UNIFORMED SERVICES UNIVERSITY
OF THE HEALTH SCIENCES
CENTER FOR THE STUDY OF TRAUMATIC STRESS

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BRAIN, BEHAVIOR, & MIND 2025 FALL LECTURE

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WEDNESDAY
SEPTEMBER 17, 2025

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The lecture met via videoconference, Dr. James Naifeh presiding.

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

(3:00 p.m.)

**MR. NAIFEH:** Hello. Welcome to the Brain, Behavior, and Mind 2025 Fall Lecture, sponsored by the Center for the Study of Traumatic Stress of the Uniformed Services University, or USU.

In collaboration with USU's Department of Psychiatry Neuroscience Program, Center for Deployment Psychology, Department of Family Medicine, and Brian and Behavior Hub.

My name is Jamie Naifeh, and I am a member of both the Center for the Study of Traumatic Stress and the USU Psychiatry Department.

Our Brain, Behavior, and Mind website, which is www.brainbehaviormind.org, has information about this event, including bios for the speaker and other participants, as well as information about previous Brain, Behavior, and Mind events.

Today's event, the 2025 Fall Lecture, will feature a presentation by our distinguished speaker, Dr. John Krystal, followed by a moderated Question and Answer session.

Please use the Q&A function at the bottom of the Zoom screen to submit questions to our speaker at any point prior to or during the Question and Answer session.

Continuing education credits are available for physicians and psychologists. We will provide more information on CMEs and CEs towards the end of the event today.

This event is being recorded. Once the required transcription is complete, we will post the video and transcript on the Brain, Behavior, and Mind website for public viewing. And then all registrants will be notified when the video is available online.

Lastly, a disclaimer. All statements, opinions, and assertions expressed during the Brain, Behavior, and Mind 2025 Fall Lecture are those of the speakers and attendees, and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, or the Department of Defense.

With that said, we will get things started

with a message from Colonel Vincent Capaldi, Chair of the USU Department of Psychiatry.

**COL CAPALDI:** Good afternoon, distinguished guests, colleagues, and friends. As Chair of the Department of Psychiatry at the Uniformed Services University, and on behalf of the Center for the Study of Traumatic Stress, it is my great honor to welcome you to the Brain, Behavior, and Mind Lecture.

This series is a global forum that brings together military and civilian experts across neuroscience, psychiatry, psychology, and public health, all committed to advancing the frontiers of brain and behavioral health.

Each Brain, Behavior, and Mind event explores new insights into health and illness, by integrating knowledge from genes to community, and from research bench to bedside care.

In doing so, we strive to advance the science and clinical care needed for diverse populations within the Department of Defense and

in our nation at large. Those who face complex and stressful environments.

This series is about bridging cutting-edge research with real-world practice. It exemplifies a vital connection between scientific discovery and clinical impact, a connection that is paramount to the Department of Defense, and for healthcare communities everywhere.

Our mission is not only to generate knowledge, but also to translate that knowledge into better care for our service members, their families and, ultimately, our nation at large.

Today's lecture perfectly embodies this mission. We're honored to host Dr. John Krystal, from the Yale University School of Medicine, who will speak on linking depression pathophysiology to the mechanisms of action of ketamine and next generation treatments.

Dr. Krystal is renowned for pioneering research that revealed remarkably rapid antidepressant effects of ketamine, a

breakthrough that has opened new avenues to those who have not responded to traditional therapies.

His work linking the biology of depression to novel treatments like ketamine paves the way for next generation interventions that could dramatically improve patients' lives.

This topic is especially relevant to us in military behavioral health, where depression significantly impacts our armed forces and DoD beneficiaries.

Innovation, fast-acting treatments, all of these can make a profound difference in readiness, resilience, and quality of life for those who serve.

In short, today's event exemplifies how we can connect neuroscience research to better clinical care for those who need it most, by bringing together leaders like Dr. Krystal and an audience of dedicated scientists, clinicians, educators, and students.

The Brain, Behavior, & Mind series continues

to fuel the exchange of knowledge that drives innovation. I want to thank the Brain, Behavior, & Mind series organizing committee for making this forum possible.

Thank you all for joining us today, and for your commitment to learning and collaboration. Together, through events like these, we strengthen the bridge between research and practice, in service of our military and our nation.

Welcome, and enjoy what I am sure will be an enlightening and thought-provoking lecture.

**DR. NAIFEH:** Thank you, COL Capaldi. Next, we'll hear a few words from Dr. Stephen Cozza, Director of the Center for the Study of Traumatic Stress. Dr. Cozza?

**DR. COZZA:** Thank you, Jamie. Good afternoon, everyone. As the Acting Director of the Center for the Study of Traumatic Stress at Uniformed Services University, it is my great pleasure to welcome you to this year's Brain, Behavior, and Mind Fall Lecture.

For those of you who may be unfamiliar with our Center, our mission is to advance common informed knowledge through a commitment to understanding, preventing, and responding to the adverse effects of trauma and stress.

We do this through a dedicated focus on research and education. Our research programs work to expand our knowledge of the medical and psychiatric consequences of traumatic events. And we use this knowledge to educate and train healthcare providers, leaders, and communities.

For more information and resources, I encourage you to visit our website at www.cstsonline.org.

We are truly pleased to have Dr. John Krystal, from Yale University, with us today. His work in this field has been pivotal, and we are eagerly looking forward to his presentation on linking depression pathophysiology to the mechanism of action of ketamine. I have no doubt that his insights will be both enlightening and thought-provoking.

I am also looking forward to the discussion and Question and Answer session that will follow the presentation, which I am sure will be a valuable and engaging dialogue for all of us.

Now back to you, Jamie.

**DR. NAIFEH:** Thank you, Dr. Cozza.

The speaker for this year's Fall Lecture, Dr. John Krystal, is McNeill Professor and Chair of Psychiatry at Yale, and Yale New Haven Hospital. He directs the Yale Center for Clinical Investigation, the Center for the Translational Neuroscience of Alcohol, and the Neuroscience Division of the National Center for PTSD.

Dr. Krystal studies the neurobiology and treatment of psychiatric disorders central to today's lecture, his laboratory discovery of the rapid anti-depressant effects of ketamine.

Dr. Krystal is a member of the National Academy of Medicine, a fellow of the American Association for the Advancement of Science, Co-Director of the Neuroscience Forum of the

National Academies of Science, Engineering, and Medicine, Editor of the scientific journal *Biological Psychiatry*, and co-Founder of Freedom Biosciences.

We will now begin Dr. Krystal's presentation, which, as Dr. Cozza said, is titled, "Linking Depression Pathophysiology to the Mechanism of Action of Ketamine and Next Generation Treatments."

**DR. KRYSTAL:** Hi, everyone. My name is John Krystal. I am the Chair of the Department of Psychiatry at Yale University, and head of the Clinical Neuroscience Division of the National Center for PTSD.

It's a real pleasure for me to be here today to talk to you about the neurobiology of depression, and its link to the mechanism of action of ketamine and next generation treatments.

Before I go on, I want to disclose my financial interests. I am funded by a variety of organizations.

I am the Co-Founder of a small pharmaceutical company called Freedom Biosciences, which is developing, you might say, next generation treatments for depression.

I consult to a variety of organizations that are developing treatments for psychiatric disorders. I have stock or options in some of those companies.

And, I have patents related to the development of treatments. In particular, two patents that were licensed to Janssen Pharmaceuticals relate to the antidepressant effects of ketamine.

The other thing to acknowledge is that all the work that I'm going to be talking about today is teamwork, and all the people on this slide contributed to the work that I'm going to be talking about today.

So, let's start, I think, at the starting point, which is that we've had antidepressants for 60 years, and they help many, many people with a variety of psychiatric conditions. And

yet, they are still less effective than we would hope for.

The STAR*D study, the largest antidepressant study in history, found that antidepressants were not as effective when started initially. And after multiple antidepressant trials over a year, about a third of patients had still not achieved a remission of their depression.

Thus, as we know, standard antidepressants can take several months to really fully kick in. And there are many patients who don't respond to their initial treatment, who don't respond to their second treatment, maybe not their third; but, eventually, have a clinical response or remission. And, unfortunately, many of these patients will relapse after achieving a clinical response.

So, what I'm going to be talking about today is ketamine as a treatment. I'll be talking about depression, major depression and the glutamate synapse. And then I'll be talking about mechanisms of ketamine efficacy. And then

some relatively new ideas about how we might enhance ketamine efficacy with cognitive behavioral therapies and combination treatments.

So this, in a way, is where things started, our paper from 2000. And in that study, what we found was that when we gave a single dose of ketamine to depressed patients, that you saw this very rapid improvement in mood, with clinical response very commonly at 24 hours after a single dose.

But, there were transient behavioral effects during the infusion of ketamine. Here's euphoria; here's a positive symptom of psychosis. And you can see that the behavioral effects are gone, completely gone, long before the clinical benefits of ketamine are seen, indicating that the therapeutic effects of ketamine are the reaction that the brain has to exposure to ketamine, not a consequence of the ongoing presence of ketamine in the body.

So, let me introduce you to someone who will tell you about their experience with ketamine.

(Video played.)

**DR. KRYSTAL:** Well, I apologize for the little bit of a commercial there at the end, but you can get a sense of what a dramatic impact ketamine treatment can have.

When we start ketamine for the first month, or esketamine, we usually give it twice a week. After that, we taper down the frequency with which ketamine is administered. Eventually, about three quarters of patients are able to be maintained every two weeks on ketamine, which is manageable in terms of burden and tolerability.

Now, one of the important things that we've learned about esketamine and ketamine that make them so impactful clinically is that they have a substantial impact on reducing relapse to depression among people who are initially responders.

And what this study shows you -- is data from Janssen Pharmaceuticals among people who had achieved a clinical response on the combination of esketamine and a new

antidepressant; and at the end of the trial, they were randomized to stay on both medications or to stop taking the esketamine and stay on their new antidepressant.

And, what you can see is an echo of what I mentioned earlier, which is that the patients who had achieved a good clinical response and still remained on placebo had a relapse rate approaching 58 percent, while patients who stayed on their antidepressant and ketamine had a very good record of sustained antidepressant effect, with only 25.8 percent relapse.

Two new studies really helped to contextualize the role that esketamine plays in our treatment programs.

First, esketamine, in the study by Reif et al. that came out in the *New England Journal of Medicine*, was shown to have an odds ratio of remission, compared to adjunctive quetiapine, of 2.

And, as adjunctive quetiapine is one of the more effective adjunctive treatments that we

have for depression, this is really striking and indicative that esketamine could very well be the most effective medication that we have currently, FDA-approved, for treatment-resistant symptoms of depression.

The second study was a study by Amit Anand et al., which also appeared in the *New England Journal of Medicine*. And what this showed was that ketamine is numerically superior and statistically non-inferior to electroconvulsive therapy in terms of its efficacy for the treatment of treatment-resistant symptoms. And which is really striking, if you think of the cost burden and medical impact of ECT treatments on patients. So, these are two key findings.

And then, long-term data, which came from Johnson & Johnson; over 1,000 patients treated an average of 42 months versus compared to historical data of patients treated for their depression, showed that long-term esketamine produced a significant reduction in suicide attempts, significant reduction in death by

suicide, and significant reduction in all-cause mortality.

Now, what all-cause mortality is, is recognizing that patients with major depression, on average, have a 10-year reduction in their life expectancy, because depression and the medical processes related to depression, such as inflammation, take their toll on the body. Cardiac disease, respiratory disease, other kinds of medical morbidity. So, more effective treatment of depression with esketamine seems to reduce that risk to life expectancy.

Ketamine is being tested for a variety of other conditions, and there are varying degrees of evidence supporting broader use of ketamine. For the moment, the evidence is strongest for treatment-resistant symptoms of depression and urgently ill patients with depression.

So, let's talk about depression and the glutamate synapse. And I realize that many people on this call, on this seminar, will know very much about the glutamate synapse, so I beg

your pardon.

Glutamate is released by glutamate neurons, and that glutamate can bind to many different receptor types. One type is the AMPA glutamate receptor. Another type is the NMDA subtype of glutamate receptor. The NMDA subtype of glutamate receptor is the target for drugs like ketamine, memantine, and other NMDA receptor-blocking drugs.

Glutamate synapses are the majority of the synapses in the cerebral cortex, and glutamate neuronal communication is the predominant form of excitatory communication in the brain.

Now, there are a number of findings related to glutamate synaptic abnormalities that lay a groundwork for thinking about what kinds of benefits ketamine might produce.

First, we now have in vivo data using the SV2A PET approach to quantifying synaptic density. And what we found is, in patients with moderate to severe depression, that there is a reduction in synaptic density in the brain.

We've also found evidence of reduced frontal cortex synaptic strength. And this is something that we measure using a carbon-13 magnetic resonance spectroscopy technique.

And the idea goes something like this. Normally, a glutamate neuron releases glutamate. It binds to a glutamate receptor, probably an AMPA glutamate receptor, and stimulates metabolic activity. In the case of depression, we believe that the number of glutamate receptors at the synapse are reduced, making glutamate synapses less effective. This is an inference based largely on the pre-clinical animal research.

And so, what you see, and what we can measure in depressed patients, actually depressed patients who had comorbid PTSD, was that, per molecule of glutamate that was released, we see a reduction in the magnitude of the metabolic response.

A third issue in depression, and one that I'm not going to have so much time to talk about

today, is impaired glutamate homeostasis. Glutamate is normally released by neurons and taken up by the astrocytes. And there is evidence in animal stress models of heightened basal ganglia glutamate tone, as well as compromise of the astrocytes and their function of taking up glutamate. We'll have to discuss this point at another time, or perhaps in the Question and Answer session.

So, why do we care about cortical synaptic efficacy and density? It's partly because if you compromise glutamate synaptic efficacy or density communication in the brain, it can become noisy and error-prone and you can compromise neuroplasticity.

From the perspective of emotion regulation, glutamate synaptic efficacy and density are really important for the top-down control of emotion, the processing of reward and behavioral flexibility, and resilience.

So, let's now talk a little bit about ketamine efficacy. A really important landmark

came from the work of my late colleagues, Ron Duman and George Aghajanian, who showed in 2010 that that ketamine could trigger the regrowth of synapses in the brain rapidly.

On the left-hand side of this figure, you see a dendrite or nerve cell input. And there are a bunch of little red arrows that highlight what are called dendritic spines, which is a key place where glutamate synapses are made. Chronically-stressed animals have reductions in the number of these synaptic connections.

And 24 hours after a single dose of ketamine, you could see a sprouting of these dendritic spines and physiologic evidence that these synapsis were restored. How does ketamine do this? Well, the animal work conducted by Ron Duman, and others now, suggest the following.

One of the things that ketamine does is reduce the activation of inhibitory nerve cells, the GABA nerve cells, reducing the release of GABA, which is inhibitory, and increasing the release of glutamate. The glutamate that's

released binds to AMPA receptors, and potentially NMDA glutamate receptors, as well. And this triggers an elevation or increase in the level of brain-derived neurotrophic factor, a nerve growth factor.

And that also triggers a shuttling of the glutamate receptors back to the synapse to restore efficacy. The elevation in BDNF triggers downstream reactions, including the activation of a protein called mTOR, or mTORC1. The activation of mTORC1 helps the brain engage in the protein synthesis necessary to regrow the dendritic spines, and reestablish the synaptic connections in the brain.

Now, this is a great story, always has been since it was introduced. And we spent the last 15 years trying to evaluate the extent to which that story applies to the antidepressant effects of ketamine.

We have found, for example, that ketamine does, in fact, increase glutamate released in the brain. And we can measure that in both

healthy individuals and depressed patients using a special carbon-13 magnetic resonance technique.

We have found, using an indirect measure of glutamate release involving positron emission tomography, that the ketamine increase in glutamate release correlates with the magnitude of the antidepressant response.

Another group, led by Boris Heifets, has used general anesthesia to block the glutamate release produced by ketamine. And they have found that interfering with glutamate release interferes with the ability of ketamine to produce antidepressant effects.

So, all these three pieces are consistent with the idea that ketamine stimulation of glutamate release is an important part of its ability to produce antidepressant effects.

So, the natural question is, do patients with depression who have synaptic deficits regrow synapses after a dose of ketamine? And we have preliminary data from this study but,

actually, now other data from other groups that are consistent with this idea.

So, what you can see is that healthy people in gray, depressed patients without synaptic deficits in blue, do not show consistent changes in synaptic density following a dose of ketamine.

However, depressed patients who have synaptic deficits and get a dose of ketamine seem to increase their synaptic density, consistent with the idea that we are regrowing synapses that were lost, as opposed to willy-nilly producing new synapses in the brain.

In those patients with synaptic deficits, that's the red line, you see that the increase in synaptic density is associated with the magnitude of the improvement in depression. However, changes in synaptic density are not in any way associated with mood improvement in patients who do not have synaptic deficits. Again, consistent with the idea that I just mentioned.

There are human data showing that ketamine also enhances synaptic efficacy. What you can see is that before and after ketamine in healthy subjects, there's no change in the magnitude of a sensory-evoked response.

In patients who don't respond to ketamine, there is no difference between the green and the blue lines. But, in depressed patients who are responders, you see that the magnitude of the sensory-evoked response measured with magnetoencephalography is increased, consistent with an increase in synaptic efficacy.

In animals, increases in synaptic efficacy in reward centers are associated with the alleviation of anhedonia as well. So, these changes in synaptic efficacy, which are occurring in many circuits of the brain, are probably pretty directly related to the clinical profile of the antidepressant effects of ketamine.

So, let's talk now about what the future might hold. Could behavioral interventions

increase the efficacy of ketamine treatment?

And there are two ideas about this. During ketamine treatment, neuroplasticity in the brain is reduced, because NMDA glutamate receptors, which are blocked by ketamine, are critical nodes for neuroplasticity. And what we have found, and what others have found, is that if you reactivate trauma memories or drug memories, maladaptive memories, and then give ketamine, you may weaken the associations that people have to those memories and make them less distressing.

Twenty-four hours after ketamine, there is enhanced neuroplasticity via the mechanisms that I was talking about. Regrowth of synapses, elevations in BDNF and other related processes.

So, 24 hours after ketamine, cognitive and behavioral therapies may have greater efficacy for depression, for PTSD, for substance use disorders, et cetera.

This is just a picture from our study, led by Ilan Harpaz-Rotem, where people had their

trauma memories activated, then they got a dose of ketamine, and they had subsequently some extinction sessions. And what you can see is that, with ketamine, you see a marked reduction in amygdala activation and in galvanic skin response over the subsequent month.

So, it's a very persistent reduction in the reactivity to trauma cues in people with PTSD, whereas midazolam doesn't produce that same benefit.

In this slide, what you can see is the impact of adding cognitive behavioral therapy after a dose of ketamine. And you can see that CBT tends to enhance the magnitude and sustain the benefits produced by a single dose of ketamine.

Now, an individual dose of ketamine doesn't last that long, so the benefits generally last somewhere between three days and two weeks. And so, you have to repeat the dose of ketamine.

Why do you have to do that? Well, work from Conor Liston's group found that the regrowth of

the synapses wasn't necessary to initiate antidepressant response, but was critical in order to have a persistent antidepressant response.

And one of the reasons for that is that, from the work of Alex Kwan's lab, on the right-hand side, is that the antidepressant effects of ketamine last about as long as the regrown synapses, which begin to disappear in the days following a dose of ketamine. In rodents, by day five, you're down to about 30 percent persistence. And that's about when the depression relapse is occurring.

So, in that context, the idea that the antidepressant effects are lasting about as long as the regrown synapses, we had generated some very interesting data. In 20 depressed patients who completed a crossover study where they got ketamine in both crossover arms, on one crossover arm they got placebo, and in another crossover arm they received the mTOR inhibitor rapamycin.

And what you can see is that rapamycin didn't have much effect on the initial antidepressant response to ketamine. There was a numerical advantage in remission that was not statistically significant.

But, by two weeks, we saw something extremely interesting. When these people got ketamine plus placebo, by two weeks only 13 percent of them were still responders. But if they got ketamine pre-treated with rapamycin, 41 percent of those patients were still responders.

These data suggest that rapamycin can extend the duration of the antidepressant effects of ketamine. And, by implication, probably are in some way preserving the regrown synapses in order to achieve that.

So, how do you preserve the regrown synapses? This brought us to think about the role of microglia, the immune cells for the brain. Microglia can protect synapses, but they could also eliminate synapses, depending on how they're being regulated.

Depression is associated with neuroinflammation. And by that we mean, in part, activation of microglia in the proinflammatory state where they contribute to synaptic elimination.

But this protective effect of microglia, this neurotrophic effect of microglia, is probably extremely important to demonstrating the antidepressant effects of ketamine, because if you eliminate microglia in animals, you prevent the expression of the antidepressant effects of ketamine.

Both ketamine and rapamycin can have some anti-inflammatory effects by affecting microglia polarization. And rapamycin, in particular, is a powerful tool to re-polarize microglia, so that they engage in adaptive autophagy, meaning picking up the garbage of the brain and promoting neurotrophic functions.

To tell this story another way, in depression, you lose synapses and ketamine regrows those synapses. Activated microglia may

contribute to the elimination of the synapses regrown by ketamine, contributing to relapse.

Ketamine regrows the synapses, and by re-polarizing the microglia to their neurotrophic state, away from their pro-inflammatory synapses limiting state, it looks like we can protect the synapses that have been regrown by ketamine, and thereby extend the antidepressant effects of ketamine.

Now, if you've been paying attention, you may have noticed a paradox in something that I said, which is that activation of mTOR is a critical step in producing the antidepressant effects of ketamine and regrowing synapses. So how could a low dose of rapamycin, which also inhibits mTOR, extend or potentiate ketamine efficacy?

An important new insight into this paradox came from a study from Lisa Monteggia's group, which was just published in *Science*, in May. What she showed was that the increase in BDNF produced by ketamine produced antidepressant

effects via two intracellular downstream pathways. One mediated by mTORC1, and one mediated by another signaling protein called ERK.

What we think is happening is that low-dose rapamycin is preferentially inhibiting mTORC1's ability to interfere with ERK. And so, we know from animal studies that a low dose of rapamycin selectively hits mTORC1 and increases ERK.

In contrast, high-dose rapamycin, which blocks the antidepressant effects of ketamine, blocks both mTORC1 and mTORC2. So, as a consequence, ERK is now inhibited by rapamycin, rather than being enhanced.

So, we think we understand this paradox now, that low-dose rapamycin enhances ketamine efficacy by re-polarizing microglia in part, and potentially in part by activating ERK.

What about psychedelics? Some people describe psychedelic drugs as among the most important experiences of their lives. They can produce rapid and robust efficacy in treatment-

resistant depression. And although psychedelic drugs have a very distinct target in the brain from ketamine, they bind to the serotonin 2A receptor, they still produce some converging effects on glutamate release, synaptic plasticity, and regrowth of spines.

There are a number of practical challenges with adopting drugs like psilocybin, which have long sessions, 6 to 8 hours, which require both preparation and support, and debriefing.

But this is a very promising treatment strategy. It might even be more accessible to people if we could develop non-hallucinogenic psychedelic drugs. And there are a variety of strategies that are being developed to do that.

One of these strategies is called biased agonism. Biased agonism means a drug that stimulates the serotonin 2 receptor, the target of psychedelic drugs, but it only activates one of its downstream signaling mechanisms via beta-arrestin.

Another strategy that's being studied is

partial agonism. A drug that stimulates the serotonin 2A receptor, but doesn't really activate it. Binds to the receptor, but doesn't effectively activate it.

And then there are other strategies now to stimulate the serotonin 2A receptor, but to block the expression of the hallucinatory activity by adding another medication that specifically blocks that hallucination-inducing pathway.

So, in summary, how does ketamine work? Restores synaptic efficacy; restores synaptic density; it restores glutamate homeostasis, didn't talk about that today; and it modulates experience-dependent plasticity interfering with maladaptive memory reconsolidation; and promoting adaptive learning.

The ketamine framework is consistent with a number of new medications that are being studied for the treatment of depression and other disorders, like PTSD. And there is another set of drugs that is being developed, which attempts

to address the disturbances in glutamate homeostasis.

So, thank you very much. It's a real treat to speak to you today, and I look forward to questions and discussion.

**DR. NAIFEH:** Thank you, Dr. Krystal, for sharing some of your fascinating research and setting the stage for our discussion. We are going now to the Q&A portion of today's event. Also joining us is our discussant, Dr. David Benedek, and our moderator, Major Thomas Nassif.

Our discussant, Dr. Benedek, is a psychiatrist and retired U.S. Army Colonel. He is the immediate past Chair of the USU's Department of Psychiatry, and is presently Professor of Psychiatry at USU, and Associate Director of the Center for the Study of Traumatic Stress. He is a distinguished Life Fellow of the American Psychiatric Association and past President of the Society of Uniformed Services Psychiatrists, a branch district of APA.

Dr. Benedek has authored more than 200 scientific publications. Notably, he was a consultant on APA's workgroup that developed the 2004 Practice Guideline for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder, and subsequently was lead author on the 2009 update for that Guideline.

Our moderator, Major Thomas Nassif, holds a PhD in Behavior, Cognition, and Neuroscience. He currently serves as the Deputy Vice-Chair of Research for USU's Department of Psychiatry, in order to promote collaboration and innovation between clinical and pre-clinical researchers across DoD psychiatry. Major Nassif was previously Chief of the Sleep Research Center at the Walter Reed Army Institute of Research.

As a reminder, please submit questions for Dr. Krystal using the Q&A function at the bottom of the Zoom window.

Dr. Benedek and Major Nassif, you may proceed when ready.

**DR. BENEDEK:** Thank you, Jamie. Hopefully

folks can hear me, and hopefully that background noise isn't coming from me.

At any rate, I'll start with some questions of my own that your great presentation prompted. And I know we're going to get some from our audience, and Tom is curating those as we speak.

So, without further ado, I wanted to start with one distinction that you didn't make, and then maybe talk a little bit about one distinction you did make.

So, for starters, during your presentation -- which, by the way, was really helpful to me in terms of understanding how ketamine works downstream -- you talk about ketamine and esketamine relatively interchangeably. And I know the difference, but I don't know that all of our audience does. So, I wanted to ask if you could just clarify ketamine versus esketamine, and then comment on the extent to which the findings and the mechanisms you discussed work for both.

**DR. KRYSTAL:** Well, first, Dave, I

appreciate your kind comments about my presentation.

And so, we have two different compounds, right? We have racemic ketamine, a mixture of the S- and the R- isomer of ketamine. And then we have esketamine, which is just the S-ketamine, also known as Spravato.

So, one distinction between the two of them is just how they're commonly delivered. Racemic ketamine is most commonly delivered intravenously and esketamine is most commonly delivered through nasal insufflation -- to the sinuses.

And that's important, because ketamine is not well absorbed orally, and you get very variable absorption even within individuals. And so, coming up with a way to get very consistent exposure to the drug is extremely important. And so, these two delivery systems are both ways to get good and consistent exposure.

The mixture of R- and esketamine brings up

the question of what's R- good for? And R-ketamine at doses of 0.5 milligrams per kilogram, the dose of ketamine that we use, are not effective yet. At least haven't been shown to be effective as antidepressants on their own.

It's possible that high doses, something like two to five times the doses that have been tested so far would be antidepressant, probably at doses where R-ketamine produces many of the same symptoms and side effects as esketamine does.

The fact that esketamine seems to be just as effective, generally speaking, as racemic ketamine so far, suggests that R-ketamine is not adding a lot of the efficacy of R/S-ketamine. And it also suggests that the effectiveness of R/S-ketamine is not reflecting the action of a metabolite of R-ketamine, which, for some of the people in the audience may be familiar with the metabolite called 2R,6R hydroxynorketamine. And that has been hypothesized to have antidepressant effects in animals as well.

But the question of whether R/S-ketamine is really exactly as effective as S-ketamine is not resolved. And, as a result, there is a multi-center study that's being conducted as we speak, funded by PCORI and led by Gerry Sanacora and Sam Wilkinson, which is looking head on, head-to-head, comparing intravenous R/S-ketamine to intra-nasal S-ketamine. And hopefully that study will, in a more definitive way, answer the question about are they about the same.

**DR. BENEDEK:** Got it, thank you for that. And then another question about a distinction that you made more clearly, which was one between ketamine and psychedelics. And I think you made that distinction based on the initial target, if I understood when you were differentiating.

**DR. KRYSTAL:** Right.

**DR. BENEDEK:** But this is sort of philosophical. Is that really where we're at in distinguishing between psychedelics and non-psychedelics, is at that initial target? Is

that why you made that distinction?

**DR. KRYSTAL:** Well, I drew that distinction perhaps to have the opportunity to draw out that distinction here.

The ketamine and psychedelics both produce profound changes in consciousness. But there are some really important differences in the experiences that people have on ketamine and psychedelics.

Ketamine predominantly produces distortions of sensory experience, distortions in one's sense of self, and distortions in sense of time, body, colors, all kinds of things. And psychedelics predominantly are creating de novo activations of the brain, so that, in a way, psychedelics are creating a state of consciousness which is competing with your environmental input and your internal information for control of your conscious state.

As a result, if you have people, people certainly my age and Bob's age, we'll remember in the '60s, if you had people coming in

intoxicated on PCP, the goal was to get them in a dark, quiet room because PCP, like ketamine, distorts sensory input. And if you reduce the degree of sensory input, you reduce the altered state of consciousness somewhat produced by these drugs.

In contrast, because psychedelic drugs are competing with your sensory world for control of your consciousness, when people are in distress on psychedelic drugs, you want them to be engaged in social contact, and normal stimulation.

And when we do psychedelic treatment and put blinders on and dim the sensory, we're accentuating the psychedelic effect, which people are trying to harness in a therapeutic way in the therapeutic session.

So these are, in some ways, similar in that they're triggering a burst of glutamate, triggering certain therapeutic forms of neuroplasticity. But, subjectively, they're somewhat different.

And, for some people, when they look back on their experience with psychedelic drugs, the altered state of consciousness is an important part of what they felt was a part of the therapeutic experience on drugs. And the subjective effects of ketamine are a little bit different. Not that people can't report similar kinds of experiences on ketamine, but I think they are perhaps a little bit more common with psychedelic drugs.

**DR. BENEDEK:** Got it, thank you. Another question that I had was a little bit about this notion of who ketamine helps.

So, you talked a bit about the subjects in your experiments who had receptor deficits responding with changes in their synaptic efficacy, synaptic deficits.

**DR. KRYSTAL:** Right.

**DR. BENEDEK:** Density. And you talked about other depressed patients who didn't have those initial deficits.

**DR. KRYSTAL:** Right.

**DR. BENEDEK:** You figured that out, you know, with imaging. But is there a way to tell who will respond to ketamine and who won't, without looking under an imaging study or scientific conditions?

**DR. KRYSTAL:** So that's a great question. And one of the things that makes answering that question for depression tricky is that we had -- in a typical study, you might have 70 or 80 percent of the depressed patients having a 50 percent reduction in depression symptoms.

And it's hard to do much better than that. So, in general, when you're looking at the depression cluster of symptoms, you don't yet have good biomarkers, at least as far as I read it, to predict ketamine effect.

What's interesting is that we see something a little different in PTSD. And, as you know, we conducted a study in 150 veterans and active duty military, two VA sites and the BAMC site, with John Roach and others at BAMC. And, in that study, the PTSD symptom response was not as

robust as the antidepressant response in the PTSD patients.

And this was a little disconcerting, a little troubling, because we really thought we would get robust anti-PTSD effects, partly because of the work that had come out of Mt. Sinai. But maybe it's a little different in men. Maybe it's a little different in military populations. Maybe it's a little different because we use different outcome measures than they did, you know, some technical reasons.

But what was really interesting is, in a study that we are in the process of analyzing, we may have a epigenomic biomarker. In other words, in the blood, looking at the pattern of the methylation or the regulation of the DNA, it looks like we may have a signature to trigger that. And so, if we could develop something like that, we could maybe make ketamine much more useful for people who have combat-related PTSD or other forms of PTSD.

**DR. BENEDEK:** Yeah, so we're closer with the

biomarker for the PTSD version. What about for depressed folks? Do we have any sense of when we can clinically see that might predict response to ketamine, as opposed to non-response?

**DR. KRYSTAL:** Yes, not as far as I know. The people who have more severe response, the more severe treatment resistance, have a little bit less good response than people who are less severely treatment-resistant. However, the differential benefit of ketamine becomes greater and greater the farther you go down the treatment resistance spectrum.

So, a lot of things which are predictors of poor treatment response to SSRIs, for example, are not predictors of poor response for ketamine. High levels of anxiety, inflammation, history of treatment resistance. In general, these are not powerful predictors of ketamine response.

And the corollary of that is that ketamine is just extremely good for treating treatment-

resistant symptoms of depression.

There was a study by Reif et al., that was published in the *New England Journal of Medicine*, that showed that the odds ratio of remitting on adjunctive ketamine, or esketamine I think in that study, were about double that of remitting on a adjunctive antipsychotic medication (audio interference).

And a multi-center study led by Amit Anand, also published in the *New England Journal*, suggested that the antidepressant response to intravenous ketamine was not inferior, and actually numerically superior, to electroconvulsive therapy.

So, the reason we don't have good predictors of who benefits from ketamine, so far, is just so many people benefit that being depressed is a predictor of a good antidepressant response to ketamine.

**DR. BENEDEK:** That's the good news, is when you're falling to the floor, everything helps. And this helps predictably. That's great.

Thanks for that.

In terms of the regimen that you -- comparing your original paper with one dose and then look at this nice effect.

**DR. KRYSTAL:** Yes, yeah.

**DR. BENEDEK:** So, the regimen that's used in treatment now and the one that you described is a couple of times a week.

**DR. KRYSTAL:** Right.

**DR. BENEDEK:** For the first little while. Help me understand, and help our listeners, watchers understand, why the sort of priming of the pump, what is the clinical significance of doing that and why we need a couple and then a tapered (audio interference).

**DR. KRYSTAL:** Sure. So, there are a couple of things that we have to keep in mind. First, because we're not mapping the duration of the ketamine response in individuals, we don't really know, when they come for treatment, whether they are people who would have had two weeks of response to their first dose, one week

response to their first dose, or three days to their first dose.

What happens -- a critical determinant about whether it would be once a week, twice a week, or three times a week, was a study led by Jaz Singh, which compared two times a week ketamine to three times a week ketamine, and showed that there was no additional benefit when you added the third time a week.

But we know if you only give one dose a week, something like a third to half of patients or more will relapse or have a return of depression symptoms within just once a week.

So, in clinical practice, we are trying to prevent that from happening. So, we're probably being a little conservative by starting with twice-a-week ketamine for some patients.

So, the interesting question you raise is, why are we able to get away with fewer doses over time? And I would say we confidently can say we're not entirely sure about how to answer that question.

It looks a little bit like a sensitization process is happening. In other words, the therapeutic effect, even though it can occur as rapidly beginning within hours of a single dose, it actually grows over multiple doses. And so, if you look at the Reif data, for example, you see that there's a continued and gradual increase in the remission rate over time.

So, people are doing better overall. And that may be one clue that they're getting more into remission, rather than response, and that is somehow a more stable state.

A second clue is that the ketamine effect has a window of a persisting change in biology. And we do not know whether there are aspects of the underlying biology, like maybe you're reversing an inflammatory state so that it's not an inflammatory state anymore, or things like that.

But, literally, the only other thing that we know about governing the duration or the antidepressant effects of ketamine comes from

that rapamycin study, where it does look like there are forces in the brain that are triggering relapse and, somehow, we're protecting the brain from those effects. We just presume that that, in some way, extends to the case without rapamycin.

**DR. BENEDEK:** Got it. Thanks, John. I know that Tom is curating some audience questions. So, Tom, please tell me when you've got enough to let me let you butt in.

But, in the meantime, I just have a couple more that I would --

(Simultaneous speaking.)

**DR. KRYSTAL:** Sure.

**DR. BENEDEK:** And one is about, you talked about the TORC driving up ERK activity.

**DR. KRYSTAL:** Yes, yes.

(Simultaneous speaking.)

**DR. BENEDEK:** I like these. These are easier than BDNF, TORC and ERK. Are there efforts to develop substances that just preferentially turn on the ERK system, other

than the glutamate and (audio interference).

**DR. KRYSTAL:** Yeah, you know, actually -- it's interesting, you mention that there have been efforts to have drugs that activate mTORC without activating glutamate receptors. There were some initial positive data, but it was a drug acting through a different protein called Sestrin.

And the Monteggia paper, Ma et al., that came out in May, identified a potential target called DUSP6, and there's a -- in animals but not yet in humans, a drug that inhibits DUSP6 that might be able to be administered in combination with ketamine. A little bit like the rapamycin effect.

I'm not aware of a drug by itself that targets ERK activation, that has shown to have this kind of robust antidepressant effect like ketamine.

**DR. BENEDEK:** Okay, so stay tuned for more developments of --

**DR. KRYSTAL:** Yeah.

**DR. BENEDEK:** TORC drivers and ERK drivers, and as you continue on your path, as well.

I want to turn things over; but, you started this journey in 1990. Does that sound right?

**DR. KRYSTAL:** Yeah, I was first administering ketamine around 1990, yeah.

**DR. BENEDEK:** And here we are in 2025; where do you think has been the biggest advance? Where have you seen the most progress in terms of what we, either we know or how we do it?

**DR. KRYSTAL:** Well, I think, like many clinical advances, that we had already, by about 1997, an idea about what the antidepressant of ketamine might possibly look like. And figuring it out -- figuring out the underlying neurobiology for ketamine effects is really, I think, has been a slow and complicated process but may very well take us to the kinds of places that you were mentioning.

Like, who do we have to give it to, how can we achieve the clinical benefits of ketamine without disassociation or addiction risk, how

can we make ketamine last a long time, how do we treat ketamine non-responders -- these are all questions that have emerged from this.

I think, after we identified the rapid antidepressant effects of ketamine, and we started incorporating ketamine treatment into our clinics, the first group of people that we tested were people who failed ECT. And now almost everybody in our clinic -- not everybody -- but almost everybody who goes on to ECT is first given a trial of ketamine or esketamine.

And, so, we're trying to figure out where in the clinical pathway a drug like ketamine goes. What would be really helpful to get there is not drugs that predict ketamine response, but markers that predict non-response to antidepressants.

Because, if we knew right at the outset who was going to fail multiple trials of antidepressants, we wouldn't put them through those trials in order to prove to us that they're treatment-resistant. We would just go

right ahead with other kinds of treatments like ketamine, esketamine, like TMS, or psychedelics, or other kinds of things, to help them to get right to effective treatments.

Because, after all, what we call treatment-resistant depression is really SSRI- or SNRI-resistant depression. And it's -- you know, these are people who might very well respond to other kinds of treatment. And it's just the history of what antidepressants we developed first that frames what we consider to be treatment resistance.

**DR. BENEDEK:** Next it'll be ketamine-resistant --

(Simultaneous speaking.)

**DR. KRYSTAL:** Yeah, absolutely. I mean, I think that's really going to be exciting, when we have treatments that target people who fail ketamine, who fail ECT, and who fail psychedelics. And our own in-house experience is that there's some capacity of, say, ECT to rescue ketamine non-responders, ketamine to

rescue ECT non-responders, probably both to rescue psychedelic non-responders, and vice versa.

So, you know, some people have thought that, okay, ketamine's the answer, or ECT's the answer, or a psychedelic's the answer. And the answer is, no single drug is going to be the answer for everybody. And, so, I think over the next five to ten years what we'll figure out is, how to triage people to one or another one of these treatment strategies that can be so helpful for treatment-resistant symptoms.

And it may be mechanistic, like a biomarker, like we talked about before. It may have to do with their clinical profile. So, for example, ketamine and esketamine are very good at managing suicidal ideation -- so maybe that's a consideration for that. Some psychedelics, like psilocybin, in some patients, few patients, can exacerbate their suicidal ideation.

So, we're going to learn where each of these kinds of treatments fits in the overall toolbox.

**DR. BENEDEK:** All right. So, we've come a long way, we got some ways to go, and you'll keep helping us figure it out. So, we appreciate that. I don't want to hog up all your time --

(Simultaneous speaking.)

**MAJ NASSIF:** Thanks so much, Dr. Benedek. So, Dr. Krystal, there have been quite a few questions about interventions and how they might complement and enhance treatment --

**DR. KRYSTAL:** Yeah.

**MAJ NASSIF:** So, there are other emerging interventions you've mentioned, such as MDMA, psilocybin, other psychedelics being studied in conjunction with psychotherapy or psychological support.

**DR. KRYSTAL:** Yeah.

**MAJ NASSIF:** And different ways that ketamine might be paired with behavioral interventions, to potentially improve treatment efficacy.

So, what are your thoughts on the role of

psychotherapy and/or psychological support, to complement not only ketamine but other similar interventions? And there's also even been a mention of, for example, arts therapy. You know, possible interventions to ameliorate lessened neuroplasticity with ketamine administration, and would this be an opportunity for something like that? So, just curious to get your thoughts about all this.

**DR. KRYSTAL:** Sure. So I think, first and foremost, my feeling about ketamine, psychedelics, ECT, TMS, Prozac, is that they are all interventions that work best when embedded in an overall treatment that's looking out for the best interest of the patient -- helping the patient to get the right treatment at the right stage of their career, and to combine different modalities as appropriate for that patient.

And one of the mistakes I think that sometimes happens is that a patient might go to a ketamine clinic in severe depression and might get the ketamine, and that might help them, but

it might not help them in the way that an overall, integrated treatment plan might. And particularly, the question of, what do you do after ketamine, for some patients.

So, I do think that there are potential synergies. I've highlighted some mechanistic synergies. I don't have experience with art therapy as a unique modality of interaction with these kinds of treatments. But I do think it's important for people to be prepared very carefully for the experiences they're going to have with ketamine or other consciousness-altering treatments -- MDMA, psychedelics.

I do think it's really important that people be supported throughout their experience while on these drugs, because it can be a very intense experience. For some people, some of the most intense experiences of their life will happen during these experiences. So, they need support. And then, they need a space to make sense of the experience.

And, so, our late colleague, Roland

Griffiths, who some people on the call will know, was loathe to use the term bad trips, because people use the phrase, bad trips, to describe emotionally intense sessions, that sometimes in the post-session processing were extremely useful for driving personal growth for those patients.

So, I do think that the psychological part is an important part of these treatments. What is particularly exciting for me as a neuroscientist, is the idea that there are potential specific synergies between the pharmacologic actions of these drugs in certain types of therapeutic changes.

And, I like to think -- in terms of the enhancement of neuroplasticity, I like to think of ketamine as a drug, or maybe psychedelics as a drug that, that there's some analogy between treatment and making horseshoes. In other words, if you have a horseshoe -- if you have a piece of metal and you pound on it all day, it's going to be really hard to pound it into shape

unless you heat the metal up and then pound it. In other words, you increase the plasticity of the metal and then you pound on it.

And psychotherapy, maybe, is a little bit like the pounding and the ketamine is a little bit like the heating. And if you just heat the metal but don't pound on it, what you get is a hot piece of metal that doesn't make itself into a horseshoe. And so I think we can enhance plasticity with these drugs, but there may be synergy with these kinds of therapies.

**MAJ NASSIF:** Yes, and there was a patient currently undergoing ketamine therapy, and talked a lot about the focus on intention setting as well. So, when you think about journaling and mindfulness and retraining your negative thinking, the sustained ketamine, the effects of these ketamine sessions. And he agreed that even interventions like that could be helpful.

**DR. KRYSTAL:** Yeah, I think we have to be open-minded. And I think, what I've learned is,

when somebody says it's really helpful, that kind of means it's helpful. At least, certainly, it's helpful for them. So, yeah, absolutely.

**MAJ NASSIF:** Great. So, there are also quite a few more mechanistic questions. And we'll go ahead and shift gears a bit here. So, does increased synaptogenesis occur with other psychotropics in depression and, if so, how does it compare to ketamine? Is ketamine comparatively more effective in doing this?

**DR. KRYSTAL:** Yeah, it's really hard to know about a comparative, because you need to test them in the same study under the same conditions in order to make these comparisons. There is some enhancement of synaptogenesis by traditional antidepressants, but it's certainly very slow, and it's not a single-dose effect like it can be with ketamine or psychedelics.

I think one thing we're pretty confident about is that the synaptic regrowth from psychedelics last longer. In other words, the

synapses are a little bit more stable than what you see with ketamine. And that may have to do with the fact that, over in the clinical practice, that you maybe give one or two doses of a psychedelic drug over one to three months, whereas with ketamine you're going to be giving many more doses, to sustain antidepressant efficacy.

**MAJ NASSIF:** Okay, excellent. Thank you for that. And there have been quite a few questions, too, about timing --

**DR. KRYSTAL:** Yeah.

**MAJ NASSIF:** And dose effects. And so, for the potential use of ketamine for PTSD, timing of ketamine administration in relation to therapy is critical due to ketamine's potential inhibitory effects on memory reconsolidation. So, is it possible that a similar critical timing effect of therapy occurs with depression and CBT, such that coordinating CBT sessions with intravenous ketamine could maximize the long-term (audio interference) and therapeutic

effects?

**DR. KRYSTAL:** Yeah. So, there are two studies that I'm aware of. Both of them have timed for depression treatment, in-person CBT and one a web-based CBT out of Mount Sinai. And both of these studies suggest, although it's early days, that if you target the psychotherapy for this window of enhanced plasticity, that you can make CBT more effective for depression.

And I think that the place -- interestingly, the place where you see the within-session psychotherapy being implicated is PTSD, activate the trauma memory and give the ketamine. And that the interesting other application is in addiction.

So, there was a really elegant study of ketamine for alcohol use disorder, conducted in London. And what they showed was that, if you gave people a drink, their favorite drink -- people with alcohol use disorder, their favorite drink, you stimulated the alcohol memories and the craving and then you gave ketamine, then you

could produce lasting reductions in alcohol craving and, actually, even some reduction in their drinking as well.

What was interesting about that study, and a little complicated -- and something we don't quite understand -- is that the London group used a little bit higher dose of ketamine than is typical. Typical ketamine dose is 0.5 milligrams per kilogram, they used 0.8 milligrams per kilogram to really disrupt the memory reconsolidation, and they had that effect.

When we use ketamine in alcohol -- patients with comorbid alcohol use disorder and depression, we -- at 0.5 milligrams, we didn't see effectiveness in reducing drinking. And there was a second study without psychotherapy, at 0.8 milligrams per kilogram, that was conducted in alcohol use disorder that also reported efficacy.

This addiction work grew out of work of our colleague, Evgeny Krupitsky, then at Leningrad

State Hospital, Leningrad State University in St. Petersburg -- now St. Petersburg University in what is now Russia. And they've been doing ketamine psychotherapy for addiction for a long time now.

**MAJ NASSIF:** Thank you for that response. So, when you look at other NMDA antagonists, such as memantine, why do they not have similar antidepressant effects? And, as well as Bupropion, dextromethorphan, seems to have a more rapid effect. What are your thoughts on that?

**DR. KRYSTAL:** So, memantine -- there are two things about memantine that are different from ketamine. One is that the memantine has a very light blockade of the NMDA receptor.

So, when ketamine binds to the NMDA receptor, it tends to get trapped in the channel and stay there, and the channel closes around the ketamine. Whereas memantine seems to flicker in and out of the channel. So, even though it blocks NMDA receptors, it tends not to

do so with the same efficacy as ketamine, even though it has similar potency at the NMDA receptor.

A second thing, which was just discovered -- one of the authors is Toomey -- is that memantine blocks Calcium-Fluxing AMPA Glutamate receptors as well as NMDA receptors. So, I mentioned that stimulating AMPA receptors may be an important part of the induction of the antidepressant effect of ketamine by the glutamate that's released by ketamine; and so, it's possible that memantine may have an off-target action that undermines its antidepressant efficacy.

The Bupropion, dextromethorphan, Auvelity is a little bit of a mystery to me. Because it's probably not producing enough NMDA receptor blockade to mimic the therapeutic antidepressant effects of ketamine. And so, what it's doing is not entirely clear. Second, Auvelity is taken every day. And if you give ketamine every day, you tend to get tolerance to ketamine effects,

rather than the sensitizing effects of ketamine.

So it may be that Auvelity is having an effect that is not the classic ketamine effect; so I would say, I at least don't understand the extent to which it has unique efficacy for TRD, the extent to which it produces real rapid antidepressant effects, or how it produces those effects.

**MAJ NASSIF:** Okay, and I appreciate that. And in terms of side effects of ketamine, one respondent had asked about bladder damage as a potential [effect of]long-term administration of ketamine for the treatment of depression. It may cause bladder damage or is that damage primarily dose-dependent? And is there a therapeutic dose that even can be maintained long-term --

**DR. KRYSTAL:** Yeah.

**MAJ NASSIF:** To avoid various side effects?

**DR. KRYSTAL:** Yeah, so it's basically kind of an irritation of the lining of the bladder. And when you get ketamine, ketamine is excreted

in part through the urine. And if you have sustained exposure to ketamine, you get a sustained exposure in the bladder to higher concentrations of ketamine, which can chronically produce irritation, and even fibrosis, of the lining of the bladder.

And you just don't get that with therapeutic dosing of ketamine. We've never had it in our clinic. And it's because you're giving ketamine for -- it's just a short-acting drug, and over time, you start twice a week, but your goal is to get it as infrequently as possible.

Where you really see this bladder problem is in people who are recreationally using ketamine. And it's almost pathognomonic. I visited ketamine treatment clinics, ketamine use disorder treatment clinics in China and in Taiwan, and people are going to the bathroom all the time.

So, it is a risk of recreational, daily exposure to ketamine, but not so much a risk, as far as I can tell, when used in the traditional

dosing.

**MAJ NASSIF:** Well, that's great to know. And, so, going back to the idea of dosing and frequency of treatment. So, you described a widely accepted regimen with ketamine of two treatments per week for four weeks, and then weekly thereafter. So, would you mind clarifying the clinical relevance of initiating the treatment course of twice-weekly treatments versus a regimen that only offers weekly treatments?

**DR. KRYSTAL:** Yeah, when you start with weekly treatments, you start getting people relapsing before their next dose. And so, that's why some people will make it to the next dose without relapse. But it's partly the people that we're treating. So, we're treating, often – treatment-refractory patients, really severely ill and sometimes extremely suicidal patients.

And so, there is an impression that the more treatment-resistant you are, the shorter the

duration of your initial antidepressant effects. So, it may very well be that the people who are most vulnerable, who most need the ketamine, need the two times a week treatment to get them to the next week without some worsening of sessions.

This is something I've heard from a number of practitioners, and I'd love to see actual data for that. But it rings true to me, because people who are more treatment-resistant are more vulnerable to relapse, no matter what the treatment that they get -- ECT, antidepressant. And so, we really want to protect those folks.

**DR. NAIFEH:** Excuse me for interrupting. I wish we had time for more questions, but we only have a few minutes left.

**DR. KRYSTAL:** Sure.

**DR. NAIFEH:** So, I want to go ahead and thank Drs. Krystal, and Benedek, and Nassif for a wonderful discussion. And before we hand it back over to Dr. Cozza for some closing remarks, I just want to turn real quick to Dr. Rachel

Shor, who can provide some guidance on receiving continuing education credits. Rachel?

**DR. SHOR:** Thank you. And thank you so much to our esteemed speaker today, for a really wonderful presentation and discussion, and for everyone who came to attend the lecture.

So, continuing education for this event is available for physicians and psychologists through the American Psychiatric Association. And those that are interested in continuing education credits, please just complete the evaluation and credit form that you're going to receive either tonight or tomorrow.

So, if you have any questions at all regarding accessing or completing the form, please feel free to contact me at the link that should be placed in the chat and also in the emails that you received regarding this event. Thank you so much.

**DR. NAIFEH:** Thank you, Dr. Shor. Now I will turn it back over to Dr. Cozza for some final comments. Dr. Cozza?

**DR. COZZA:** Sure. Thank you, Jamie. Well, on behalf of the Center for the Study of Traumatic Stress, I want to extend our deepest gratitude to John, for sharing your work related to the pathophysiology of depression, mechanisms of ketamine. But also doing it in a way that was so clear and understandable. And I know the audience appreciates it. Very, very complicated.

The other thing I would say is it's wonderful to hear about these new developments, especially for many of us who've been practicing in the field for so long. It gives us a sense of optimism and hope, particularly in the management of treatment-resistant and refractory depression -- which for all clinicians, has plagued us for years. So really looking forward to see those developments as time moves on, and new answers to that very thorny problem.

In addition, a special thanks to our team here. Thank you, Dr. Naifeh, for so expertly guiding today's agenda. And to Drs. Benedek and

Nassif, for skillfully moderating an engaging discussion session. And, also, to the audience, for your engagement and the insightful questions. We've certainly learned a lot today.

I also want to acknowledge the hard work that goes on behind-the-scenes, and thank those on our planning committee, Drs. Naifeh, Mash, and Shor, for putting together this superb event. We really owe them some gratitude.

And before we conclude, I want to invite you all to look ahead with us. Please save the date for our upcoming all-day Brain, Behavior, and Mind conference, which will be held virtually in April 2026. Keep an eye out for announcements about registration in the coming months.

And, as with today's Lecture, continuing education credits will be provided for the conference at no charge to our participants. So, we look forward to you joining us at the Spring Conference.

And thank you again, for everybody being here. And a great gathering. Back to you,

Jamie.

**DR. NAIFEH:** I think you said it all, Dr. Cozza. Thank you. I hope everyone does keep an eye out for our Brain, Behavior, and Mind 2026 Spring Conference announcement. We have a truly outstanding lineup of speakers. So, watch for those. And we'll see you soon. Goodbye.

(Whereupon, the above-entitled matter went off the record at 4:28 p.m.)