Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest

MEETING SUMMARY

MARCH 2025

REAGAN-UDALL FOUNDATION
for the Food and Drug Administration

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This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $1,720,109 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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Introduction and Background

The Reagan-Udall Foundation for the FDA, in partnership with the U.S. Food and Drug Administration (FDA), held a hybrid public meeting entitled "Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest." The public meeting explored the scope of ketamine use, emerging areas of therapeutic interest, potential safety concerns, and online promotion of and access to ketamine. Speakers included clinicians, academic researchers, patient advocates, professional organizations, and federal partners.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor[1] antagonist, is a racemic mixture of the S and R enantiomers. S-ketamine has a greater affinity for the NMDA receptor and is thus more potent. Ketalar® (ketamine HCL solution), a Schedule III drug, has been approved for human use by the FDA as a prescription-only intravenous (IV) or intramuscular (IM) injection for induction and maintenance of general anesthesia.[2] Ketamine's effects on neuroplasticity may be the underlying mechanism leading to potential rapid antidepressant effects.[3] Early research suggested neuroprotective properties associated with ketamine; however, recent studies suggest that ketamine may also cause neurotoxicity.[4]

In 2019, the FDA approved esketamine (Spravato® nasal spray), the S-enantiomer of ketamine, for use in treatment-resistant depression in conjunction with an oral antidepressant.[5] Lessons learned through the development and regulatory review process for esketamine might have applications for the development of ketamine for emerging therapeutic areas. Additionally, the supplemental new drug application (sNDA) pathway is an established route for a company to submit data on emerging uses to be considered as a new indication for an approved drug.[6]

The Current and Changing Landscape

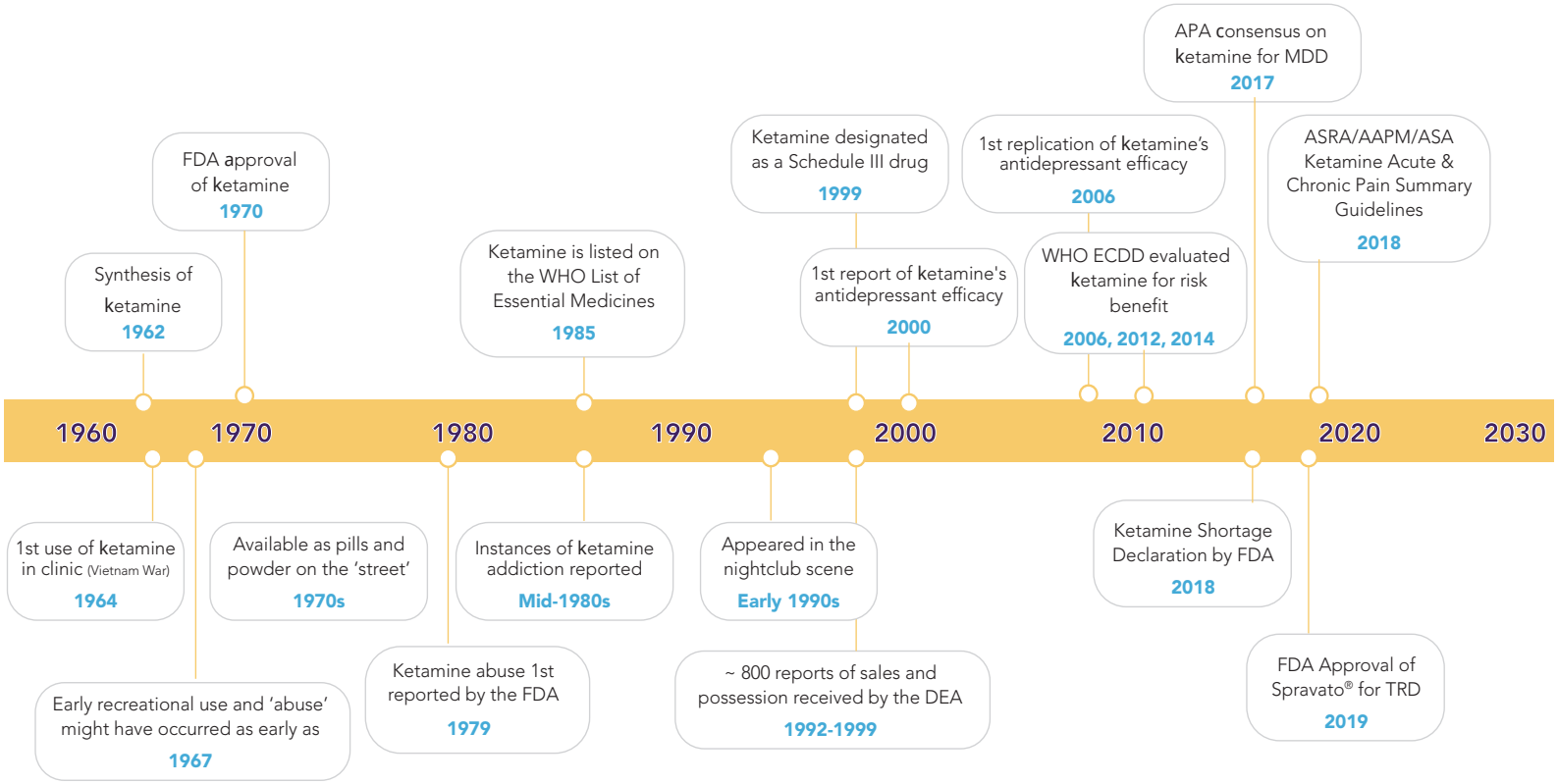
Originally synthesized in 1962 for anesthesia, ketamine saw extensive use during the Vietnam War in field hospitals and was listed on the World Health Organization List of Essential Medicines in 1985.[7] Research into the potential antidepressant effects of ketamine began in the 1990s, with the first report of ketamine's potential antidepressant therapeutic effects published in 2000.[8] Since that time, studies evaluating the efficacy and safety of ketamine use for mental health diagnoses, pain, and numerous other conditions exploded.

1. An NMDA receptor is a receptor for glutamate, a neurotransmitter that plays a key role in brain function, learning, and memory.
2. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Published 2022. Accessed October 14, 2024. http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=016812.
3. Duman RS, Aghajainian GK, Sanacora G, Krystal JH. Nat Med. 2016 Mar; 22(3): 238–249. doi: 10.1038/nm.4050.
4. Choudhury D, Autry AE, Tolias KF, Krishnan V. Ketamine: Neuroprotective or Neurotoxic? Front Neurosci. 2021;15:672526. doi: 10.3389/fnins.2021.672526.
5. U.S. Food and Drug Administration. FDA Approves New Nasal Spray Medication for Treatment-resistant Depression; Available Only at a Certified Doctor's Office or Clinic. Published March 5, 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified.
6. U.S. Food and Drug Administration. Drugs@FDA Glossary of Terms. www.FDAgov. Published online August 2, 2023. https://www.fda.gov/drugs/drug-approvals-and-databaes/drugsfda-glossary-terms#S.
7. World Health Organization. WHO Model Lists of Essential Medicines. www.who.int. Published July 2023. Accessed September 15, 2024. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists.
8. Berman RM, Cappiello A, Anand A, et. al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry;47(4):351-4. doi: 10.1016/s0006-3223(99)00230-9.

Dr. Gerard Sanacora from Yale University, a psychiatrist and ketamine subject matter expert, and Dr. Joseph Palamar from New York University Langone Health, an epidemiologist specializing in drug use, presented timelines of medical and nonmedical use of ketamine, respectively. Figure 1 was adapted from these presentations to highlight significant timepoints in the history of ketamine.

In recent years, use of ketamine in clinical settings has increased despite limited safety data and clinical knowledge gaps. Figure 2 depicts the rapid increase in clinicians providing ketamine for the treatment of psychiatric disorders through 2016.

Figure 1: Timeline of Selected Ketamine-Related Events[9]

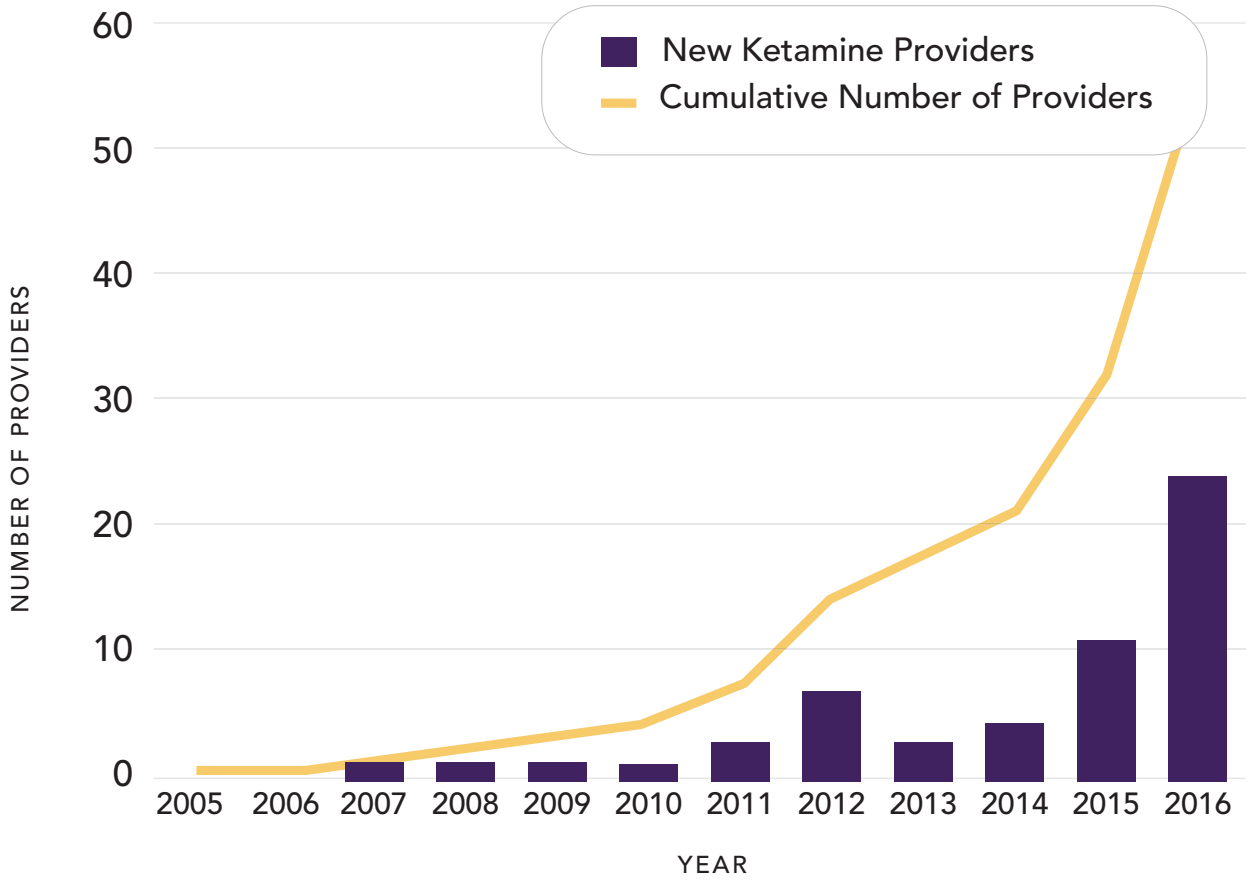


LEGEND

AAPM – American Academy of Pain Medicine
APA – American Psychiatric Association
ASA – American Society of Anesthesiologists
ASRA – American Society of Regional Anesthesia and Pain Medicine
DEA – Drug Enforcement Administration
MDD – Major Depressive Disorder
TRD – Treatment-Resistant Depression
WHO ECDD – World Health Organization Expert Committee on Drug Dependence

9. Adapted from Sanacora G, Overview of the Changing Ketamine Landscape and Palamar J, Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

Figure 2: A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders[10]



Total Number of Physicians Initiating the Practice of Providing Ketamine Off Label for the Treatment of Psychiatric Disorders per Calendar Years (Bars) and Cumulative Number of Ketamine Providers Over Time (Line)

10. Wilkinson ST, Toprak M, Turner MS, et al. Am J Psychiatry. 2017 Jul 1;174(7):695-696. doi: 10.1176/appi.ajp.2017.17020239.

TWO

Current Scope of Ketamine Use in Clinical Settings

Clinical Guidance

Consensus statements and guidelines provide guidance for clinical practice, summarize the evidence base available up to the time of publication, and call out gaps in the literature. The Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders[11] panel identified major questions surrounding the use of ketamine (Table 1). The 2017 publication provided consensus statements based on available data to guide the use of ketamine as an off-label treatment of mood disorders, primarily treatment-resistant depression (TRD). The consensus document also addressed potential risks associated with ketamine and acknowledged the paucity of robust evidence to guide clinical decision-making.

The U.S. Department of Veterans Affairs (VA) has also written national protocol guidance for the use of ketamine infusion for TRD and severe suicidal ideation.[12] This guidance is accompanied by close tracking of adverse events and reasons for medication discontinuation.

Table 1: Framework for the Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Clinically Relevant Questions Regarding Ketamine's Rapid Onset Antidepressant Effects[13]
• What is the optimal dosing strategy for ketamine, including dose, route, and frequency?
• What is the longer-term effectiveness of the treatment?
• What is longer-term safety of the treatment approach?
• What are the critical moderators of response or adverse effects?
▸ Diagnosis, subtypes, genetic, or endophenotypic differences in response
▸ Drug-drug interactions (regarding both safety and efficacy)

Ketamine has shown potential for both acute and chronic pain relief, particularly in conditions like complex regional pain syndrome (CRPS) and spinal cord injury. Acute pain off-label uses include, but are not limited to the following: moderate to severe postoperative pain; pain refractory to opioids or with limiting side effects; opioid-tolerant patients; patients with sickle cell anemia; and patients with obstructive sleep apnea. Key points from consensus guidelines for acute and chronic pain published in 2018 were presented. Logic behind the recommendations was provided as well as controversies and unanswered questions. It was emphasized that for every treatment for pain, there needs to be a defined endpoint, and that all pain treatment must be personalized.

11. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. 2017;74(4):399–405. doi:10.1001/jamapsychiatry.2017.0080.

12. VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, Office of Mental Health Somatic Treatment Field Advisory Committee. Ketamine Infusion for Treatment Resistant Depression. 2022. https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Ketamine_Infusion_for_Treatment_Resistant_Depression_Rev_Jul_2022.pdf.

13. Sanacora G, Overview of the Changing Ketamine Landscape; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

Clinical Considerations

Throughout the meeting, panelists highlighted various challenges and areas of promise in the use of ketamine for TRD and pain conditions. Tables 2 and 3 list considerations for ketamine administration with regard to dose, frequency of administration, outcome measurement, duration of therapy, and maintenance therapy.

There is a lack of comprehensive research on the benefits and risks of single and repeated doses of ketamine above 0.5 mg/kg per dose. A significant gap exists between evidence from clinical trials and real-world practices – practitioners and ketamine clinics in the community are using higher doses, titrating doses, and dosing at a greater frequency and for longer durations than what is described in the literature. TRD doses in most published research studies do not exceed 0.5 mg/kg per dose, but despite the lack of benefit and safety data, doses in clinical practice can exceed 0.8 to 1 mg/kg/dose per anecdotal reports. It is unknown how these practices influence treatment efficacy and affect short- and long-term safety.

> "I think we're really stuck between this balance of trying to make what I would consider a lifesaving treatment for many people available, but doing it in a way that's safe and responsible. We can't deny the fact that there's real toxicity associated with the use of ketamine, and there's real risk for drug diversion if it's not done carefully. So, I think we really need to balance those two." **– Dr. Gerard Sanacora**

For chronic pain treatment, ketamine is often administered in higher doses under controlled conditions. Although clinicians frequently titrate doses to optimize patient outcomes, randomized controlled trials have yet to explore these dosing strategies thoroughly.

Speakers and panelists emphasized the need to focus on the maintenance phase of treatment for depression, acknowledging that most patients with TRD relapse within one month.[14] Dr. Eric Hermes, from the Veterans Health Administration (VHA), emphasized the importance of data to guide decisions on maintenance treatment, where the balance between risks and benefits must be carefully managed. Currently, data on the long-term safety and maintenance dosing for ketamine is lacking, leaving clinicians to rely on clinical judgment whether the potential benefits of maintenance therapy outweigh potential and unclear risks with repeated or extended ketamine use.

> "But what I think that we need to keep reminding ourselves that there isn't a one size fit all here, different patients need different things."
>
> **– Dr. Brittany O'Brien**

14. McIntyre RS, Rosenblat JD, Nemeroff CB, et. al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry 2021;178:383-399. doi: 10.1176/appi.ajp.2020.20081251.

Table 2: Considerations for Ketamine Administration [15,16,17,18,19,20]

	Contributing Factors
Dose	• Dose-response effect • Peak blood levels • Rate of rise to peak blood levels • Safety
Frequency of Administration	• Patient response • Safety
Positive Treatment Response	• Defined clinical endpoints • Should consider function, psychological and emotional well-being, sleep, medication use and satisfaction in addition to pain relief • Pain dimensions (e.g., sensory, affective, cognitive)
Duration of Therapy	• Duration of symptom relief • Safety
Maintenance Therapy	• Appropriate candidates • Indication for use • Safety

15. Sanacora G, Overview of the Changing Ketamine Landscape; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

16. Cohen SP, Scope of Ketamine Use in Clinical Practice; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

17. Schwenk ES, Viscusi ER, Buvanendran A, et. al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):456-466. doi: 10.1097/AAP.0000000000000806.

18. Cohen SP, Bhatia A, Buvanendran A, et. al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43(5):521-546. doi: 10.1097/AAP.0000000000000808.

19. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. 2017;74(4):399–405. doi:10.1001/jamapsychiatry.2017.0080.

Table 3: Considerations for Ketamine Administration from Professional Society Guidelines [21, 22, 23]

Professional Society	Reasons for Use	Key Considerations from Guidelines
AAPM/ASA/ ASRA	**Acute and Chronic Pain**	**Dose:** There is moderate evidence to support higher dosages of ketamine over longer time periods for chronic pain (e.g., a single, outpatient infusion at a minimum dose of 80 mg lasting more than 2 hours), then reassess before initiating further treatments. The majority of acute pain studies used bolus doses of less than 0.5 mg/kg and infusion rates of less than 0.5 mg/kg per hour (8 µg/kg per minute). **Frequency of Administration:** A "series" of infusions should not be administered by route, but rather tailored to patient response. Considering the risks of long-term ketamine treatment, limiting these to no more than 12 per year is reasonable, though deviations may be made in exceptional circumstances (recommendation based on a moderate level of certainty). **Treatment Response:** A ≥ 30% decrease in pain is considered clinically meaningful in conjunction with patient satisfaction and objective indicators of meaningful benefit. **Duration of Therapy:** Single outpatient infusions should provide relief lasting > 3 weeks, while inpatient or serial outpatient infusions should provide relief lasting > 6 weeks (recommendation based on a moderate level of certainty). **Maintenance Therapy:** The guidelines did not delve into long-term maintenance prescribing.
APA	**Mood Disorders**	**Dose:** There is insufficient information to support doses or routes of administration other than the standard regimen of 0.5 mg/kg per 40 minutes IV. **Frequency of Administration:** The number and frequency of treatments should be limited to the minimum necessary to achieve clinical response. **Treatment Response:** Patients should be monitored closely using a rating instrument to assess clinical change to better reevaluate the risk to benefit ratio of continued treatment. **Duration of Therapy & Maintenance Therapy:** It is strongly recommended that the relative benefit of each ketamine infusion be considered in light of the potential risks associated with longer-term exposure to ketamine and the lack of published evidence for prolonged efficacy with ongoing administration.

AAPM – American Academy of Pain Medicine
APA – American Psychiatric Association
ASA – American Society of Anesthesiologists
ASRA – American Society of Regional Anesthesia and Pain Medicine

21. Schwenk ES, Viscusi ER, Buvanendran A, et. al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):456-466. doi: 10.1097/AAP.0000000000000806.

22. Cohen SP, Bhatia A, Buvanendran A, et. al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43(5):521-546. doi: 10.1097/AAP.0000000000000808.

23. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. 2017;74(4):399–405. doi:10.1001/jamapsychiatry.2017.0080.

The VHA Experience

Dr. Eric Hermes presented the VHA's national rollout of ketamine and esketamine for TRD and acute suicidality. The VHA has developed a community of practice with over 600 providers and a national training program for ketamine use. Ongoing challenges included providing equal access to ketamine therapy for all veterans, noting that not all VHA health systems have implemented ketamine clinics, and the persistent undertreatment of veterans with TRD.

Dr. Hermes also presented a 2020 retrospective review of veterans treated with IV ketamine.[24] The patient group had severe and treatment-resistant depression, high comorbidity (70% with comorbid PTSD), and received a mean of 18 infusions (decreasing in frequency over time) over approximately 12 months. Half of study patients showed improvement (a minimally clinically important difference demonstrated by at least a 5-point decrease in the PHQ-9 score from baseline) and 26% responded (a 50% reduction in PHQ-9 score from baseline) to treatment.[25] This study provided information about patient outcomes based on a protocol using a prescribed dose and frequency of administration.

Clinical Research

Evaluating ketamine's effectiveness in clinical trials comes with many challenges. Placebo effects can be significant in pain and psychiatric conditions and the potential for dissociation with ketamine makes blinding patients difficult. Clinical studies should also evaluate expectations and contextual effects of ketamine therapy in various settings. Hyperbolic claims in media and advertising shape patient beliefs, often leading to inflated expectations about ketamine's efficacy in treating mental health conditions. Media influence on patient perceptions can influence study outcomes and may introduce bias if not measured or accounted for appropriately.

> "…if we think that the kinds of information that the patients are getting is important. Well, what beliefs are being shaped by the media that patients consume?" **– Dr. Boris Heifets**

24. Pfeiffer PN, Geller J, Ganoczy D, et. al. Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System. J Clin Psychiatry. 2024 Jan 8;85(1):23m14984. doi: 10.4088/JCP.23m14984.

25. PHQ -9: Patient Health Questionnaire-9. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.

Challenges in collecting safety data were also highlighted. Quantifying and prioritizing risk has not been elucidated. Inconsistent reporting of adverse events resulting from off-label use or the use of compounded ketamine products makes tracking difficult. Evaluation of real-world ketamine clinic data also has limitations. Many patients leave treatment and the reasons for their dropout remain unclear, contributing to gaps in safety data.

Lastly, research protocols may not allow for the wide variety of doses, titration practices, and dosing duration and frequencies that are being used in some clinical practice settings. Without this evidence base, however, it remains unknown whether many of the current practices are safe or effective.

Knowledge Gaps and Areas for Future Research[26]

- More thorough characterization of the long-term efficacy, safety, and tolerability of IV ketamine
- Characterization of the relative efficacy, tolerability, and safety of oral, intranasal, subcutaneous, and IM formulations
- Who are the best candidates for ketamine (patient selection, contraindications, who is at increased risk and needs closer monitoring)?
- The optimum dose, frequency, and duration for the condition being treated
- The relationship between dose and patient outcomes
- Critical moderators of response
- Correlation between dissociative effects of ketamine and therapeutic response
- Identification of clinical endpoints
- Comparative effectiveness data (e.g., IV ketamine vs. IN ketamine; IV ketamine vs. esketamine; ketamine vs. neurostimulation; ketamine vs. 2nd generation antipsychotics)
- Long-term effectiveness and safety
- The possibility of tachyphylaxis/therapeutic tolerance
- Characterization of the efficacy, tolerability, and safety of administration in less restrictive treatment environments (e.g., physician's offices, self-administration at home under certain conditions)
- What is known about the expectations about ketamine therapy that patients bring with them into treatment? How much does that influence outcome?
- Patient accessibility to the treatment(s); insurance coverage; patient preference; ability to adhere to the treatment regimen

26. Items collated from meeting discussions and material from Sanacora G, Overview of the Changing Ketamine Landscape; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

THREE
Safety Concerns and Potential Risks

"…potent therapy, by definition, carries risk." **– Dr. Boris Heifets**

Adverse Effects

The following adverse effects (AEs) are most commonly reported with ketamine administered in a clinical setting: psychiatric side effects including dissociation, dizziness, drowsiness, and lightheadedness; hemodynamic effects (increased heart rate and/or blood pressure), and urinary symptoms (dysuria, nocturia, urgency, incontinence).[27] Vomiting, confusion, and impaired consciousness, which increases the risk of physical harm, have been reported by recreational ketamine users. [28]

Much remains unknown about the long-term safety profile of ketamine, especially with higher doses, repeated use, and the various administration routes being used in practice. Dr. Steven Cohen, from Northwestern University Feinberg School of Medicine, postulated a potential dose-dependent relationship between ketamine and AEs, with more serious AEs resulting from higher individual doses and potentially cumulative dosing.[29] Potential consequences of long-term use include misuse and neurotoxicity resulting from long-term ketamine exposure.[30] Interestingly, more adverse events have been reported with nonmedical use compared to ketamine administered in controlled clinical settings. The question remains whether this discrepancy is due to the ketamine itself or potential adulterants present in ketamine products purchased on the street.[31]

> "…[there is an] apparent discrepancy between what we're seeing in terms of toxicities and side effects in patients who got ketamine for medical reasons versus those who are abusing it. That begs the question of why is that discrepancy there? Why are patients who are getting ketamine infusions in our settings not having really any of these toxicities, or at least anything that's nearly as severe as what's being described. I think that's a question that we don't completely have answers to." **– Dr. Eric Schwenk**

27. Ehret MJ, Patient Safety and Managing Adverse Effects of Ketamine; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use- ketamine-emerging-areas-therapeutic-interest.
28. Palamar JJ. Recreational Ketamine Use, Misuse of Prescribed Ketamine, and Associated Adverse Effects; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.
29. Cohen SP, Scope of Ketamine Use in Clinical Practice; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine- emerging-areas-therapeutic-interest.
30. Choudhury D, Autry AE, Tolias KF, Krishnan V. Ketamine: Neuroprotective or Neurotoxic? Front Neurosci. 2021; 15:672526. doi: 10.3389/fnins.2021.672526.
31. Schwenk E, Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

At-Home/Unsupervised Use

At-home or unsupervised ketamine administration raises significant safety concerns. The impact of ketamine prescribing solely via telehealth, with multiple doses of medication mailed to a patient's home, has yet to be understood. Potential risks associated with at-home or unsupervised use are provided in Table 4.

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

Table 4: Safety Concerns and Potential Risks Associated with Unsupervised (At-Home) Use of Ketamine and Dispensing Multiple Doses at One Time [32]

Issue	Example(s)
Dysphoric reactions with no supervision	Consequences of people alone and experiencing anxiety or a panic attack and not understanding what is happening to them or what to do
Patient self-harm or harm to others	Driving after dosing; supervising children when not fully conscious or aware; risk of accidental ingestion of ketamine by a child
Diversion	Selling extra ketamine doses
Stockpiling and use of large doses	Risk of overdose or overuse
Alternate routes of administration	Lozenges broken up for inhalation; ketamine extraction from oral or sublingual dosage forms
Abuse potential	Development of ketamine use disorder
Seeking illegal supply after introduced	"Street" price turns out to be cheaper than a visit plus the home-delivered medication

32. Adapted from Palamar J, Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

Polysubstance Use

Recreationally, there is an emerging trend in the co-use of ketamine and alcohol, increasing the risk of impaired or loss of consciousness. Alcohol was the primary substance in cases reporting co-drug use, sometimes leading to fatalities.[33] There is also the concern of people drinking alcohol with unsupervised administration of ketamine (home use).

Knowledge Gaps and Areas for Future Research

- The long-term safety of ketamine use
- Significant drug-drug interactions with prescription drugs, alcohol, and drugs from the nonmedical drug supply
- The possibility of withdrawal and withdrawal-emergent suicidality
- Risks when ketamine is used in patients with underlying medical conditions (e.g., hypertension, cardiovascular disease, diabetes, alcohol or other substance use disorders)
- Reasons for the apparent discrepancy between toxicities and AEs in patients receiving ketamine for medical reasons vs. those who are recreationally using or abusing ketamine
- Factors driving ketamine misuse and abuse

33. Palamar J, Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

FOUR

Policy and Regulatory Challenges

Federally, ketamine is classified as a Schedule III controlled substance. A ketamine prescription requires a provider, working within their scope of practice, to be licensed in the state where the ketamine is being prescribed, and registered with the Drug Enforcement Administration (DEA). Dispensing ketamine for medical use requires a legitimate prescription from a licensed provider meeting the aforementioned requirements and the dispensing pharmacy to be state-licensed and DEA-registered.

FDA Risk Alerts for Compounded Ketamine[34, 35]

- Ketamine is not FDA approved for the treatment of any psychiatric disorder. FDA is aware that compounded ketamine products have been marketed for a wide variety of psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder); however, FDA has not determined that ketamine is safe and effective for such uses.
- Compounded drugs, including compounded ketamine products, are not FDA approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing. Therefore, compounded drugs do not have any FDA-approved indications or routes of administration. Although compounded drugs can serve an important medical need for certain patients when an FDA-approved drug is not medically appropriate, they also present a risk to patients and should only be used under the care of a health care provider.
- Use of compounded ketamine products without monitoring by a health care provider for sedation (sleepiness), dissociation (disconnection between a person's thoughts, feelings, and sense of space, time, and self), and changes in vital signs (such as blood pressure and heart rate) may put patients at risk for serious adverse events.
- Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms. For FDA-approved ketamine (see Ketalar® prescribing information), the expected benefit outweighs these risks when used at appropriate doses for FDA-approved indications and routes of administration.
- Despite increased interest in the use of compounded ketamine, FDA is not aware of evidence to suggest that it is safer, is more effective, or works faster than medications that are FDA approved for the treatment of certain psychiatric disorders.

34. Center for Drug Evaluation and Research (CDER). FDA Alerts Health Care Professionals of Potential Risks Associated with Compounded Ketamine Nasal Spray. U.S. Food and Drug Administration. Published online February 16, 2022. https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray.

35. Center for Drug Evaluation and Research (CDER). FDA Warns Patients and Health Care Providers about Potential Risks Associated with Compounded Ketamine Products, Including Oral Formulations, for the Treatment of Psychiatric Disorders. U.S. Food and Drug Administration. Published online October 10, 2023. https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine.

36. U.S. Food and Drug Administration. KETALAR - ketamine hydrochloride injection Prescribing Information. www.FDA.gov. https://www.accessdata.fda.gov/spl/data/705c4709-580e-4f02-8a74-bc9aa0641fe2/705c4709-580e-4f02-8a74-bc9aa0641fe2.xml.

The FDA issued public compounding risk alerts in 2022 and 2023 to inform the public about adverse events and concerns with the off-label use of compounded ketamine. These alerts were not meant to prohibit compounding, but to educate the public on its potential risks.

In 2024, the Alliance for Pharmacy Compounding issued best practices for compounding ketamine.[37] These guidelines focused on the safe preparation and dispensing of compounded ketamine products, emphasizing pharmacists' legal obligations, monitoring for diversion, patient education, and thorough documentation. The implementation of robust operational protocols, monitoring pharmacy inventory for diversion, and ensuring compliance with DEA regulations, particularly around constructive transfers and distribution of compounded ketamine by outsourcing facilities, were key points of emphasis. Compounding facilities must also adhere to controlled substance laws and ensure that prescribing practitioners operate within their appropriate scope of practice.

Regulatory frameworks, supervision, and guidance for safe ketamine administration vary across states. Table 5 provides examples of state-specific regulations.

Dr. Lisa Harding from Yale University advocated for viewing regulation as a means to ensure safety, rather than simply as a restrictive measure. This perspective was echoed in discussions of how state pharmacy boards monitor ketamine dispensing, sales, and compounding practices, with a focus on patient safety, especially as more patients have access to ketamine treatments at home. An increasing trend of out-of-state pharmacies dispensing ketamine underscores the need for cross-state collaboration to ensure consistent standards of care.

The panel highlighted the importance of data collection, particularly through Prescription Drug Monitoring Programs (PDMPs), to track ketamine use and ensure safe practices. They also emphasized the need for greater collaboration among state boards, physicians, and pharmacists to ensure the safe and appropriate use of ketamine while taking into account regulatory challenges, access issues, and gaps in care.

37. Alliance for Pharmacy Compounding. Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies. Published online April 1, 2024. https://a4pc.org/files/APC-Ketamine-Best-Practices-April-2024.pdf.

Table 5: State-Level Policies and Laws Related to Ketamine[38]

State	Policy/Law	Specifications
Arizona	State Board of Nursing Advisory Opinion	• Defines when registered nurses (RNs) are operating within their scope of practice with respect to administering ketamine for various indications (pain control/analgesia, depression, and sedation), but not anesthesia
Florida	State Department of Health Rulings	• Allows RNs with Advanced Cardiovascular Life Support (ACLS) training to administer low doses of ketamine (up to 0.5 mg/kg) provided it does not rise to the level of sedation or anesthesia
Oregon	State Department of Justice Opinion	• Infusion of sub-anesthetic doses of ketamine for the treatment of disorders of mood, anxiety, trauma, and stressors resistant to medication and psychotherapy in an outpatient clinic setting is within the scope of practice for Certified Registered Nurse Anesthetists (CRNA) • The disorder must be determined by a licensed independent health care practitioner • Assumes that the CRNA owns and manages clinic where treatment occurs
Utah	Anesthesia and sedation requirements – *Unprofessional Conduct – Whistleblower Protection* places requirements on various sedation levels in an outpatient setting, implicating use of ketamine	• Healthcare personnel required to have certain training • There must be direct supervision of the patient • Must have at least one individual in the procedure room who has advanced airway training and can rescue a patient who entered a deeper than intended level of sedation • An anesthesia provider who is providing ketamine for a non-anesthetic purpose must have an individual with airway training on site (not necessarily in the procedure room)

Knowledge Gaps and Areas for Future Research

- Research is needed to monitor the quickly changing legal and illegal ketamine landscape and how much off-label prescribed ketamine is being diverted

38. Mailhot SA, Policy and Regulatory Challenges for the Medical Use of Ketamine: State Review; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

FIVE
Online Promotion and Access

Depending on the specific circumstances, promotion of medical products and health claims are regulated by different agencies under different authorities. Within FDA's Center for Drug Evaluation and Research, the Office of Prescription Drug Promotion (OPDP) regulates advertising and promotion of prescription drug products to ensure that the advertising is "truthful, balanced, and accurately communicated."[39] The FDA does not review all promotional communications before they are published, but firms voluntarily seeking feedback may submit draft promotional communications to the agency prior to publication or initial dissemination.[40] OPDP takes action when potentially violative advertising is identified. In the case of approved ketamine drugs, OPDP evaluates direct-to-consumer and health care provider promotional communications made by or on behalf of the manufacturer, packer, or distributor, with a focus on any false or misleading claims.

The Federal Trade Commission (FTC) has jurisdiction of over-the-counter (OTC) drug advertising and enforces truth in advertising laws. As described by Mr. Richard Quaresima from the FTC, the Federal Trade Commission Act (FTCA) specifically outlaws deceptive practices in or affecting commerce.[41] With regard to health products, claims about the potential health benefits of a product could be considered deceptive under the FTCA if the claim is either false or not substantiated. Substantiation has been defined as "competent and reliable scientific evidence to support the claim."[42] Competent and reliable scientific evidence will vary based on the claim and product, but in general is considered to be rigorous clinical evidence generated by a properly conducted clinical trial.[43]

Roles of each organization specific to drug promotion are provided in Table 6.

Table 6: Drug Promotion and Advertising Responsibilities

	FDA OPDP	FTC
Oversight	Direct-to-consumer and health care provider ads issued by or on behalf of manufacturers, packers, and distributors	Prioritizes direct-to-consumer advertising
Authority	Food, Drug, and Cosmetic Act	Federal Trade Commission Act
Drug Advertising Review	Prescription drug products	OTC drugs, dietary supplements

39. Center for Drug Evaluation and Research (CDER). The Office of Prescription Drug Promotion (OPDP). www.FDA.gov. Published 2024. https://www.fda.gov/about-fda/cder-offices-and-divisions/office-prescription-drug-promotion-opdp.

40. Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER). Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs. www.fda.gov. Published April 11, 2022. Accessed December 20, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-docu.

41. Federal Trade Commission. Federal Trade Commission Act. Federal Trade Commission. Published July 19, 2013. Accessed October 11, 2024. https://www.ftc.

42. Federal Trade Commission. Health Products Compliance Guidance. https://www.ftc.gov/. Published December 20, 2022. Accessed December 16, 2024. https://www.ftc.gov/business-guidance/resources/health-products-compliance-guidance www.ftc.gov/business-guidance/resources/health-products-compliance-guidance43.

43. Ibid.

Accuracy in advertising is essential in direct-to-consumer marketing. Dr. Michael DiStefano, from Colorado University Anschutz, Skaggs School of Pharmacy and Pharmaceutical Sciences, noted that the modern sub-anesthetic ketamine marketplace is not comprised of prescription drug manufacturers, packers, or distributers, for which the FDA regulates prescription drug promotion. Instead, wellness clinics, telehealth services, or med spas advertise ketamine. Dr. DiStefano presented findings from a study analyzing ketamine advertising on 17 websites representing 26 physical clinics in Maryland.[44]

Websites promoting FDA-approved prescription drugs must contain key components which include the name of the drug, at least one approved use, and the most significant risks of the drug.[45] Many ketamine infusion clinic websites lacked transparency and often made misleading, false, or deceptive claims. The study by Dr. DiStefano and colleagues included the following findings:

- Some clinics falsely claimed overexaggerated success rates for treating various conditions (e.g., Lyme disease). Websites also listed multiple conditions ketamine could treat without quality evidence.
- Some websites stated ketamine was non-addictive, downplaying the risk of abuse or misuse. Five sites minimized these risks, three falsely claimed ketamine is non-addictive, and seven did not mention any risks at all.
- Some websites inaccurately claimed FDA approval for ketamine in mental health treatments. Many failed to disclose that ketamine's use for mental health is off-label.

Overall, Dr. DiStefano concluded that consumers were not consistently provided with accurate, necessary information to make informed decisions about ketamine treatment.

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

44. Crane MA, DiStefano MJ, Moore TJ. False or Misleading Claims in Online Direct-to-Consumer Ketamine Advertising in Maryland. JAMA Netw Open. 2023;6(11):e2342210. doi:10.1001/jamanetworkopen.2023.42210.

45. U.S. Food and Drug Administration. Basics of Drug Ads. www.FDA.gov. Published June 19, 2015. Accessed December 16, 2024. https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads

Several online sectors promote the use of and access to ketamine (Table 7). Each sector offers specific products and claims resulting in a multitude of potential risks to consumers. Discerning which online sources and what information is trustworthy can be overwhelming.

Table 7: Online Advertising of Ketamine

Online Sector	Advertising Audience
Wellness and infusion clinics	Consumers
Telehealth services providing diagnosis and the drug itself	Consumers
Online drug sellers marketing and selling ketamine	Consumers
Compounding pharmacies	Consumers, Prescribers

Educating patients to evaluate the legitimacy of online health services, verify the credentials of providers, and spot misleading claims was emphasized as a crucial step. Dr. Ilisa Bernstein, from Bernstein Rx Solutions, provided best practices for accessing online clinical services. Example questions for consumers to consider when they evaluate a service include:[46]

- Are you talking to a real health care clinician?
- Are you talking to a real person or is it an AI computer?
- Can you verify the credentials of that clinician?
- Is the platform you're using HIPAA compliant?
- Is your personal information protected?
- Are there these claims that are too good to be true?
- What are the reviews?
- What does your health provider say about the service?

For health care providers and consumers who wish to report potentially misleading ads, both the FDA and the FTC have programs accepting public input – the Bad Ad program[47] and ReportFraud.ftc.gov.[48]

46. Bernstein I, Online Promotion and Access to Ketamine; June 27, 2024. https://reaganudall.org/news-and-events/events/understanding-current-use-ketamine-emerging-areas-therapeutic-interest.

47. Center for Drug Evaluation and Research (CDER). The Bad Ad Program. U.S. Food and Drug Administration. Published September 15, 2020. https://www.fda.gov/drugs/office-prescription-drug-promotion/bad-ad-program.

48. Federal Trade Commission. Report Fraud. ReportFraud.ftc.gov. https://reportfraud.ftc.gov/.

Two themes pertaining to online advertising loom large:

1) what are the specific risks to consumers, and
2) who has regulatory authority over different aspects of advertising for these sectors?

In an area where the clinical evidence base continues to grow, what is in-bounds and out-of-bounds in the realm of advertising continues to evolve. Ongoing need exists for joint efforts across regulatory bodies, the medical community, and professional societies to address the complex challenges surrounding ketamine promotion, particularly in balancing safety, access, and accurate information.

Knowledge Gaps and Areas for Future Research

- What do we know about the kind of information patients are getting about safety and efficacy?
- What beliefs are being shaped by the media that patients consume?
- Who can consumers rely on to ensure that efficacy and safety claims are truthful and evidence-based?

SIX

What Is Needed for Progress/ Future Directions

Panelists discussed the clinical use of ketamine for mental health and pain treatment, highlighting significant knowledge gaps, regulatory challenges, proliferation of misinformation, and issues related to access, affordability, and equity. They identified essential areas for progress to expand the evidence base and protect consumers.

The panel collectively agreed on the urgent need for more comprehensive data from both controlled studies and real-world sources to better understand ketamine's therapeutic potential, safety profile, and the various contexts in which it is used. Such data are crucial for informing benefit-risk discussions with patients and updating practice guidelines. Gathering robust data requires funding, which is challenging to secure for off-label drug uses. Alternate funding mechanisms are needed to support research and data collection and support robust studies that reflect real-world clinical practices. Creation of patient registries to collect real-world data was suggested, which would improve understanding of ketamine's effectiveness, safety, indications for maintenance treatment, and therapeutic outcomes.

The FDA emphasized its commitment to modernizing clinical trials and exploring real-world evidence while maintaining a strong focus on ensuring the safety and efficacy of treatments, noting the established supplemental new drug application pathway for submitting data to have a new indication considered.

Panelists expressed concern over the proliferation of clinics offering ketamine without proper oversight, potentially exploiting vulnerable patients. They underscored the importance of understanding what drives individuals to seek ketamine treatment in the community. Ensuring access, affordability, and equity in treatment was deemed crucial, with hope expressed for ketamine's accessibility in safe and less restrictive settings, if proven effective and safe for treatment of conditions for which ketamine is not currently approved.

The urgency of creating a coherent policy framework was stressed to avoid a patchwork of state regulations and to ensure patient safety. One panelist noted, "There has to be a policy framework that can support good care," highlighting the need for policies that prevent the exploitation of patients, especially those who cannot afford treatment or are more susceptible to misinformation.

In summary, the panel highlighted the necessity of improved data collection, regulatory guidance, and collaboration across federal and state agencies regarding the use of ketamine for emerging therapeutic purposes. Addressing knowledge gaps, combating misinformation, and developing policies that support quality care while preventing the exploitation of patients were identified as key areas requiring immediate action.

SEVEN
Conclusions

There are significant challenges in balancing the availability of ketamine for those who could benefit from it and the need to ensure both that its use is safe and that patients can make informed decisions about their treatment without the influence of false or misleading claims. Key areas of interest include determining for which conditions and in which populations ketamine has clinical benefits, understanding optimal dosing regimens, and characterizing and monitoring safety concerns. Establishing research priorities and better surveillance strategies is important for addressing these questions. Collaboration among stakeholders is crucial for devising strategies that provide access to treatment while implementing necessary safeguards to protect consumers.

Appendix

APPENDIX: AGENDA

Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest

Hybrid Public Meeting

Thursday, June 27, 2024, from 9 am – 4 pm Eastern Time
1333 New Hampshire Avenue NW; Rooftop Meeting Room
Washington, DC, 20036

MEETING DESCRIPTION: The Reagan-Udall Foundation for the FDA, in collaboration with the FDA, is hosting a hybrid public meeting on "Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest." Ketamine is a Schedule III controlled substance that is FDA-approved for induction and maintenance of general anesthesia. Although ketamine is not approved for the treatment of conditions such as depression or chronic pain, there has been increased interest in the use of ketamine for these types of conditions.

This public meeting will explore topics such as the scope of ketamine use, including use of approved products and compounded products, for these emerging areas of therapeutic interest; potential safety concerns; and online promotion of and access to ketamine. Speakers will include clinicians, academic researchers, patients and patient advocates, professional organizations, and federal partners.

AGENDA

9 am Opening Remarks

Speakers:

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

9:10 am Session 1: Overview of the Changing Ketamine Landscape

Presentation:

- Gerard Sanacora, MD, PhD, Yale University

9:30 am Session 2: Scope of Ketamine Use in Clinical Practice

Presentations:

- Steven P. Cohen, MD, Northwestern University Feinberg School of Medicine, Uniformed Services University School of Medicine
- Eric Hermes, MD, Veterans Health Administration

Panel Discussion:

- Mikhail Kogan, MD, George Washington University Center for Integrative Medicine
- Brittany O'Brien, PhD, Baylor College of Medicine
- Jessica Poole, DNAP, CRNA, Pennsylvania Association of Nurse Anesthetists
- Sandhya Prashad, MD American Society of Ketamine Physicians, Psychotherapists, and Practitioners

11 am BREAK

11:10 am **Session 3:** Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products

Presentations:

- Joseph Palamar, PhD, MPH, New York University Langone Health
- Megan Ehret, PharmD, MS, BCPP, University of Maryland Baltimore School of Pharmacy

Panel Discussion:

- Francesca Cunningham, PharmD, U.S. Department of Veterans Affairs
- Mark Rogge, PhD, University of Florida College of Pharmacy
- Eric Schwenk, MD, Thomas Jefferson University

12:05 pm LUNCH

1:15 pm **Session 4:** Policy and Regulatory Challenges for the Medical Use of Ketamine

Presentations:

- Seth Mailhot, JD, Husch Blackwell
- A.J. Day, PharmD, RPh, National Community Pharmacists Association

Panel Discussion:

- Gail Bormel, RPh, JD, U.S. Food and Drug Administration
- Lisa Harding, MD, Yale University
- Lisa Robin, Federation of State Medical Boards
- Jenni Wai, RPh, MBA, Ohio Board of Pharmacy

2:15 pm **Session 5:** Online Promotion and Access to Ketamine

Presentations:

- Michael DiStefano, PhD, MBE, Colorado University Anschutz, Skaggs School of Pharmacy and Pharmaceutical Sciences
- Boris Heifets, MD, PhD, Stanford University School of Medicine

Panel Discussion:

- Ilisa Bernstein, PharmD, JD, Bernstein Rx Solutions
- Richard Quaresima, Federal Trade Commission

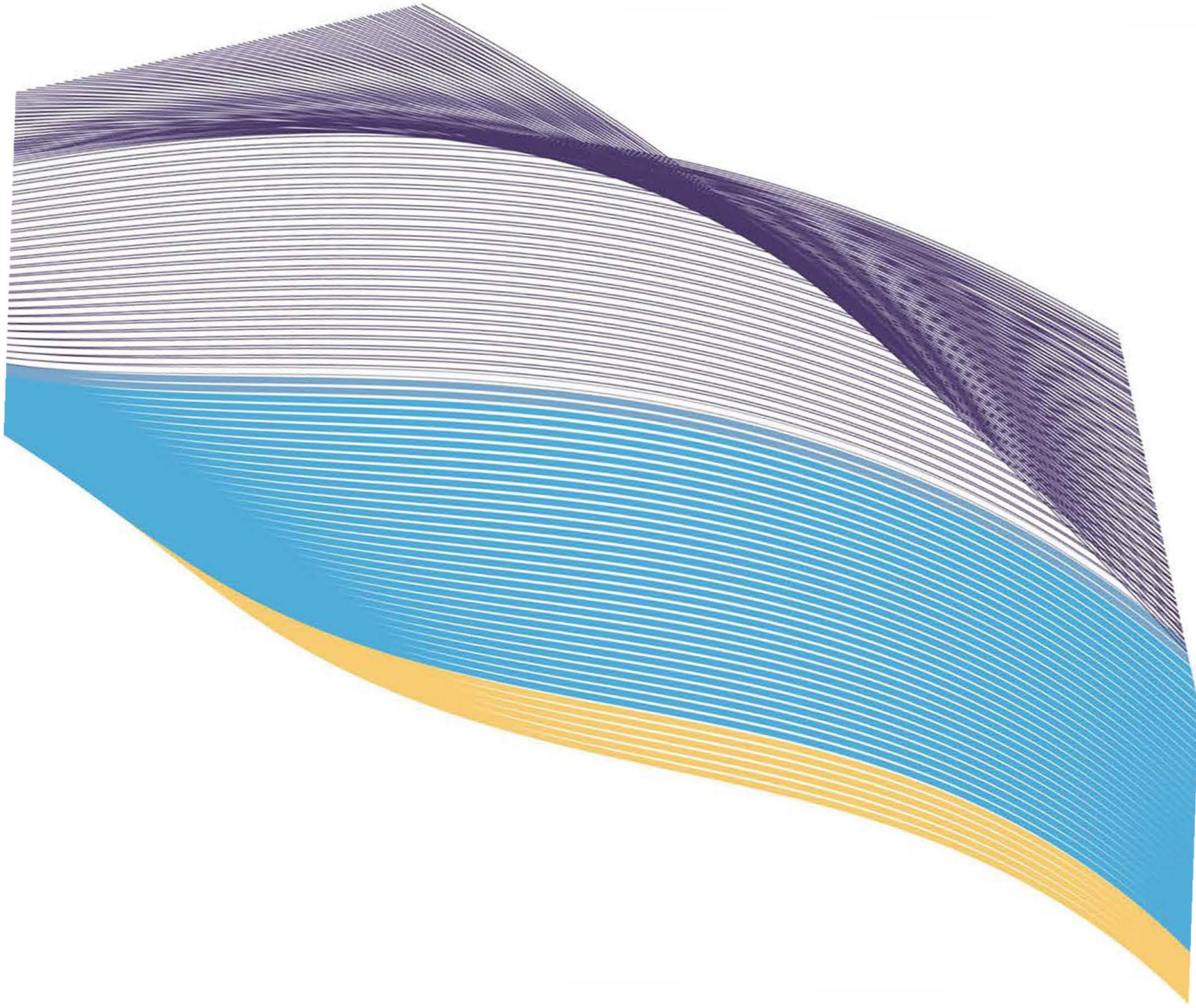
3 pm BREAK

3:10 pm **Session 6:** Potential Future Use of Ketamine

Panel Discussion:

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

4 pm ADJOURN



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