Pioneering Ketamine Treatment for Depression

[00:00:00]

Ketamine Questions Intro

Dennis Charney: Hello, and welcome back to The Vitals, the Mount Sinai Health System's groundbreaking roundtable video podcast. I'm your guest host for the episode, Dr. Dennis Charney, a biological psychiatrist and former dean of the Icahn School of Medicine at Mount Sinai. The subject today of ketamine treatment for depression has received a lot of coverage in the media, often without attention paid to the little things, like science or data.

So questions pile up. How does ketamine work as an antidepressant? What is the research currently telling us? And what does the next generation of treatment look like? To walk us through all of this, we're joined by Doctors Adriana Feder and James Murrough, both professors of psychiatry here at the Mount Sinai Health [00:01:00] System, and both at the forefront of research and treatment.

Welcome, James, and welcome, Adriana.

Adriana Feder: Good

James Murrough: to be here.

Dennis Charney: Today we're gonna talk about ketamine, uh, which is a treatment for depression. Uh, in, in fact, it's, unquote, "the market" in which doctors can prescribe ketamine. It's called the Spravato.

Discovery at Yale

Dennis Charney: I wanna start by talking about, like, how was ketamine actually discovered as a new treatment, because, uh, it's very different than other antidepressant drugs like Prozac and, and Zoloft i- in, in a couple of ways.

One, ketamine works very fast. It can work in a few hours, and it can work for patients who have not responded effectively with other antidepressant drugs,

and we're gonna get into that. But first I wanna talk about how it [00:02:00] was discovered, and I was one of the discoverers of ketamine with John Krystal, who's now the chair of psychiatry at Yale.

But when we made the discovery, it was back in the mid 1990s, so we were a lot younger, and at that point I was at Yale and so was John, and we were working together. Now, w- we had done a lot of work with the traditional antidepressants, like I mentioned, Prozac and Zoloft, and we were unsatisfied with the rate in which those drugs worked and how fast they worked.

Traditionally, those drugs take several weeks or in some cases, uh, cases even months, and they don't work for everybody. Right. And depression is a very serious disease. Some patients are suicidal and even commit suicide, so we wanted to do better. Now, the traditional antidepressants work through a systems called monoamines.

That's like [00:03:00] norepinephrine or adrenaline or the neurochemical serotonin. So we felt we, we needed to make a discovery that was different than those drugs. So we had done a lot of studies in trying to maximize the effect of the available drugs at that time, and we really couldn't do it. So we thought there might be another chemical system in the brain that might work better than those monoamines, and that system is glutamate, another neurotransmitter in the brain The drug that came to our mind at that point that affected glutamate was ketamine.

Ketamine had been around for decades. It actually was being used as an anesthetic agent. It was also recreationally used and was known as Special K. But we thought maybe it could be an antidepressant. So initially we did a study when we were at Yale in ri- [00:04:00] seven patients and s- when, uh-- who were depressed, and when we did that work, it was like a miracle.

Patients who were depressed in many cases for a very long time, when we gave them ketamine, they got better in a few hours. Now, John and I were experienced clinicians, and even though it was only a small number of patients, we felt this was real and it was spectacular.

From Skepticism to FDA

Dennis Charney: So we ended up publishing a small paper in a journal called Biological Psychiatry, and nobody believed it.

The field did, the field did not believe it. They felt you couldn't get patients better so quickly, and there was concern about ketamine because it was used recreationally as Special K. So I, I left Yale at that point to go to the National Institutes of Mental Health, and they got the group there who working [00:05:00] closely with me, Carlos Zarate and Husseini Manji, and we said, "Okay, let's do another study with ketamine."

And we found the same result, and we published that in another journal. And after that second paper, that second study, the field started to believe that actually ketamine might work in seriously depressed people, and it works fast. And so it did change the field. A lot of people said it was the biggest change in the treatment of depression for 50 years.

And ultimately, in a collaboration with a drug company, Janssen, part of J&J, ketamine was approved by the FDA as a treatment for treatment-resistant depression, and is now marketed as Spravato. So that's a brief description of how ketamine came to be, and then now it's used all over the world. And I have J- James Murrough here, Adriana Fetter [00:06:00] here, who have a lot of experience with using ketamine.

So I thought we would start, James- Yeah ... with you. Yeah. What, what's been your clinical experience-

James Murrough: Yeah ...

Dennis Charney: in using ketamine for treatment-resistant depression?

James Murrough: Yeah. Thanks, Dennis.

Mount Sinai Trials

James Murrough: Also, maybe even before I answer that, I'm thinking back to-- So I, during my training in psychiatry, I met Dennis and Adriana, I think after the initial study was done at Yale that Dennis described, and then the second one at the NIMH.

Then Dennis moved to Mount Sinai, became the dean, and started a new research program, and that was kind of happening, uh, as I was training to become a psychiatrist here, and the first order of business was, let's actually replicate it again, right, at Mount Sinai and a few other things. Right. 'Cause one

of the memories I'm having of those sort of early days is when I started working with it, set up the first research studies, uh-

Dennis Charney: Yeah, [00:07:00] but that

James Murrough: was some- With you.

This was-

Dennis Charney: That's a long time ago

James Murrough: now ... this was 2000, mid-2000s. Yeah.

Dennis Charney: Yeah. 20 years ago.

James Murrough: Yeah. Yeah, exactly. And even though the first two studies were published, I think the first study had seven or eight people, the second one had maybe 20, single infusion versus placebo saline, there were still a lot of questions.

It was still as-- an uphill battle, a lot of people not convinced, maybe rightly so, and that's science. In those days, we did a lot of things to really further that, and one of the first things we did, as, was ask the question-- 'Cause one of the questions as a sort of a junior doctor and researcher at the time, I would go to conferences, and people knew about the early studies, and we were starting to do things at Mount Sinai, and one of the questions I heard was, "But you were giving a potent anesthetic to someone with depression, and then they're reporting they don't have depression anymore," or something to this effect.

Right. "Could you have given any anesthetic?" [00:08:00] I remember hearing-- I remember presenting a poster of the first study- And people that don't remember this, the first study ever to give more than one infusion to a patient as an actual treatment was developed and done at Mount Sinai. Yeah. I remember presenting that data and people saying, "How do you know it's..."

They didn't, I think, like, they didn't forget they were depressed 'cause an anesthetic, so-

Dennis Charney: By the way, though, we had to remind them that the dose of ketamine that we used- It was- ... was way below-

James Murrough: That's right ...

Dennis Charney: the anesthetic dose. That's right. So it wasn't working as a s-

James Murrough: That's right ...

Dennis Charney: as part of anesthesia.

James Murrough: That's right. But one of the things we did, and now even to this day set the standard of how do you have a control condition? We used a different anesthetic, and that turned out to be, I think, a major contribution to the field. We used midazolam, Versed. And in the first-- the-- what I think of as the third landmark study of ketamine in severe depression, the first one being at Yale, the second one being at NIMH, the third one being at Mount [00:09:00] Sinai.

This time comparing a single dose of ketamine to a different anesthetic, a much higher bar for a placebo, and it was a multi-site study, and it was in about three times as many individuals. So that was really exciting. Now to your question, so now way before-- This was way before the Spravato days, way be- Well,

Dennis Charney: then we d- we did the first repeated dose study.

James Murrough: So we

Dennis Charney: did- It was started with a single dose, but then-

James Murrough: That's right ...

Dennis Charney: we did the repeated dose.

James Murrough: That's right. So the first s- So we did the first of what we were calling an active control, an active placebo, ketamine versus midazolam, but at the same time, no one had ever at least published on giving more than one infusion.

So we gave-- We r- we looked at-- Uh, we said, "What about-- What's another model of a medical treatment for severe depression?" We thought ECT, Monday, Wednesday, Friday for at least two weeks. So that became the-- And that up till maybe still now, that was known as the Mount Sinai schedule- Right ... of ketamine, Monday, Wednesday, Friday for two weeks.

And even before we started using it clinically in those early days of the [00:10:00] treatments, yeah, we saw some miracles, I think it's fair to say. Did every single patient, were they-- Was every patient cured? No.

Dennis Charney: So d- you-

James Murrough: But we saw- Can you give

Dennis Charney: us an example?

James Murrough: Well, I, I was, I was thinking earlier before we started of a case fairly early on.

It's often the first one or two that you see stick in your mind. This was a woman. She was in her 50s and had done very well, had recurrent depression, but had been in a depression for I think more than two or three years by the time we saw her in the research clinic. And one of the things we know d- depression is one of the most serious medical conditions there are, in part 'cause it's so chronic and there's so much disability.

So- Like we hear so many times, this person had stopped being able to work. She had withdrawn from her family, and her life was not at all what she'd wanted, and she had been struggling for years. Came into the research program, and I think these were the days where we were still just doing the single infusion.

And I remember after her treatment, [00:11:00] so we would have them come back the next day, and that was kind of the, what we call in clinical research, the primary outcome. What is their depression measure one day after the treatment? And I can still remember also the staff, like the research coordinator and stuff Woman comes in and is like you do a double take, kinda looks like a different person, just brighter, wearing makeup, and just describing a, like a feeling of a lifted weight starting around after she went home from the clinic, persisting at least till just that morning.

And sitting around, "Okay-"

Dennis Charney: Maybe

James Murrough: it's real. Maybe- ... "We're onto something here" Maybe

Dennis Charney: it's

James Murrough: real. Something's going on.

Dennis Charney: So it-

James Murrough: Yeah ...

Dennis Charney: it all started with a few patients.

James Murrough: Right.

Dennis Charney: And clinicians who were knowledgeable and said, "Maybe we got a real thing here."

James Murrough: Yeah.

Dennis Charney: A- and now ketamine's been used in millions of-

James Murrough: Amazing

Dennis Charney: depressed patients. It's

James Murrough: amazing.

PTSD Breakthroughs

Dennis Charney: And let me jump to Adriana. Now, A- Adriana h- has led studies looking at whether ketamine actually c- can work in [00:12:00] post-traumatic stress disorder. It's not approved yet by the FDA for that condition, but Adriana, can you say a little bit about how did you get started in looking at whether ketamine can work in post-traumatic stress disorder, and what were some of the results?

Adriana Feder: Sure. Sure. Also, many years ago, shortly, uh, after I had joined your research team, you became interested, because of the overlap between depression and PTSD, and they often present together, patients suffer both from PTSD and depression, you became interested in looking at whether ketamine might also not help with PTSD.

And I've always been interested in the topics of trauma and resilience. And the, in patients, there aren't, even to this date, that many effective and approved

treatments for patients with PTSD. There are some that work. Only two medications remain FDA-approved for PTSD.

Dennis Charney: And [00:13:00] that's actually incredibly bad-

Adriana Feder: Yes

Dennis Charney: uh, because PTSD is so serious, it's common, and to have only two medicines who act- that actually don't work that well-

Adriana Feder: Yes, they,

Dennis Charney: they- ... uh, to offer to those patients.

Adriana Feder: Yes, and also exposure-based psychotherapies are the standard of treatment, and yet even for those therapies, over s- half of patients have no response or insufficient response or don't tolerate the treatment.

And so I wanna say that patients with PTSD experience recurrent-- They cannot move past their experience of trauma. They experience recurrent intrusive thoughts and memories and also nightmares about the trauma. They avoid any triggers, so they have a more restricted life, and also restricted emotionally because they become distant from friends and sometimes family, and they cannot experience the full range of emotions, like positive emotions.

And so the first study that I led with [00:14:00] you here at Mount Sinai of ketamine for PTSD was with patients with more severe forms of chronic PTSD.

Dennis Charney: And just to interrupt for a moment And so w- what, what was the nature of the PTSD? What was c- in those patients, what was causing the post-traumatic stress disorder?

Adriana Feder: So in a lot of these patients had experienced an assault or a sexual assault, and they had persistent symptoms for many years. And others, we had a, a 9/11 responder who had assisted in the aftermath of the 9/11 attacks on the World Trade Center and kept reliving that experience. Hmm. And there were some accident survivors, severe accident survivors.

And so what we saw, the primary outcome, we were interested, just like the first studies of depression that you, James, and Dennis mentioned, we were initially interested in the rapid response, the acute response. And I think that actually that first [00:15:00] single infusion of ketamine study where we looked at the

response a day later was the first study that we conducted actually comparing it to the psychoactive placebo midazolam that you had mentioned- Right

James. And it showed a su- superior response. It was a randomized control trial, and it showed a superior response at 24 hours to ketamine compared to midazolam. And we saw a subset of patients, not everyone, but there was a subset of patients who, again, a few hours after felt a relief, like this blanket- Hmm

weightlifting. Mm-hmm, mm-hmm, yeah. And also felt that they could connect more with others after an initial infusion and sometimes a few hours later.

Repeated Infusions Protocol

Adriana Feder: And we followed that study at Mount Sinai with a first repeated study of ketamine for PTSD compared to midazolam. Repeated, yeah. Repeated infusions.

Repeated. Um, the first study of repeated infusions of ketamine, and we used that same frequency and total number of infusions three times a [00:16:00] week for two consecutive weeks. And that was also supported by the fact that in the first study, the average time to losing the initial response was two to three days, and so we thought that we liked that frequency of infusion.

And-

Dennis Charney: That's actually how we came up with the frequency.

James Murrough: Yeah.

Dennis Charney: That we found- Yeah ... that if you gave a single dose, it worked right away, it was a very strong effect, but it was not like an antibiotic. 24, 48, 72 hours later, some symptoms returned, and that's how we thought, "Let's give it repeatedly so there's no loss of effect."

And so we thought Three times a week. Now actually it's marketed with Spravato as twice a week. Yeah. Yes. And that works very effectively.

Adriana Feder: Where there was interestingly in depression, there were studies showing that twice a week works equally well for depression-

James Murrough: Yes, yes ...

Adriana Feder: as three times a week. Eventually, yeah.

Dennis Charney: Mm-hmm, yeah.

Adriana Feder: Potentially, however, in PTSD, it might not be, it might be necessary to give it, and that still [00:17:00] needs to be studied further three times a week. But with that three times a week study, we found a, a robust rapid response, and, uh, we measured it two weeks after the first infusion of six infusions.

And again, patients on two-thirds of patients in the ketamine group were significantly better compared to only 20% in the midazolam

Dennis Charney: group. Yes, it has a big effect. Y- we know in depression, you're very sad, you may even be suicidal. Uh, and by the way, we know that ketamine can work for suicidal patients. So we, we do have a good feeling what's happening to those depressed patients.

What Improves in PTSD

Dennis Charney: When a PTSD patient is getting better. What is getting better in those patients?

Adriana Feder: A range of symptoms are getting better, including those that are unique to PTSD, the nightmares, the intrusive thoughts, and also jumping or being very reactive to certain sounds or triggers that are reminders of trauma. So [00:18:00] for example, I can think of a patient who had been a witness, very close, close m- witness of a shooting, and she had described that every time she opened the door...

It, the shooting occurred outdoors, outside a supermarket, and every time she opened her door to go outside, she would feel this intense fear-

Dennis Charney: Yes ...

Adriana Feder: come over her. And so after the first or second infusion, that feeling s- subsided significantly. She didn't... She felt she could open the door and walk outside

Dennis Charney: and- So it cha- it changed her life.

Adriana Feder: It, it- It

Dennis Charney: opened it up ...

Adriana Feder: it did change her life and, and we have some patients who stopped, during the period of infusions and subsequent weeks of after repeated infusions, also stopped having nightmares. And I also have an example of a 9/11 survivor who felt very tense and afraid whenever she heard an airplane pass overhead, and [00:19:00] that also f- she experienced relief from that.

That one actually was from a combination that I can talk about later of ketamine with an exposure-based psychotherapy from a pilot study that we conducted. I do wanna say that depressed mood or a feeling of not being able to enjoy life or connection with others is also part of PTSD. And so in addition to these de- decrease in sudden arousal or reactivity, we also see an improvement in feeling connected to others, wanting to go out more, feeling more able- Mm-hmm

to enjoy activities, things like that in patients with PTSD.

Why Combine Psychotherapy

Dennis Charney: Yeah, that's an important topic, and I wanna actually get to that now, and that is, what is the role of psychotherapy? Because my own feeling is that most patients need a combination.

James Murrough: Yeah.

Dennis Charney: If they've been depressed for many years-

James Murrough: Yeah ...

Dennis Charney: it's affected their life, and in a way, they need rehabilitation.

Yeah. And the same is true [00:20:00] with PTSD patients. James, your opinion, and actually I know you're doing a study now- Yeah ... looking at a therapy along with giving ketamine.

James Murrough: Yeah. So you're exactly right. I would say the sort of standard recommendations for the treatment, particularly of more chronic or

serious forms of depression, is usually the patient will benefit from a combination of medicine and psychotherapy.

So in some ways, that's the starting point.

Neuroplasticity Explained

James Murrough: It kind of makes sense, and you can think of it from a sort of also biological level of if the drug is helping the brain to start to recover, we know that chronic stress causes dysfunction in the brain, including loss of dendrites and other things in cortex, and that can lead to low, called neuroplasticity, even difficulty learning.

If you're given a medicine that can boost that, and it seems like ketamine in particular from a neurochemical standpoint, that sort of seems to be its hallmark of increasing [00:21:00] neuroplasticity. Other drugs like Prozac also do it, but probably to a lesser degree and takes longer. Mm-hmm. But ketamine does it quickly.

That was kind of one of the early biological insights, as you well know, with how is ketamine working in the brain that by stimulating glutamate, it's driving these sort of pro-plasticity pathways. And it would stand to reason that if somebody is in a therapeutic environment, then that's gonna interact with that plasticity, and they can learn more in whether the learning is sort of unlearning maladaptive habits or unlearning repetitive negative thinking, negative self-talk, the cognitive biases that are part of depression.

So they probably interact. That being said, most treatments, including ketamine Most medicines are studied a little bit in a vacuum, so they're not studied together with psychotherapy. So we actually don't have a ton of data or, like, big comparative studies about what if-- There's been some of this work, right?

Right. What if someone's-- You compare [00:22:00] people to, with just therapy to just medicine and to both, and there's been some sort of landmark studies done, but-

Dennis Charney: Generally not with ketamine, though.

James Murrough: Not with ketamine. I don't think that's been done at all with ketamine, and the marketed form of ketamine, which is S-ketamine, Spravato, as you mentioned before, was certainly done without regard to therapy.

Typically, in these s- trials, if a participant that gets enrolled in a study, let's say with ketamine, if they're in regular psychotherapy, they can stay.

Dennis Charney: Right.

James Murrough: Yeah. You're not supposed to start new therapy or stop. That's just controlling baseline. But it's never really been compared. Do, do people do better?

So exactly. So we're doing a study right now at Mount Sinai that we're very excited about.

Ketamine Assisted Therapy Study

James Murrough: In the context of the sort of rediscovery and interest in psychedelics, one of the thinking with psychedelic medicines, whether it's the classic serotonergic psychedelics like psilocybin or the so-called empathogens like MDMA for trauma, which many people may be aware of, some of those models of treatment, the therapy was [00:23:00] really an integral part Something we came to learn a few years ago is that practitioners in the community were actually using ketamine in a, let's call it psychedelic-assisted therapy model.

So this would mean the patient would come in, they would have chronic depression or PTSD or a combination, and they would undergo a treatment with a potent psychoactive drug. But it turns out one that you can actually get and doctors can prescribe off-label is ketamine.

Dennis Charney: Yes.

James Murrough: T- today you can't, a doctor can't prescribe psilocybin today.

They, they just can't get a hold of it, MDMA, but you can legally with ketamine. And come to find out in the last number of years, practitioners in the community started using ketamine to bring about these acute psychedelic-like experiences, dare I say it like that, and material comes up. And we know that material comes up.

In even the earliest studies that I was part of at Mount Sinai, patients would describe to us anecdotally, they would have [00:24:00] these sometimes profound experiences. Sometimes they would-- This was when they're on the

drug and then when they come off the drug, it takes about an hour and they'd tell us about their experience just anecdotally, right?

We're asking about side effects and other things, and they'd say, "Geez, Doc, that was pretty interesting. I felt like I went to the end of the universe and back," or, "I felt like time stood still." Or some of them would even... I think I was telling you about an example a couple of weeks ago. A patient spontaneously said to me that he had examined some of the problems in his life from a different perspective and came to some solutions.

He's telling me this after, and it-- they were, like, working. So it wasn't just so-Part

Dennis Charney: of recovery.

James Murrough: Part of recovery. So we don't know. So a really interesting question is we don't know with ketamine, and maybe it's a similar question with some of the other sort of potent, rapidly acting treatments that might be making their way down the pike, like psilocybin or MDMA.

What's the role of psychotherapy? So we're doing a clinical trial right now, I think it's the first of its kind, in people with depression that [00:25:00] are treatment-seeking and if they enter the study, they get ketamine, the, what we call the standard Mount Sinai model. They'll get it two or three times a week for a few weeks without any specific therapy.

Or they get ketamine in the context of this psychedelic-assisted therapy model, and this is a little bit different than just someone seeing their therapist once a week and they're also taking their medicine. That's a standard combination of therapy and medicine that we usually would recommend or prescribe for the treatment of depression.

But this is actually meeting with a therapist. The therapist is there during the ketamine experience, during the dosing, and then is working with the material that comes up, often in the immediate one to two hours after the person has had an experience on ketamine.

Why Study Integrated Care

James Murrough: They're there at the clinic, a clinical setting, calming, muted lighting, that type of thing, music.

Adriana Feder: Again- And that's such an important study to conduct because, as you said, practitioners in the community are doing this

James Murrough: kind of- We were surprised. It [00:26:00] turns out they were doing it, and this is an intensive, potentially costly intervention, but if it's effective and safe, we wanna know about it.

Adriana Feder: Yes.

James Murrough: So we hope to learn, we hope to know, ask an empirical que- Our gut is that probably if people get the integrated therapy, that's gonna be a good thing.

Maybe the effect of ketamine will be enhanced. Maybe it'll last longer, but as good-

Dennis Charney: It could be life-changing.

James Murrough: Yeah. Yeah. But we need to know the answer. We don't know. We think, but we gotta actually get the data.

Dennis Charney: Right.

How to Join the Trial

Dennis Charney: So if somebody's interested in this trial-

James Murrough: Yes ...

Dennis Charney: people listening to this podcast-

James Murrough: Yes ...

Dennis Charney: how can they find out more about

James Murrough: it?

Contact me. Find me on the Mount Sinai website. Send me an email, james.muro@mssm.edu. The Depression Center has a website, so please go there, and we'd love to hear from you.

Dennis Charney: So James, thank you- Yeah ... for that. That's-

James Murrough: Yeah ...

Dennis Charney: that's very important-

James Murrough: Yeah ...

Dennis Charney: to look at the role of therapy and u- the use of ketamine as a combination.

Adriana, you're also [00:27:00] interested in this topic, and I think what you're doing is also very important. Why don't you describe the work that you've been doing in looking at the treatment with ketamine along with a different kind of psychotherapeutic approach?

Exposure Therapy Explained

Adriana Feder: I have been looking at ketamine combined with an exposure-based psychotherapy, a brief exposure therapy called written exposure therapy.

And to backtrack a bit, I have ment- I had mentioned earlier that exposure-based psychotherapies are the therapies that have the most evidence base. Now,

Dennis Charney: I'm sorry to interrupt.

Adriana Feder: Yeah.

Dennis Charney: Some of our listeners may not know-

Adriana Feder: Oh ...

Dennis Charney: what exposure

Adriana Feder: means. No, that's a good point. So if you could describe that. So exposure-based psychotherapy is a type of psychotherapy that focuses on the trauma and the memories and feelings and thoughts, and also sensations like sounds or smells.

And the patient is asked to focus repeatedly on those with the idea that there will be a habituation or a decrease in anxiety and [00:28:00] re-experiencing

over time. And those have been shown to be quite effective for PTSD, but patients sometimes with more severe forms of PTSD are drop out of these therapies because it's hard to sit there with memories of the trauma, or it's not effective for everyone.

And one important finding in PTSD is that many patients with PTSD have a decreased ability to extinguish their fear. So their fear extinction learn- learning is compromised in PTSD. And that is thought to potentially be due to disconnection between regions in the brain that are involved in fear extinction and emotion regulation.

In fact, PTSD has been called- Now,

Dennis Charney: fear... Or just to-

Adriana Feder: Yeah ...

Dennis Charney: elaborate on that. Fear extinction means- Yeah ... despite dealing with your fear repeatedly, it doesn't diminish.

Adriana Feder: Yep.

Dennis Charney: And so extinction means, and we wanna promote this, that the more and [00:29:00] more as you face your fears, the fears are reduced, and you can get on with your life without being in- facing your fear in a way that you're inhibited in your life.

And your approach is to enhance the extinguishing of those fears-

Adriana Feder: That's right ...

Dennis Charney: in combination with ketamine.

Adriana Feder: That's right. And what we found in a pilot study of looking at the brain in patients with PTSD who received repeated infusions, is that in those patients who for whom ketamine worked in PTSD, we, looking at their brains with neuroimaging, we saw that the frontal cortex had better regulation of the amygdala, which is the key initial emotional, emotion response region of the brain.

And so it seems that when you give repeated infusions to start with, and perhaps add [00:30:00] an exposure-based or trauma-focused psychotherapy, that the infusions might prime the brain to improve the connectivity and brain function in these patients with PTSD that might enhance the function of trauma-focused psychotherapy.

And we chose this brief psychotherapy called written exposure therapy that consists of five sessions, and there's less therapist involvement. It's easier to train therapists, and we just published-

Dennis Charney: Let me-

Adriana Feder: Yeah ...

Dennis Charney: stop you for a moment. Sure. Then what is Written exposure therapy

Adriana Feder: Yeah. Sure

Dennis Charney: Can you describe that-

Adriana Feder: Yeah

Dennis Charney: to our listeners?

Adriana Feder: In written exposure therapy, the first session, the therapist explains the idea of focusing on the memory of the trauma and writing about it. Although initially it might be very scary, it might lead to fear extinction or habituation to the memory, or decreased fear over time. And then following [00:31:00] that, each of the sessions consists of a brief touching base with the therapist and the patient, and then the patient writes for 30 minutes about the trauma and their memories, vivid memories of the trauma, and also the meaning of the trauma in their life and their impact.

And we think that by giving ketamine, and importantly, this is a different model than the one that James spoke about n- fro- compared to ketamine-assisted psychotherapy, we administered the wr- written exposure therapy sessions on different days from the infusion, infusions. And that is because we think that the infusions improve connectivity in the brain, make those circuitry, those circuits involved in emotion regulation work better, and potentially increase the efficacy of the trauma-focused psychotherapy.

Dennis Charney: So the bottom line is that you're both taking the approach [00:32:00] that, that ketamine is doing s- certain things. It's improving mood in depressed patients-

James Murrough: Yeah ...

Dennis Charney: and other symptoms. And in PTSD, ketamine alone diminishes the impact of traumatic memories. But now you're both taking the approach of to enhance that effect with different forms of psychotherapy, and I want our listeners to understand that.

James Murrough: Mm-hmm.

Dennis Charney: That ketamine can work by itself-

James Murrough: Yeah ...

Dennis Charney: but we think we have ways now here at Mount Sinai to further enhance the effect so their life has more meaning, that it, it could have long-term positive effects, both in patients with severe depression and in patients with the PTSD.

Ketamine and Suicidality

Dennis Charney: James, I wanna go back to you for a second.

Feeling suicidal-

James Murrough: Yeah ...

Dennis Charney: obviously is, in a sense, the worst form of depression.

James Murrough: Yeah

Dennis Charney: And you've been interested in looking at the impact of ketamine on suicidal [00:33:00] thinking-

James Murrough: Yeah ...

Dennis Charney: with the hope that it would then prevent suicide. Yeah. Can you say a little bit about

James Murrough: that? Yeah, yeah, absolutely. Yeah. S- suicide is a devastating outcome of depression that everybody's trying to prevent.

The majority of individuals who die by suicide have a diagnosis of major depression. From my perspective, the treatment, the-- there's lots of ways, and suicide is a crisis in this country, and there's lots of different ways to come at it, social, other things. But from a medical perspective, the rapid treatment of a severe depression is kinda the best, is critical.

And so ketamine, on one hand, is a-- it's already a great candidate because it's now established to be rapidly effective for depression. From the early studies at Mount Sinai, and I was gonna ma-

Dennis Charney: Let's give Mount Sinai credit

James Murrough: Okay, I have to say.

Dennis Charney: Credit is due.

James Murrough: I have to say. So we, we looked at, we've been talking a lot about different symptoms of depression, symptoms of PTSD.

So for listeners out there, there's, [00:34:00] I think there's nine criteria for depression, and there's a range of symptoms. Sad mood is certainly one, but fatigue, inability to experience pleasure, chronic negative thinking, disrupted sleep, loss of appetite, and suicidal thinking or wanting to die, and there's others.

And we were very curious early on which symptoms in depression, let alone PTSD, is ketamine active against. And I was kinda hoping that it would be clear which cluster, 'cause that would be scientifically interesting, 'cause then we'd know which circuits do we go after in the brain. Which-- But it turned out it was kinda across the board.

So ketamine was- looked pan-active in depression. Well, that's a good thing for patients. Wh- which is good for patients. But even there, consistently we saw there was a dramatic reduction in suicidal thinking, and in particular, we noted in the early studies, even for people that didn't meet a threshold of what we would consider a sort of clinical remission or response [00:35:00] from their depression, often their suicidal thinking went to zero.

So there was-

Dennis Charney: So what did you do about that? What did we do about it? So you observed that.

James Murrough: We observed it, and actually, again, as a young researcher working with you and the team, designed what was the first study- Specifically to look at reduction in suicide as the primary outcome from depression. And what we did is we invited people that were admitted to Mount Sinai Hospital that could have had depression, bipolar disorder, PTSD, OCD, or anxiety dis- kind of anything in the mood and anxiety spectrum, not schizophrenia or autism.

But if you had a sort of stress-related mood affective disorder, didn't matter, you could come in if you were admitted for suicidality. And that was the first, a small study. I mean, we had 10 and 10, 12 and 12 published.

Dennis Charney: And so what did you find?

James Murrough: We find that ketamine was superior to our old friend midazolam at reducing suicidal thinking, [00:36:00] and that work's been fol- followed up now multiple times, and it's been very exciting.

That finding has really stuck.

Dennis Charney: Right.

James Murrough: Ketamine seems to have specific activity against suicidality, and if you think what other medicines in psychiatry have that? Lithium-

Dennis Charney: And may- I was gonna say lithium probably ...

James Murrough: and maybe clozapine-

Dennis Charney: Yeah ...

James Murrough: in psychosis, and now ketamine. So that's very exciting.

Dennis Charney: And you deserve a lot of credit for that study.

Uh, you were the first, along with the NIMH group, right?

James Murrough: Yeah. Very similar. Around the, right around the same

Dennis Charney: time. Right around the same time.

James Murrough: Yeah.

Dennis Charney: And ultimately, the FDA has been convinced of that.

James Murrough: Yeah.

Dennis Charney: Right?

James Murrough: I think the first label, I think that I'm aware of-

Dennis Charney: Ketamine is labeled as an effective treatment for suicidality

James Murrough: for depression with suicidal ideation. That's right.

Dennis Charney: Yeah. The, so the message there is that, to those listening, if you're seriously depressed and if you're even have suicidal thinking, or even if, unfortunately, maybe even a plan- [00:37:00]

James Murrough: Yeah ...

Dennis Charney: there's hope.

James Murrough: Yeah.

Dennis Charney: We like to s- we don't like to say, but we often say that suicide i- is a permanent solution to a temporary problem.

James Murrough: Right.

Dennis Charney: And here we have a drug, ketamine-

James Murrough: Yes ...

Dennis Charney: that can help you get out of that.

James Murrough: That's right.

Dennis Charney: Right?

James Murrough: Yep.

Dennis Charney: Yep.

Brain Circuits and Hopeful Wrap

Dennis Charney: Let's talk, again, toward the end here, but ketamine does affect the brain, and that's probably in, in certain ways that probably relate to why it works right away and works for serious f- forms of depression and PTSD.

Adriana, you've done some research on the impact of ketamine on different brain circuits. Would you like to review that?

Adriana Feder: Yes. I'm-- my research was on PTSD, and we found that in treatment responders, patients with PTSD who feel better after repeated infusions of ketamine, they showed more better regulation of emotion [00:38:00] regulation and improvement in the function of emotion regulation circuits.

More the prefrontal cortex had the better ability to tone down the overactivation of the basic emotional region, emotion respond region, the amygdala. And that's why actually we were, as I mentioned before, interested in combining ketamine with a psychotherapy, and we actually found in a preliminary study that was recently published that adding written exposure therapy to repeated infusions of ketamine, uh, actually resulted in patients remaining better for several months.

For those who responded to the combined treatment stayed better when we talked to them at the six-month time point. So that's a very exciting potential, uh,

Dennis Charney: for the future. It may have more pro- it-- we haven't proven this yet, but it may have more profound effect on those very same circuits that are underlie some of the symptoms of PTSD.

Adriana Feder: Of PTSD, exactly. And what's [00:39:00] needed now is a larger randomized control trial where we compare the combination versus the therapy alone or the ketamine alone.

Dennis Charney: Yep. #

James Murrough: NIH.

Dennis Charney: And, you know, James, you've done a lot of work on what-

James Murrough: Yeah,

Dennis Charney: yeah ... ketamine does to the brain. Yeah. What, what are the

James Murrough: highlights

Dennis Charney: there?

James Murrough: Yeah, yeah.

So I'm thinking about the first study we published. So if you do a simple experiment where you take people in a depression and you show them emotionally salient pictures, and in the simplest case you show pictures of other people and they can be expressing like a sad, negative affect or like a happy positive, very consistent finding in depression, you look at a part of the brain, there's a-- deep in the brain, it's an old evolutionarily old part of the brain that was really important for positive affect The basal ganglia.

These regions are-- do not show normal activation when people look at positive images when you have them in a scanner, right? And ketamine reversed that in 24 [00:40:00] hours after treatment. So we imaged a bunch of healthy adults that did not have depression and then individuals with serious depression before treatment, and we saw what we expected to see, which was their brain had an abnormal lack of response to positive salient information in the environment in the form of smiling human faces.

And the next day, at a brain level, you couldn't really tell the difference between the depressed brains and the healthy. So this kind of showed that ketamine was doing something at this, within this sort of a, an, a complementary critical brain system to the one Adriana's talking about, which supports positive emotion.

This is in the basal ganglia, and for those of you aficionados out there, this is also described as the ventral striatum or nucleus accumbens. So that was an early finding, and that's been replicated, that ketamine rapidly increases the ability of the brain to [00:41:00] respond to positive stimuli. And I'll just say one other finding from us and others, Adriana mentioned the prefrontal cortex, very important for abstract thinking- That's the

Dennis Charney: front part of the brain.

James Murrough: Yeah. Kind of the newest in the history of humans, and it tends to be relatively offline, relatively in a depression, and we think that maybe that also is related to how in a depression someone's emotions, they feel like they don't have control over it. They have difficulty thinking. They have difficulty planning.

These are all things that are critical for the prefrontal cortex, and ketamine now across a number of studies one way or another has been showed to bring that prefrontal cortex online more, more integrated with the rest of the brain. So it's increasing the function of these important prefrontal cortical systems and at the same time increasing the ability of some of these more basic hedonic or almost instinctual systems in the brain to respond to positive information in their environment.

So those are two, two, [00:42:00] two, two, I think, important signals that we've been seeing.

Dennis Charney: Thank you. So we're gonna wrap up, but I ran a-- I wanna wrap up in this way. We've talked a lot about ketamine and how it can work for the most serious forms of depression, including patients who have suicidal thinking, and how it works for serious forms of post-traumatic stress disorder.

And so the me-- I wanna leave you with this, and that is there's hope And you can get treatment that will help you with your depression. And one, one place you can get it, and here I'm biased, is here at Mount Sinai. That we are one of the very best places in the world to get treatment for depression using both established approved treatments like ketamine, but also we're never satisfied We're always looking to do better, to [00:43:00] develop new medicines, looking at combination treatments with psychotherapy.

We're never satisfied. So James, I wanna let our audience know again-

James Murrough: Yeah ...

Dennis Charney: how can they-

James Murrough: Yeah ...

Dennis Charney: get in contact to the program-

James Murrough: Yeah ...

Dennis Charney: that you lead, our depression and anxiety program.

James Murrough: Yeah. Find us online. Google Depression and Anxiety Center Mount Sinai. You'll find us. Look for me. We're embedded-- The Depression Anxiety Center is embedded within the Department of Psychiatry, which is a large, uh, uh, amazing department, lots of clinical resources.

If people can get their way to the Department of Psychiatry, then they'll be able to find us as well. And to learn more about Mount Sinai's work in treating depression, uh, or to book an appointment with a Mount Sinai expert, scan the QR code on your screen or click the link in the description below.

Dennis Charney: Let me ask you this question.

What do you feel that patients with depression and patients with PTSD, what do they get wrong about the nature of [00:44:00] their illness, and what's the course of their illness? Can they get better?

James Murrough: Yeah. Two things spring to mind. One is we see this over and over. When someone is in a depression, it feels like it will never end, and that's like the nature of the beast and whether-- and patients will describe it.

They have different ways of describing it, feeling like they're down in a hole looking up. But so many times when we're fortunate and gratified when a patient gets out of that episode of depression, they'll say, "Doc, I gotta tell you, I thought I was never gonna get better." And we hear that again and again.

So in some ways, depression is insidious because the disease itself is telling the person they will never get better, and the extension of that is why bother? Why go to the doctor? Why take the pill? So it's not so much they get it wrong, it's just that's what the illness is telling them. And then another thing that we hear a lot, and it's cliché, but it's very common, is it's not like a biological illness 'cause it's depression.

It's just how you feel. And whether it's the patient's telling us my loved one or my family, probably [00:45:00] meaning well, is saying, "Just get over it," right? So we still hear that a lot, and I have to pick up, you know... I have a textbook on the neurobiology of mental illness on my desk and point to the brain and show this is a biological illness.

So I think there's still a lot of misunderstanding. Psychiatry is a disorder of brain, and we have medicines and psychotherapies to correct those problems. But there's still a lot of misunderstanding and kind of thinking that depression or other forms of mental illness is a, a problem with your willpower, right?

Things like that. So that's a big misconception that we're trying to combat every day.

Dennis Charney: Thank you for that explanation. And Adriana?

Adriana Feder: Yes, I think it's similar for PTSD. There's a lot of stigma, and also sometimes the patient might carry the burden because people don't understand the trauma happened a long time ago.

Why didn't you get better? Why aren't you over it or able to move forward? And also patients, individuals who suffer from PTSD, they're very [00:46:00] fearful, and they live more and more restricted lives and might be fearful of going outside or... So we commonly see a level of avoidance of seeking treatment, seeking care.

And again, the idea, the message of hope- Yeah ... that you are conveying, Dennis, it very important because there are more and more treatments available for these conditions, and it's worth really reaching out and seeking care.

Dennis Charney: And as clinicians, we never give up.

James Murrough: That's right.

Adriana Feder: Yep.

Dennis Charney: Thank you, Adriana. Thank you, James.

James Murrough: Thank you. Thank

Adriana Feder: you.

Dennis Charney: That's all for this episode of The Vitals. I'm your guest host, Dr. Dennis Charney. Subscribe to The Vitals and the Mount Sinai Health System's other video podcast programming on YouTube, Apple Podcasts, Spotify, or wherever you get your podcasts. To learn more about Mount Sinai's work in treating depression or to book an appointment with a Mount Sinai

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