And then are there things that we should be thinking about doing that would help the state regulators? I will say when I saw some of those slides in the last session, I just thought, "Ooh, I'm glad I don't sit on a state board of anything." What a challenge.

Lisa Robin (02:03:29):

So yes, I really appreciate being here and it just is so apparent that there is such a gap. And I think if we don't have some guidance, and I loved what you said, I think this is an area where we really need some guidance from FDA if possible. Otherwise, you're going to have just a patchwork quilt of regulations that are going to come from the states. And that's why it's imperative before it gets too far down the path, that all of these voices come together to look at what makes sense. There has to be a policy framework that can support good care.

(02:04:11):

And I think with all of these loopholes and off-label use; yes, providers can do that, how far can they go with it? Are people being taken advantage of? Yes, there are patients that are being exploited, I would say on some of this. You're expecting them to sift through all of this. There is so much misinformation about everything and they're desperate and they maybe can't get access. And then also the disparity, because they're not going to have the financial means. So you're only being able to [inaudible 02:04:49] certain people and then lots of populations that probably really need this help are not going to be able to access it because it's not being paid for. So it's a plea for us to come together. We've worked for years with SAMHSA on guidelines and all sorts of things around OUD treatment most recently. And I just hope we can all work together and we need the experts. Medical boards are great people and they've got great physicians on there and great consumers, but we have to bring in experts in this field. Some boards have psychiatrists, many don't. There's not enough psychiatrists anyway. So thank you.

Susan Winckler (02:05:32):

Yeah, yeah. Well, I think you've captured some of the call to work that we were thinking about. So Dr. Sanacora, we heard from you first in the morning and there's been a lot of information shared since then. Thoughts? What would you want to highlight and then we want to keep talking.

Dr. Gerard Sanacora (02:05:51):

There has been a lot of information. I think for me, excuse me. The thing I've been most struck with is this knowledge gap and the hurdles to filling the knowledge gap. And the fact that we're hearing misinformation even up here on the screen, certain things that are said really with very little data behind it, but things that are said with confidence and things are posted on web pages. But if we don't have the data, we can't say anything really one way or the other. And we've been put in a really difficult situation in many ways to try to get this data, because there are really pretty firm rules around what we can do. For example, we've recently been awarded some PCORI funding to do a large head-to-head study of Spravato versus IV ketamine and looking at that. But in order to move ahead with that to get an IND, it really limits what dosing. So really limits the dosing to 0.5 milligrams per kilogram or 60 milligrams, but no more than eight lifetime doses, a maximum. As we saw in all the presentations, that's well below what the typical clinician is giving in the community. So we're really put in a difficult situation that if we want to know practical information about is this treatment safe and effective, but we can't do the study because we're not allowed to look at the doses that's being used clinically. So there's this real disconnect between what's being done in the community and what we're able to study and what's considered safe by FDA standards.

(02:07:27):

I really applaud you for pulling this group together to try to come to some cohesive way of moving forward, because as it is right now, we're kind of stuck. We're like, "This is what the real world is doing, but when it's considered unsafe and we're not able to study it." So it's a difficult situation.

Susan Winckler (02:07:43):

So is that a place where in the medical product world, real-world evidence is often discussed, but when we talk about real-world data and real-world evidence, it's often from healthcare claims and it seems like this is a space where... Could we use the real world data to at least help inform and justify saying, "Well, here's why we'd like the dose to be in this space"? And actually, Captain Galfen, I'd love your thoughts on the real world data you've generated in the Department of Defense use, and how should

we be thinking about its real world data to generate real world evidence that may not be what's dispositive, but can it help us structure the studies better or something else?

Dr. Gerard Sanacora (02:08:37):

Exactly. And we've heard it a few times today that there's multiple different types of data that's very important. Registry type data. Looking at real world that way is very important, but also having some more controlled clinical trial type data to come together with that is really important. And I think we need both types of data to really be informed about what is safe and efficacious. So I think we do need both of that, but we need to be doing studies that reflect what's being used in the real world. And if what's being used in the real world is really that dangerous, we should know about it. And that message should get across.

Susan Winckler (02:09:15):

Right. Right, right. And that'll require some information about what are the formulations that are being used? That it'll require a little bit of the granularity of the data that maybe we're not quite thinking through today.

Dr. Gerard Sanacora (02:09:27):

Exactly.

Susan Winckler (02:09:27):

Yeah. But Captain Galfen, help us understand you've got the use and the performance use. Can you give us a little bit of a better picture of what does that data look like? Because it's also delivered in an environment where I'm guessing there's not a scanning of any... Well.

Captain Gerald Gelfand (02:09:47):

So most of the analysis that we're able to do, particularly of our experience in the battlefield comes from the Joint Trauma Registry. So the Joint Trauma System does maintain a registry of those patients that go through the evacuation in the medevac process. Is that data 100% complete? No, there are often gaps by virtue of how the patient was initially cared at the point of injury and the movement of that information in that record with the patient as they go through the evacuation system. But typically, once they get to one of the more stable roles of care, the picture becomes pretty clear. And we have pretty reliable information. So most of our analysis comes from the data that is part of that trauma registry.

(02:10:33):

And what it has shown is, I've already touched upon usage that we see more usage in special forces of ketamine than in regular line forces. Interestingly enough, our experience in Iraq and Afghanistan, patients that were local, so basically indigenous populations, got more ketamine than military personnel. Not exactly sure why that was, but it was one of the patterns that was observed in the data. So we have a lot of interesting areas like that. Certainly we've been able to demonstrate that even at higher doses than our prescribed in the TCCC guidelines, again, because of administration errors or titration effects, that the side effects didn't really seem to present themselves in any significant way. That there was no evidence that there was any need for advanced airway support or any other more complicated interventions related to those treatments.

(02:11:36):

When they did some analysis, like I said, they were using higher doses than were prescribed by the TCCC guidelines. It's actually believed, that's looking at cumulative dose, and that was probably just that they were titrating to effect. And that's how those doses came to be, the numbers we saw. So I think what we're seeing, and similar along the lines, that what's happening in the real world as reflected in our trauma management system and our experience in the combat environment demonstrates how these drugs become optimally used in the therapeutic context with respect to specific patients. And again, granted, we're looking at cumulative data, each patient is obviously going to titrate differently. Having used ketamine in the inpatient setting now for at least 15 years. I've got patients that we titrate, they're on the floor with rates of 60 milligrams per hour and they're sitting there and they're perfectly fine, no issues, and you've got one, some, you've got them on 10 and they're zonked.

(02:12:41):

So it's obviously each patient, individual different, but we're able to show with the gross data, the overall effectiveness and safety, and that the literature supports what we're doing and what we did was based on the literature.

Susan Winckler (02:12:58):

Yeah. Which helps us paint that broader picture. But then, so at least there you have gaps in data, but you're capturing the information. I'm wondering in some of the emerging cash-based environments, how do we engage, are there ways to engage those who are, I'm setting aside the online promoters who actually don't deliver anything, excluding them from our discussion. But where you have the, it's meeting a need. Are there ways to gather the information from those experiences? Assuming it's a legitimate medical practice, so I'm making some assumptions, so I'll set my assumptions aside. But are there ways to gather that information to engage them in? Is that where the registry effort might best be?

Dr. Gerard Sanacora (02:14:01):

Exactly. I think some type of registry effort. Like I said, the REMs, when I presented earlier, that forces. It's really a carrot and a stick and in that case, it's mostly the stick. You have to register, you have to do everything. You have to collect that data. And then even one step further, the company will actually go out and then troll through databases and everything to look for death records.

Susan Winckler (02:14:27):

Right. That's a very structured system, yes.

Dr. Gerard Sanacora (02:14:28):

Which is very different than some of the reports that's out there. It's like, "Oh, we gave it to 7000, 12,000 people and we heard back from 3000, everybody was fine." Well what about the 9000 that didn't respond? They could have all died and we wouldn't know that. But it's very expensive to do this. It's very time demanding. For years, I've been advocating for some type of registry. And it has to be with a carrot in a stick. It has to be some way of providing something to help the clinicians do this. But it has to be mandatory or else you're not going to get that data.

Susan Winckler (02:15:07):

Well, and I was thinking that registries in the rare disease space, for example, grow from first there a, best described as a phone book, who has this rare disease. And then you engage to the registry

component, which is, well, could we engage you in this exercise where the information is gathered so that we can learn from it? We might have to start voluntary, but I see the intrigue of the patient registry may be more to gather the experience so that we know what's happening to then inform the clinical trial.

Dr. Gerard Sanacora (02:15:50):

Exactly. Even to know what dose. I was shocked when I'm learning that the average dose that people are getting by the end of treatment is above one milligram per kilogram. That is well above what most FDA guidance would say is safe. Most of the guidance would say 60 milligrams per day max and no more than eight doses. But what people are getting in the community is much above that. There's a disconnect there.

Susan Winckler (02:16:19):

Right. Well, and then I think that's where the question is so can we do better? Is that an anecdotal report or is there a way to engage and gather it, gather that information?

Dr. Gerard Sanacora (02:16:31):

Exactly.

Susan Winckler (02:16:33):

So we've done a lot on registries and the data gap. And through the idea this is a place where we need for the repurposed drug, there would be benefit in navigating the FDA process for additional indications for a repurposed drug. What else should we be thinking about, Dr. Leff, if you think as, so say there were to be a new indication and it became within SAMHSA's scope of work. You don't even have to assume that. You could just say hypothetically.

Dr. Michelle Kim Leff (02:17:09):

So I'll tell you what we're doing now and it's a relatively new effort, but for about the past two years or so, we stood up a work group and it is comprised of staff from prevention and treatment and mental health services. And we're really, even though we may not be monitoring and looking at data in our mental health clinics, we are definitely very interested in scanning what's going on in terms of national surveys. And this has been stood up and led by the indomitable Dr. Cameron Wolfe, who's sitting here in the audience. And we are interested because of the prevention aspect too. We're really interested in what's going on, even outside of the clinics. We're looking at illicit and illicit use. And really trying to get a sense of what's going on and thinking about risk reduction strategies, thinking about all sorts of things.

(02:18:14):

I think what's happened though is we've started getting into this work and it's what people are saying in the clinics about these patient registries, the more we know what we want to look at, it just gets, we just are getting in this rabbit hole. And we look at these national surveys and we say, "Oh, we asked about this, but now we need to increase the question." Each question becomes 10 questions the next year because we need to know that much more detail and for us to really understand what's going on. So that's part of our problem right now, I don't have any solutions.

Susan Winckler (02:18:51):

Well, but I think it speaks to particularly as we think first part of the day when we were saying, I asked part of the question was why is ketamine being used clinically in these therapeutic areas? And it was areas of unmet need. Particularly in psychiatry in those components if you have treatment resistant depression or something else. So what I'm hearing from you is that from SAMHSA's mental health services component, there's certainly at least interest in-

Dr. Michelle Kim Leff (02:19:22):

Absolutely very strong interest. And we are trying our best to try to look at the trends, look at national data. We're working with radars, which Dr. Palamore had mentioned. And so yeah, we're trying some things out, but it's very challenging.

Susan Winckler (02:19:45):

Yeah. Yeah. Yeah. So we know we need to pursue this to have more data to get the regulations to help us do this safely. What are other things we should be thinking about?

Captain Gerald Gelfand (02:20:03):

Going back to one of my initial points, I think recognition that each aspect of this may require different avenues of pursuit. So what you might need to address the mental health uses is not the same as what you might need to address the acute pain uses or the chronic pain uses. There may be some relationships, and certainly when you're looking at overall safety data, you could pull those populations together and get combined safety information, but you might not need the same level of evidence to permit one to move forward. And while the other one, well, the evidence isn't there because of it hasn't been investigated to that level, it hasn't been used to that degree to show that it's truly beneficial. But there's plenty of examples of drugs that showed plenty of promise at first, but then when it came time to application, they did not work.

(02:21:03):

In some areas. Maybe this is where ketamine will fall, and maybe that's some of the mental health ones, who knows? Because those represent relatively new indications. But when you're looking at indications that have been in practice for 40 years, then okay, there is evidence to say that even though this is off-label use, it continues to be used in this context successfully to accomplish very specific therapeutic goals.

Susan Winckler (02:21:30):

Yeah. So part of that adjacency, and it is important that we think about the indications and what it is and what we know and how to pursue developing the evidence for those indications, which earlier today there was the suggestion thinking too about pragmatic clinical trials or other ways to generate evidence that that may be helpful.

Dr. Gerard Sanacora (02:21:59):

Again, that's what I was saying. The pragmatic clinical trials are really important, but some of the limitations that put on make them not real world.

Susan Winckler (02:22:07):

Right. I did use different words. There's real world. There's pragmatic trials and clinical trials.

Dr. Gerard Sanacora (02:22:13):

Exactly. And I think we just have to align how dangerous is this use? Because if it is that dangerous, that's scary because it's being used widely and more widely every day. But we can't even do the work to tell us what is being used, whether it's safe, whether it's efficacious. We are actually stymied from doing that work, which is at least semi real world.

Susan Winckler (02:22:40):

Yeah. Which might be a space for clinical trial innovation and see how that persists.

Captain Gerald Gelfand (02:22:44):

And a lot of times the safety consideration comes from animal studies that have no correlate in actual human experience with the drugs. And this is borne out in historical analyses of studies and drugs that have been approved. And the animal data suggested one thing. And then over time, I think like midazolam and pregnancy, how it was considered to be avoid it because it could potentially cause issues with fetal development. And now the evidence in human use that human doses probably is perfectly fine/

Dr. Gerard Sanacora (02:23:18):

But I agree. But it should be enough of a caveat to say, "We want to know this." Not just close our eyes to it and say, "We're not going to look."

Captain Gerald Gelfand (02:23:25):

No, I agree with you. But when you have now generations of experience and literature that now say, "Yeah, maybe this wasn't actually correlating to any human."

Dr. Gerard Sanacora (02:23:39):

I'm agreeing with you. I'm saying it would just be nice to have that data to actually look at it and show that.

Susan Winckler (02:23:44):

Yeah. Yeah, that's really helpful. So I'm going to turn to each of you. I'm going to ask a question and then I'll fill for about 30 seconds so that you can decide how you're going to answer it. But I'm going to turn to each of you. You each get your own last word to do one of two things, either to highlight something that you heard today that was a bit of an aha, maybe something you didn't know in this space. Alternatively, what is the one thing that you would suggest as we look at the next steps in exploring ketamine, what might a next step in exploring ketamine be?

(02:24:22):

So let me repeat those mostly so it gives you more time to think of your answer and they can think about what they might've said, but the alternatives are first, alternative is something that you heard today that you want to underscore and just be like, "Yeah, that was helpful to me." Or the second, what is your admonition for what might be a helpful next step as we continue to explore therapeutic uses in ketamine? I am going to go with Caroline first.

Dr. Caroline Huang (02:24:56):

Thanks, Susan. I think I will go with the, I think the message that every panel mentioned, which is that we need more and better data. And I think more and better data help us make better regulatory decisions. And the way that we get there I think has to be a combination of looking at some of the established pathways that we already have for using our risk benefit approach, but also trying to recognize that there are spaces for innovation when done carefully and appropriately. You can't really comment broadly on some of the questions and the specific discussions that folks have raised on this stage and others. But I would go back, I think to some of the comments that I made about the modernizing clinical trial space and trying to think better about how to use real-world data and real world evidence. They're really tricky questions.

(02:25:41):

I think there are some examples maybe to draw on from other types of therapeutic spaces and whatnot and some other examples of things being repurposed. But it really comes down to wanting to make sure that when we're able to review them, we have the data that we need to make a good decision about whether things can be approved safely and effectively. And if they're not able to do that, then we need to think about where are the data gaps and how do we address them?

Susan Winckler (02:26:04):

And that there may be many sources of data because it's a product that has been used for a long time, albeit some of these uses are new. I'm just going to go down the line. So now you know your order, what you're going to be called on.

Captain Gerald Gelfand (02:26:19):

So thank you. So one thing, and I think this was highlighted by Gerald as well, is in many respects getting good clarity and guidance from our FDA partners as to what we should be looking for. And I'll give an example. There were some draft guidance put out as far as approving analgesic medications in the future, and it needed to demonstrate non-inferiority to existing medication options, which represents a significant departure from demonstration of effectiveness against placebo.

(02:26:52):

Now, if we're looking at in the context of a drug like ketamine, then okay, what we're looking at is a first specific indication, and also a way to move away from opiates as our principal analgesic source. And if we're being told, "Well, you have to show that this drug is not inferior to morphine in providing analgesia." And I would say, "Good luck," because morphine is very effective. And what ends up happening is you have to play with how you administer it. And you have to see, well, where it's the highest bioavailability for each one? Maybe we can play that game and use the context where ketamine is more bioavailable in particular administration, then the morphine equivalent would be.

(02:27:39):

But if you're comparing it to something that is a potent opiate because that is the standard now that we've been told or has been suggested in the draft guidance, then how are you going to move forward with any kind of analgesic? Because yeah, maybe it's not as good as an opiate, but it's good enough and it avoids all the issues that comes with opiates. So I think this is one of the dilemmas we face in moving forward and trying to develop new indications for ketamine or get old indications for ketamine approved by the FDA is, okay, are we setting standards or bars in response to events that happened in the past that are now going to prevent us from actually moving forward, and advancing patient care, and providing treatments that avoid the pitfalls and the harms that we've faced to date?

Susan Winckler (02:28:35):

So that helps us in thinking through, that's a very granular example on making sure we pay attention to that indication component in that this is a product where there are the indication realm is at least multiple. Dr. Leff.

Dr. Michelle Kim Leff (02:28:54):

So I'm going to go a little blue ocean here, and I'm going to say, Caroline, yep, yep. Go army. We talked about this. We talked about this.

Susan Winckler (02:29:06):

All right.

Dr. Michelle Kim Leff (02:29:08):

So Caroline has all the safety data, you've done all the trials, and I would just, what I heard today, and I heard about the bioavailability of oral ketamine, but I would hope, and this is just dreaming, that if this is safe and if this is efficacious, that we would have a root of administration and the ability to have it in the least restrictive setting that would keep it safe so that it would be available for everyone in the US. And there have been studies which show that when you have infusion centers, actually one of Dr. Harding's studies that show that people who live in rural areas drop out of studies because they can't get there twice a week or three times a week. So that's what I would hope for with all these other caveats in place.

Susan Winckler (02:30:10):

Right. Which I think it makes sense and is something to keep in mind that it won't be in the FDA review, but we can think about it in the product development is will this reach the populations who we've heard so much about today? Yeah. Dr. Sancor.

Dr. Gerard Sanacora (02:30:29):

I would try to meld a few of the events. I think what-

Susan Winckler (02:30:31):

That's why you're fourth.

Dr. Gerard Sanacora (02:30:31):

I think very important what Carol said, knowledge is power. If we have more information, it's so critical. And really having representative samples, almost all the work done in this field is not representative of the US population. It's a very thin sliver. So we really need more information. But the one thing I'll add is it costs money. And it's really difficult to get funding to do this. Having some mechanism of funding to collect this data is so critical. We all agree that having the data is important. We may agree on the best ways of doing that or may not, but I can tell you without some funding it's not going to happen. And this falls into that strange thing where it's not something where companies are going to make money off it, really. It's very difficult. So who's going to fund this? And that becomes a real challenge. And when you do get funding, how are you going to ensure that that will get the information you need? I think that's critical.

(02:31:34):

The last point, a little bit of a left turn from where we were, but I think is really critical to bring back is a little bit what Dr. Heifens brought up. The fact that these treatments are part of a treatment system in general, and there's huge contextual effects. We take that personally in psychiatry and mental health, but it's across all of medicine. These contextual effects are huge. And trying to understand a little bit more of how much is the drug specific, whether the dose really matters, whether that dissociative experience matters. People are talking about today, it definitely does. The data really doesn't support that. I think in reality, if you think it matters then it probably will matter. If you're told it doesn't matter, then it's probably not going to matter so much.

(02:32:20):

But I think we really need to understand the whole aspect of the treatment, the contextual effects, the actual specific pharmacologic effects, and to understand this across the broad population of the US, not just the sliver of it. I'll just stop with that.

Susan Winckler (02:32:34):

Very helpful. And Lisa will turn. I always like to give a regulator or representative of regulators the last word. So Lisa Robit.

Lisa Robin (02:32:44):

We're often not the most popular.

Susan Winckler (02:32:48):

Remember it's the cool kids club. We said that in session one.

Lisa Robin (02:32:55):

Yes, I agree with everything. And I think what was an aha moment to me was this lack of the posity of real research or any evidence for what seems very, in some cases very sexy, I guess.

Susan Winckler (02:33:09):

At least very popular. Yes.

Lisa Robin (02:33:13):

But we must do all of that and we need the research and we need to look at this, but we have a real problem in the states because there is a proliferation of these clinics and from my understanding of talking to my boards that many of them are not doing good medicine, and not having oversight by not very much oversight, if any. And so I think we don't have time just to do nothing. So there's going to be some bad outcomes. I fear because you've seen it in a lot. And I was very upset to hear that now the IV hydration, which is another thing that's got a lot of people worried about, are also offering the ketamine. And I think we must realize what's going on out there. And as it was said early in the day, it's the wild west. So thank you.

Susan Winckler (02:34:14):

So there we go. So we all right, we've got to get to work. That was the last word. And so as we finish up today, I'll just say let's thank our panel for helping us think about the future. Thanks to you and to all of our speakers. What an illuminating day. My talking points say that I was supposed to say that we answered many of our questions on the clinical uses of ketamine, and I can't say that, but we did share a

lot of information about those emerging clinical uses, about the challenges that we see about the reality and the environment. And so I hope that you have learned a lot.

(02:34:53):

Just a reminder, we will be posting the taping, so the recording of today's material, the transcript, and all of the slides later this week. Thank you so much. Be well and take care.