# Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest

## The public meeting will begin shortly

Thursday, June 27, 2024

9 am – 4 pm Eastern Time

Funding Disclosure: 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.

REAGAN-UDALL FOUNDATION FOR THE FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

# Welcome

**Susan C. Winckler, RPh, Esq.**
Chief Executive Officer
Reagan-Udall Foundation for the FDA

# Hybrid Meeting

REAGAN-UDALL FOUNDATION FOR THE FDA

Joining online:
Microphone and video will remain off during the meeting
Share your questions using the Zoom Q&A function

Joining in-person:
Please write your questions on the index cards provided

This public meeting is being recorded
The slides, transcript, and video will be available at www.ReaganUdall.org

# Today's Agenda (Eastern Time)

REAGAN-UDALL FOUNDATION FOR THE FDA

| | |
|---|---|
| **9 am** | Welcome & Opening Remarks |
| **9:10 am** | Session 1: Overview of the Changing Ketamine Landscape |
| **9:30 am** | Session 2: Scope of the ketamine Use in Clinical Practice |
| **11 am** | Break |
| **11:10 am** | Session 3: Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products |
| **12:05 pm** | Lunch |

# Today's Agenda (Eastern Time)

REAGAN-UDALL FOUNDATION FOR THE FDA

| | |
|---|---|
| **1:15 pm** | Session 4: Policy and Regulatory Challenges for the Medical Use of Ketamine |
| **2:15 pm** | Session 5: Online Promotion and Access to Ketamine |
| **3 pm** | Break |
| **3:10 pm** | Session 6: Potential Future Use of Ketamine |
| **4 pm** | Closing Remarks & Adjourn |

REAGAN-UDALL FOUNDATION FOR THE FDA

# Opening Remarks

**Marta Sokolowska, PhD**
Deputy Center Director for Substance Use and Behavioral Health
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REAGAN-UDALL FOUNDATION FOR THE FDA

# Overview of the Changing Ketamine Landscape

**Gerard Sanacora, MD, PhD**
Yale University

# Overview of the Changing Ketamine Landscape

Gerard Sanacora, M.D., Ph.D.

George D. Gross and Esther S. Gross Professor of Psychiatry,
Yale University School of Medicine
Director Yale Depression Research Program
Co-Director Yale New Haven Hospital Interventional Psychiatry Service

# Disclosures

The Yale School of Medicine

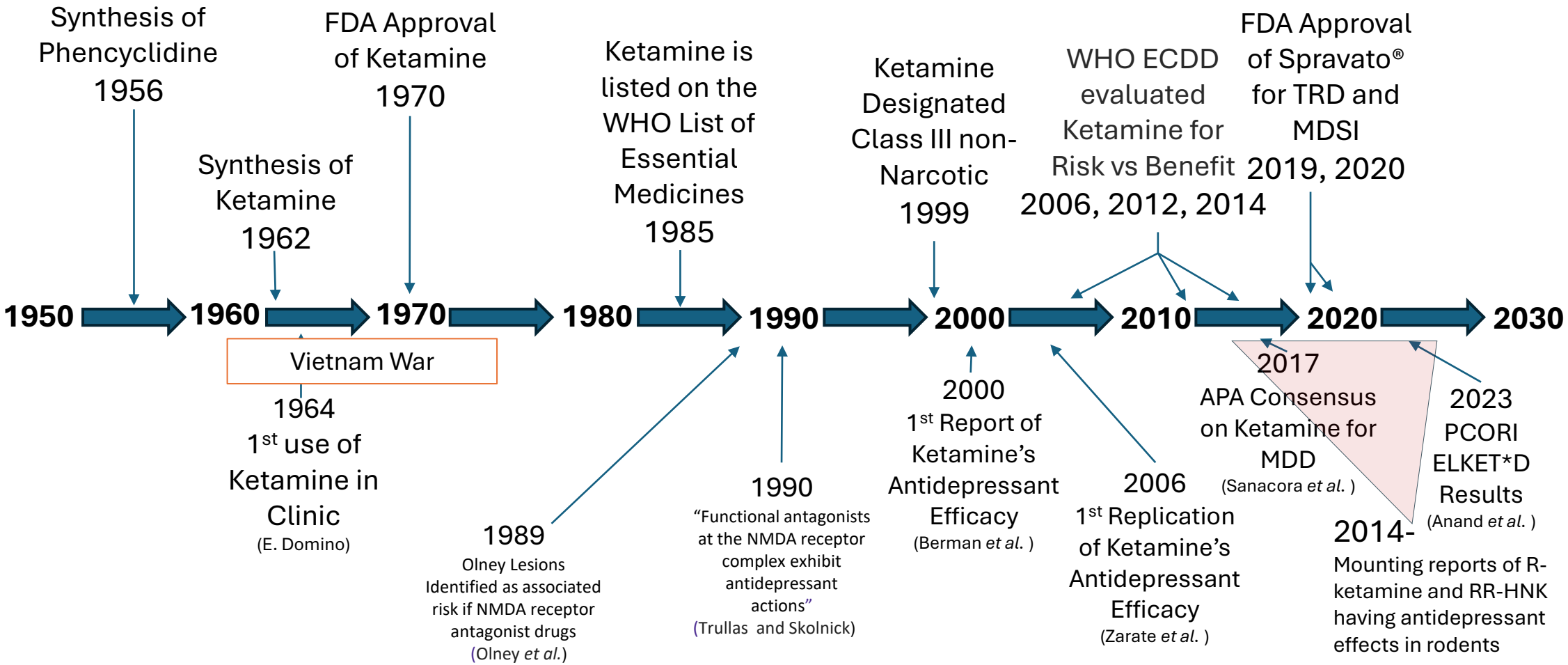
- In the past 2 years Dr. Sanacora has served as a consultant or scientific advisory board member to Ancora/Embark, Aptinyx, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Bristol-Myers Squibb, Clexio, Cowen, Denovo Biopharma, ECR1, EMA Wellness, Freedom Biosciences, Gilgamesh, Janssen, KOA Health, Levo Therapeutics, Merck, MiCure, Navitor Pharmaceuticals, Neurocrine, Novartis, Perception Neuroscience, Praxis Therapeutics, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Transcend Therapeutics, Vistagen Therapeutics, and XW Labs; and received **research contracts** from Johnson & Johnson (Janssen), Merck, and Usona Institute. Dr. Sanacora **holds equity** in Biohaven Pharmaceuticals, Freedom Biosciences, Gilead, Relmada, Tetricus and is a co-inventor on a **US patent** (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research. **Yale University has a financial relationship** with Janssen Pharmaceuticals and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest Office

Off-label use discussed

Several including;

Ketamine

# Ketamine Timeline (Depression Centric)



# Biological Explanations for Delayed Onset

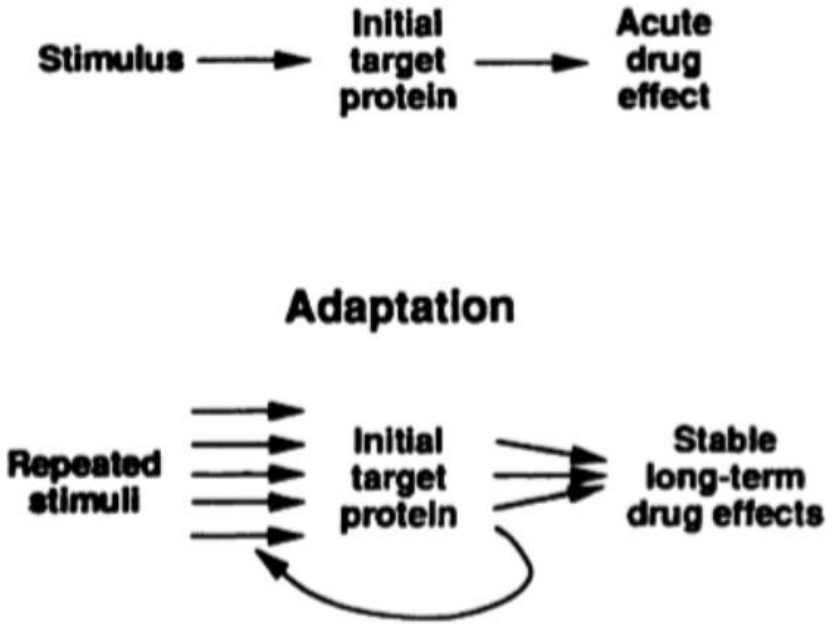
## Initiation and Adaptation: A Paradigm for Understanding Psychotropic Drug Action

Steven E. Hyman, M.D., and Eric J. Nestler, M.D., Ph.D.

*Objective:* This article describes a paradigm—initiation and adaptation—within which to conceptualize the drug-induced neural plasticity that underlies the long-term actions of psychotropic drugs in the brain. *Method:* Recent advances in neurobiology are reviewed. *Results:* Recent developments in cellular and molecular neurobiology provide new conceptual and experimental tools for understanding the mechanisms by which psychotropic drugs produce long-lived alterations in brain function. Because of the availability of more robust animal models, the mechanisms by which drugs of abuse produce dependence are better understood than the mechanisms by which antidepressants, antipsychotics, and lithium produce their therapeutic effects. Nonetheless, the fundamental types of mechanisms appear to be similar: chronic drug administration drives the production of adaptations in postreceptor signaling pathways, including regulation of neural gene expression. Whether the results are deleterious or therapeutic depends on the precise neural systems targeted by a particular drug. *Conclusions:* Biological investigation in psychiatry has often focused too narrowly on synaptic pharmacology, especially on neurotransmitter turnover and neurotransmitter receptors. This review focuses on molecular and cellular changes in neural function that are produced as adaptations to chronic administration of addictive drugs such as psychostimulants and therapeutic drugs such as antidepressants. To understand normal brain function, psychopathology, and the actions of psychiatric treatments, and to exploit the eventual findings of psychiatric genetics, psychiatric research must now extend its efforts beyond the synapse, to an understanding of cellular and molecular neurobiology (in particular, postreceptor signal transduction) as well as to a better understanding of the architecture and function of neural systems. A paradigm is presented to help understand the long-term effects of psychotropic drugs, including the latency in onset of their therapeutic actions.

(Am J Psychiatry 1996; 153:151–162)

FIGURE 1. Initiation of and Adaptation to a Psychotropic Drug[a]



# Identifying the Glutamate NMDA Receptor as a Possible Target for Antidepressant Drug Development

*European Journal of Pharmacology*, 185 (1990) 1–10
Elsevier



EJP 51446

## Functional antagonists at the NMDA receptor complex exhibit antidepressant actions

Ramon Trullas and Phil Skolnick

*Laboratory of Neuroscience, National Institutes of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, U.S.A.*

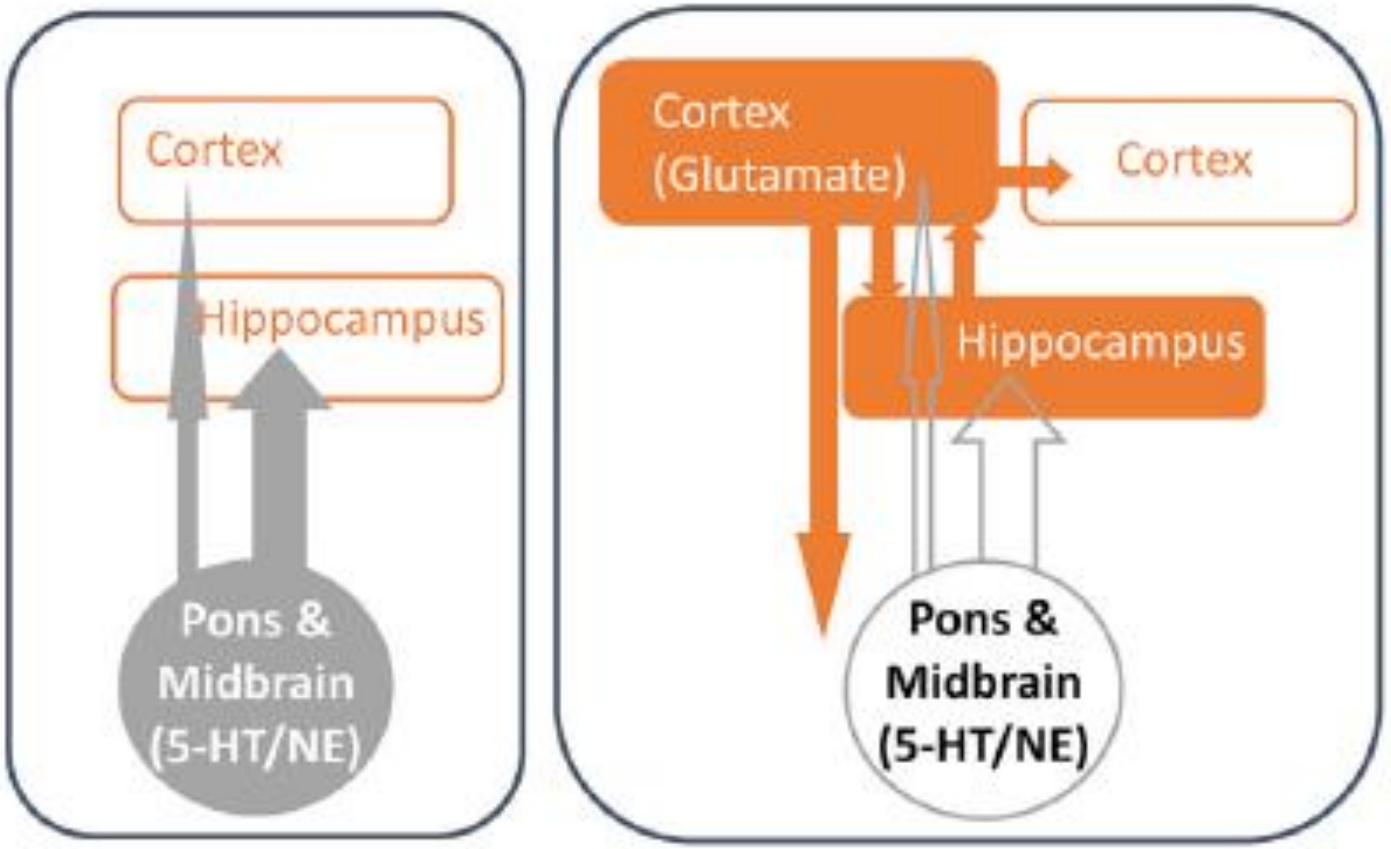
Received 22 February 1990, revised MS received 22 May 1990, accepted 29 May 1990

Inescapable, but not escapable, stress inhibits the induction of Long Term Potentiation (LTP) in the $CA_1$ region of hippocampus, a process that is dependent upon activation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Since inescapable stress also produces a syndrome of behavioral depression sensitive to clinically effective antidepressants, we examined the actions of functional antagonists at the NMDA receptor complex in animal models commonly used to evaluate potential antidepressants. A competitive NMDA antagonist (2-amino-7-phosphonoheptanoic acid [AP-7]), a non-competitive NMDA antagonist (Dizolcipine [MK-801]), and a partial agonist at strychnine-insensitive glycine receptors (1-aminocylopropanecarboxylic acid [ACPC]) mimicked the effects of clinically effective antidepressants in these models. These findings indicate that the NMDA receptor complex may be involved in the behavioral deficits induced by inescapable stress, and that substances capable of reducing neurotransmission at the NMDA receptor complex may represent a new class of antidepressants. Based on these findings, the hypothesis that pathways subserved by the NMDA subtype of glutamate receptors are involved in the pathophysiology of affective disorders may have heuristic value.

# Changing Theories of Mood Disorder Pathophysiology

**Historically dominant monoaminergic theory**

**Shift to cortical and limbic pathology**

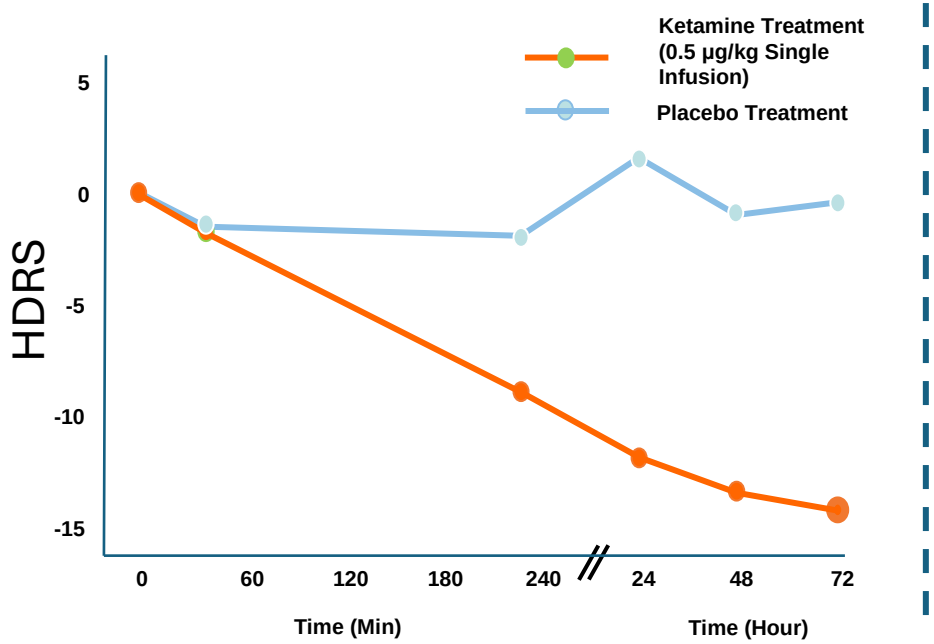



"If one viewed depression as a disorder of cortico-limbic function, then glutamatergic and GABAergic signaling would be implicated. This perspective shift led us to test the effects of the NMDA glutamate receptor antagonist as a probe of alterations in glutamate signaling associated with depression."

Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Neuron. 2019 Mar 6;101(5):774-778

# Initial Reports of Ketamine's Rapid Antidepressant Action

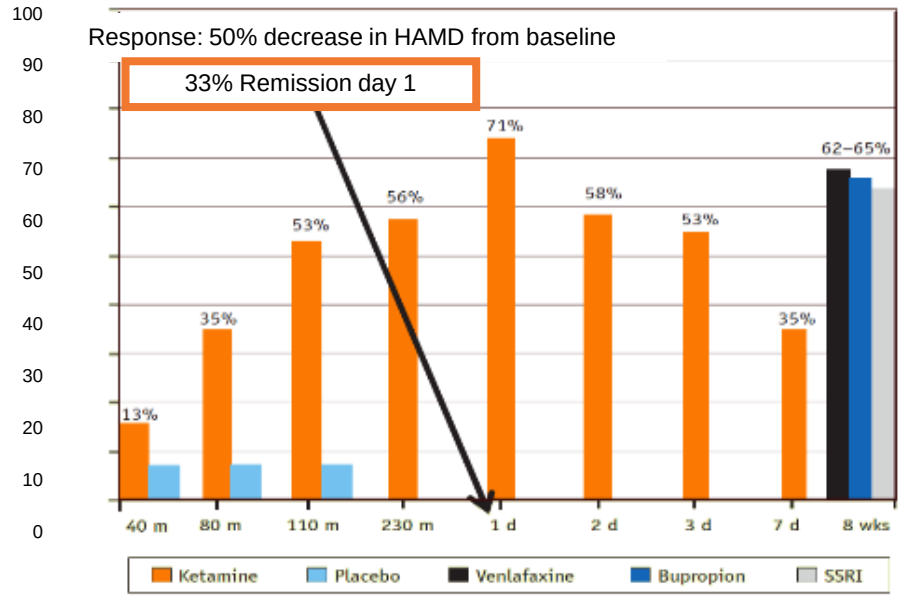
*"To the amazement of our patients and ourselves, we found that ketamine produced rapid, profound, and surprisingly durable antidepressant effects that were temporally dissociated from the brief acute behavioral effects of the drug"* Krystal JH, et al. Neuron. 2019 Mar 6;101(5):774-778




RCT IV Ketamine vs. Saline (N=8)

HDRS = Hamilton Depression Rating Scale for depression.

Berman R, et al. *Biol Psychiatry.* 2000;47:351–354.



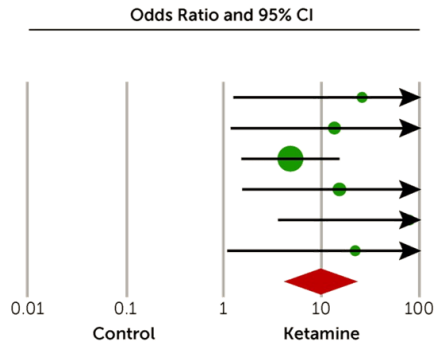

RCT IV Ketamine vs. Saline (N=18)

Zarate et al. *Arch Gen Psych*. 2006.

# IV Ketamine – Efficacy in MDD/TRD

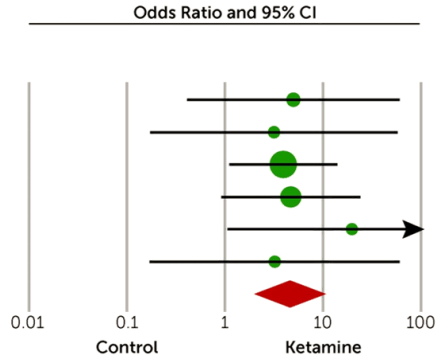
A At 1 day

| Study | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Diazgranados et al. (85) | 26.053 | 1.359 | 499.339 | 2.164 | 0.030 |
| Lapidus et al. (84) | 13.600 | 1.238 | 149.455 | 2.134 | 0.033 |
| Murrough et al. (87) | 4.833 | 1.578 | 14.803 | 2.759 | 0.006 |
| Sos et al. (91) | 15.294 | 1.610 | 145.305 | 2.374 | 0.018 |
| Zarate et al. (88) | 79.545 | 3.762 | 1681.833 | 2.811 | 0.005 |
| Zarate et al. (86) | 22.176 | 1.133 | 434.158 | 2.042 | 0.041 |
| | 9.865 | 4.366 | 22.293 | 5.503 | 0.000 |



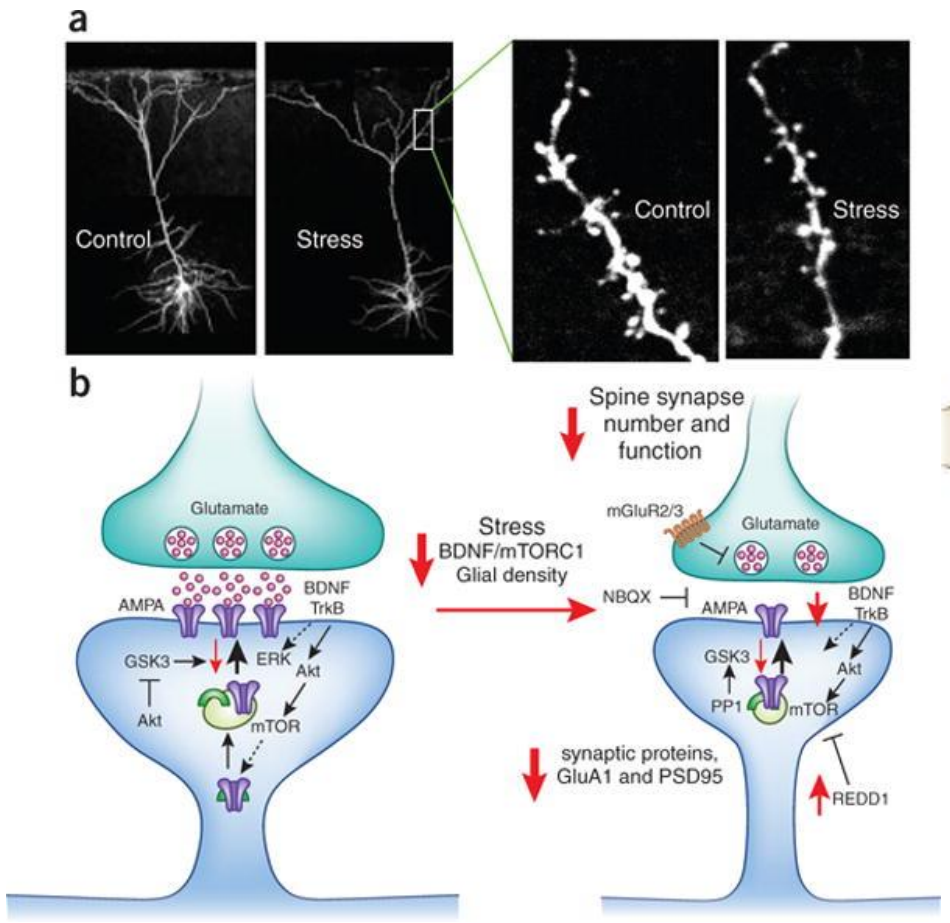

B At 1 week

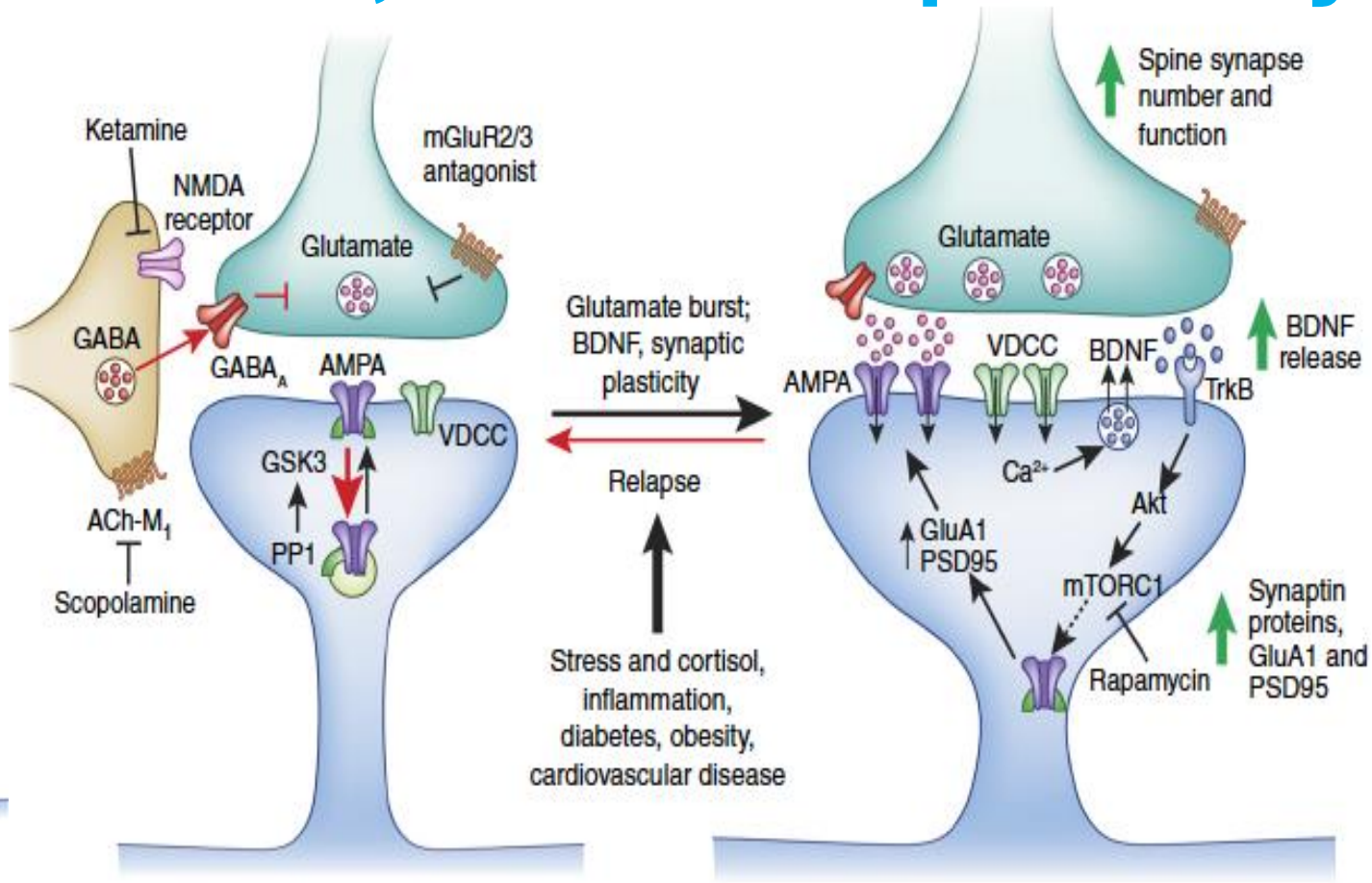
| Study | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Diazgranados et al. (85) | 5.000 | 0.426 | 58.636 | 1.281 | 0.200 |
| Lapidus et al. (84) | 3.171 | 0.179 | 56.222 | 0.787 | 0.431 |
| Murrough et al. (87) | 3.937 | 1.149 | 13.492 | 2.181 | 0.029 |
| Sos et al. (91) | 4.706 | 0.950 | 23.302 | 1.898 | 0.058 |
| Zarate et al. (88) | 19.783 | 1.060 | 369.109 | 1.999 | 0.046 |
| Zarate et al. (86) | 3.222 | 0.176 | 58.849 | 0.789 | 0.430 |
| | 4.610 | 2.076 | 10.236 | 3.754 | 0.000 |




Newport DJ et al. *Am J Psychiatry*. 2015.

# NMDA Receptor, Glutamate Burst, and Neuroplasticity

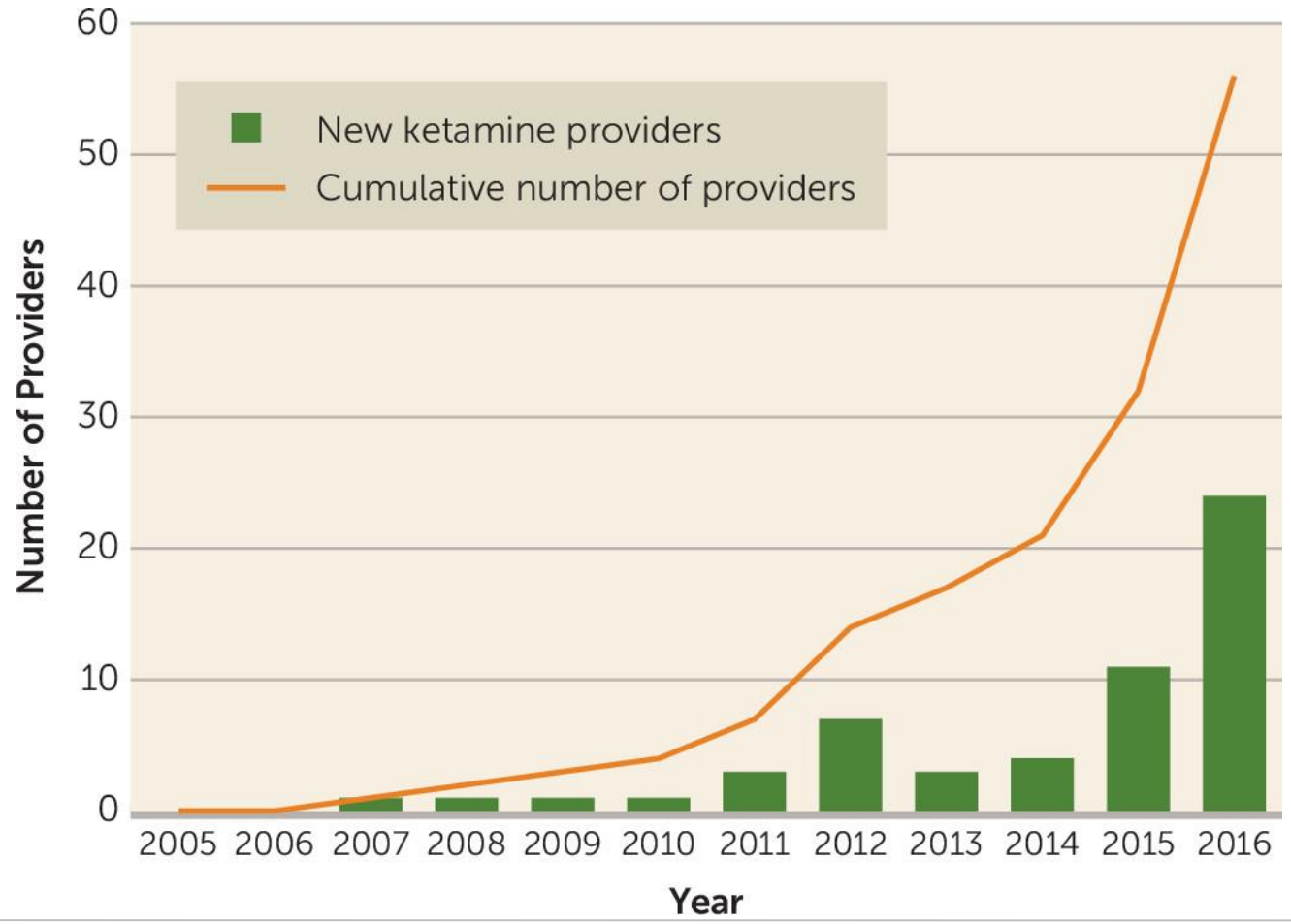



Duman, Aghajainian, Sanacora, and Krystal Nat Med. 2016 Mar; 22(3): 238–249.

# Rapid Increase in Clinicians Providing Ketamine for the Treatment of Psychiatric Disorders

**A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders**




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

Wilkinson et al. Am J Psychiatry. 2017 Jul 1;174(7):695-696

# Potential Risks

## Pathological Changes Induced in Cerebrocortical Neurons by Phencyclidine and Related Drugs

JOHN W. OLNEY, JOANN LABRUYERE, MADELON T. PRICE

**Phencyclidine (PCP), a dissociative anesthetic and widely abused psychotomimetic drug, and MK-801, a potent PCP receptor ligand, have neuroprotective properties stemming from their ability to antagonize the excitotoxic actions of endogenous excitatory amino acids such as glutamate and aspartate. There is growing interest in the potential application of these compounds in the treatment of neurological disorders. However, there is an apparent neurotoxic effect of PCP and related agents (MK-801, tiletamine, and ketamine), which has heretofore been overlooked: these drugs induce acute pathomorphological changes in specific populations of brain neurons when administered subcutaneously to adult rats in relatively low doses. These findings raise new questions regarding the safety of these agents in the clinical management of neurodegenerative diseases and reinforce concerns about the potential risks associated with illicit use of PCP.**

**Science**, Volume 244, Issue **4910** Jun 1989

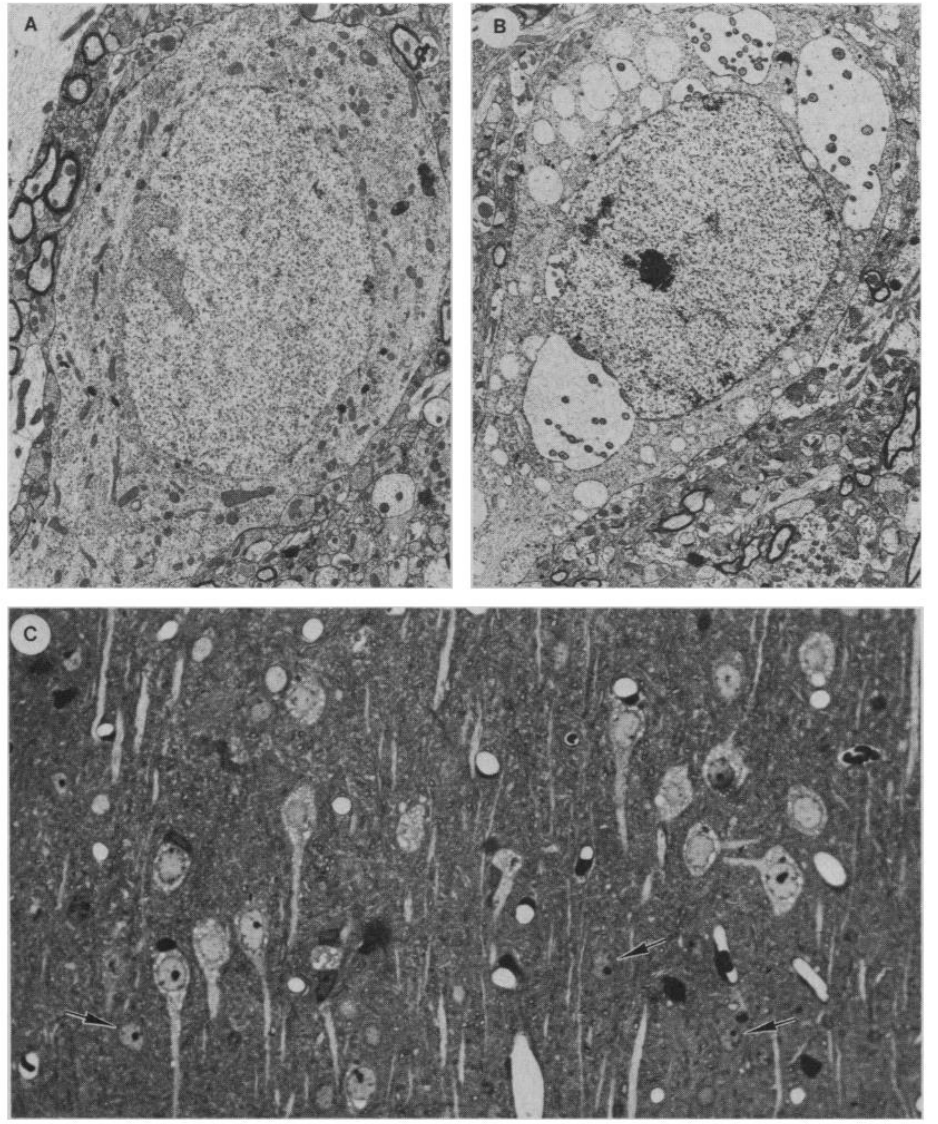



**Fig. 1.** (**A**) Electron micrograph depicting a large posterior cingulate cortical neuron from the brain of a normal untreated rat. The cytoplasm of this neuron contains many normal-appearing mitochondria, and there are no abnormal vacuoles (×7000). (**B**) A large posterior cingulate cortical neuron from a rat treated with PCP (5 mg/kg sc) 4 hours earlier. Very few normal mitochondria are evident in the cytoplasm but many vacuoles are present, some of which contain multiple small, round structures that appear to be remnants of mitochondria. The neuropil surrounding this neuron is well preserved, and there are many normal-appearing mitochondria in the neuropil components (×7000). (**C**) Numerous vacuole-containing large neurons in layers III and IV of the posterior cingulate cortex of a rat treated 4 hours earlier with MK-801 (1 mg/kg sc). Smaller neurons in other layers (arrows) are free from vacuoles (×200).

Addiction Biology
PRECLINICAL STUDY
Chronic ketamine exposure ind
impairment of brain functions
cynomolgus monkeys
Lin Sun[1], Qi Li[2], Qing Li[1], Yuzhe Zhang[1], Dexia
Department of Medical Psychology, Shandong University School of Me
Development, University of Hong Kong, China[2] and School of Biomedic
ABSTRACT
Ketamine, a non-competitive N-methyl-
drug among young drug abusers world
working, episodic and semantic mem
to healthy volunteers. However,
anomalies and neurochemical h
ketamine could impair a range
exploration of the neurochem
ined the abnormalities in bo
deoxynucleotidyl transfer
Bax, Bcl-2 and caspase-
anesthetic ketamine
increased cell death
control monkeys,
ketamine admini
functions due

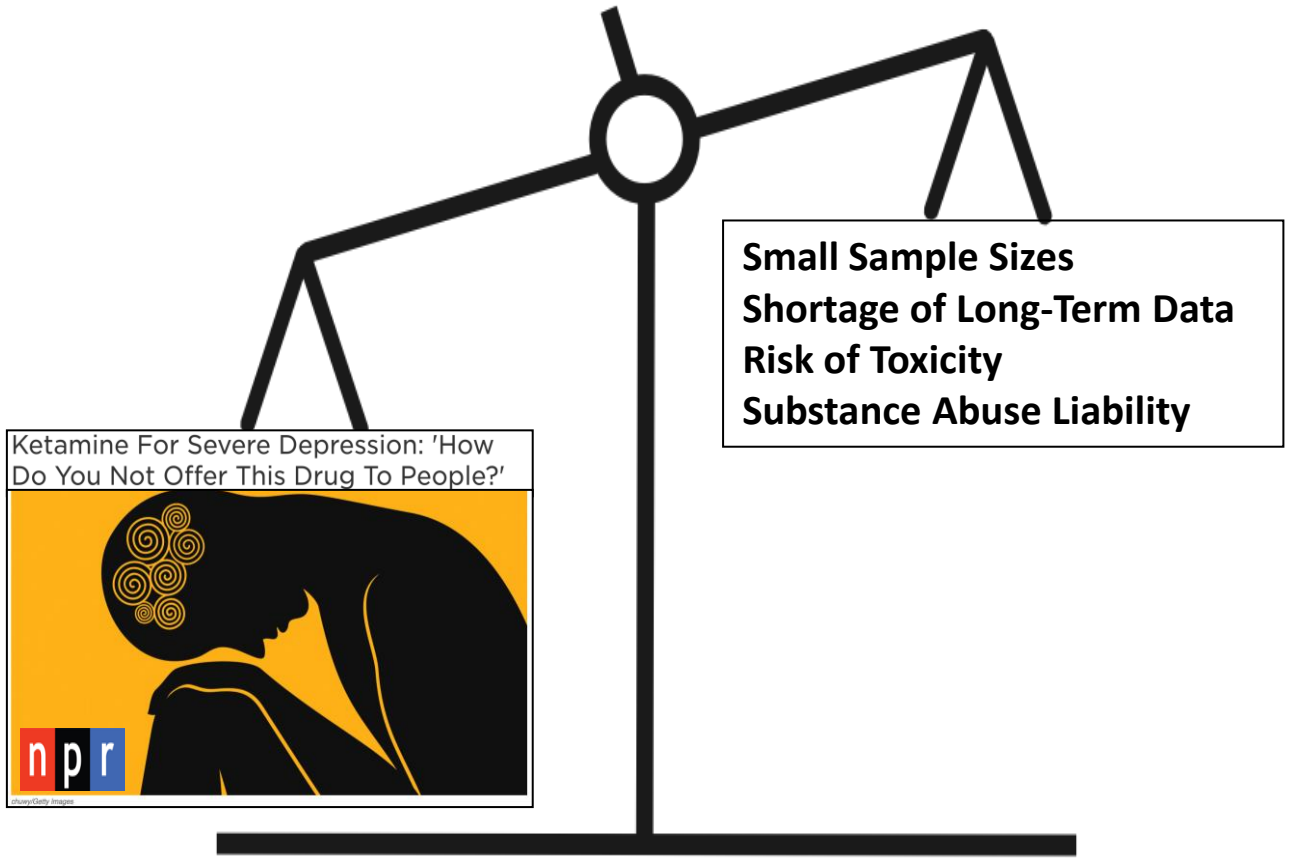
frontiers in
NEUROANATOMY
Brain damages in ketamine addicts
magnetic resonance imaging
Chunmei Wang[1†], Dong Zheng[2†], Jie Xu[3], Waiping Lam
[1] Brain Research Center, Institute of Chinese Medicine, The Chinese University
[2] Department of Neurology, Guangzhou Brain Hospital, Affiliated Hospital of G
[3] Department of Anatomy, Zhongshan School of Medicine, Sun Yat-Sen Univ
[4] Faculty of Medicine, Brain Research Center, School of Biomedical Scienc
Edited by:
Yun-Qing Li, The Fourth Military Medical University, China
Reviewed by:
Yun-Qing Li, The Fourth Military Medical University, China
José A. Armengol, University Pablo de Olavide, Spain
*Correspondence:
D. T. Yew, Institute of Chinese Medicine, The Chinese Universi
Hong Kong, Shatin, New Territories, Hong Kong SAR, China
e-mail: david-yew@cuhk.edu.hk
†These authors have contributed equally to this work.
Ketamine, a known
been used as an
ketamine has
prolonged
studies on
docume
emplo

frontiers
in Neuroanatomy
Brain C
Long
A S
Ketamine abuse has been shown
dependence-induced pathologica
drug abuse, the presence of whi
were measured using in vivo
44 drug-free healthy volunteers
and left temporoparietal cortice
severity of drug use (as measur
abnormalities of white matter in
suggest a microstructural basis
Received February 21, 2010. Revised April 17, 2010. Accepted April 25, 2010. Advance Access publication June 2, 2010
© The Author (2010). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.
For Permissions, please email: journals.permissions@oxfordjournals.org
California State Univ
Marcos, United States
Valerio Ricci,
San Luigi Gonzaga University
Hospital, Italy
Keywords: keta

doi:10.1093/brain/awq131
BRAIN
A JOURNAL OF NEUROLOGY
Frontal white
chronic ketami
study
Yanhui Liao,[1,*] Jinsong Tan
Tieqiao Liu,[1] Xiaogang Che
[1] Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha, Hunan, 410011, People's Republic of China
[2] Kangda Voluntary Drug Rehabilitation Center, Changsha, Hunan, 410007, People's Republic of China
[3] Department of Addiction Medicine, Hunan Mental Health Institute, Second Xiangya Hospital, Central South University, 139 Renmin (M) Road, Changsha, Hunan, 410011, People's Republic of China
[4] University of Cambridge, Department
*These authors contributed equally to th
Correspondence to: Dr Wei Hao, Mental Health Institute, Second Xiangya Hospital, Central South University, 139 Renmin (M) Road, Changsha, Hunan, 410011, People's Republic of China
E-mail: weihaochangsha@googlemail.co
Correspondence may also be addressed
University of Cambridge, Department of Psychiatry, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK
E-mail: pcf22@cam.ac.uk

frontiers in
PSYCHIATRY
Long-term heavy ketamine use is associated with spatial memory impairment and altered hippocampal activation
ORIGINAL RESEARCH ARTICLE
published: 04 December 2014
doi: 10.3389/fpsyt.2014.00149
Celia J. A. Morgan[1,2]*, Chris M. Dodds[1], Hannah Furby[3], Fiona Pepper[4], Johnson Fam[5], Tom P. Freeman[2], Emer Hughes[5], Christian Doeller[6], John King[2], Oliver Howes[4,5†] and James M. Stone[4,5†]
[1] Centre for Clinical Psychopharmacology, University of Exeter, Exeter, UK
[2] Clinical Psychopharmacology Unit UCL, University College London, London, UK
[3] Neuroimaging Sciences, Cardiff University, Cardiff, UK
[4] Institute of Psychiatry, Kings College London, London, UK
[5] Department of Experimental Medicine, Imperial College London, London, UK
[6] Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands
Edited by:
Manjin Liffijn, Baylor College of Medicine, USA
Reviewed by:
A. D. Lê, Centre for Addiction and Mental Health, Canada
Langsuo Ma, University of Texas Health Science Center at Houston, USA
*Correspondence:
Celia J. A. Morgan, Department of Psychology, University of Exeter, Perry Road, Exeter, Devon EX4 4QG, UK
e-mail: celia.morgan@exeter.ac.uk
†Oliver Howes and James M. Stone have contributed equally to this work.
Ketamine, a non-competitive N-methyl-d-aspartate receptor antagonist, is rising in popularity as a drug of abuse. Preliminary evidence suggests that chronic, heavy ketamine use may have profound effects on spatial memory but the mechanism by which heavy ketamine use impairs spatial memory processing. In a sample of 11 frequent ketamine users and 15 poly-drug controls, matched for IQ, age, years in education. We used fMRI utilizing an ROI approach to examine the neural activity of three regions known to support successful navigation: the hippocampus, parahippocampal gyrus, and the caudate nucleus during a virtual reality task of spatial memory. Frequent ketamine users displayed spatial memory deficits, accompanied by and related to, reduced activation in both the right hippocampus and left parahippocampal gyrus during navigation from memory, and in the left caudate during memory updating, compared to controls. Ketamine users also exhibited schizotypal and dissociative symptoms that were related to hippocampal activation. Impairments in spatial memory observed in ketamine users are related to changes in medial temporal lobe activation. Disrupted medial temporal lobe function may be a consequence of chronic ketamine abuse and may relate to schizophrenia-like symptomatology observed in ketamine users.
Keywords: ketamine, drug abuse, hippocampus, memory, spatial memory, NMDA receptor

# Balancing the Potential Benefits with the Current Knowledge and Potential Risks of Ketamine Treatment




JAMA Psychiatry | Special Communication

## A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Gerard Sanacora, MD, PhD; Mark A. Frye, MD; William McDonald, MD; Sanjay J. Mathew, MD; Mason S. Turner, MD; Alan F. Schatzberg, MD; Paul Summergrad, MD; Charles B. Nemeroff, MD, PhD; for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments

**IMPORTANCE** Several studies now provide evidence of ketamine hydrochloride's ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders.

**OBSERVATIONS** This review and consensus statement provides a general overview of the data on the use of ketamine for the treatment of mood disorders and highlights the limitations of the existing knowledge. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option.

**CONCLUSIONS AND RELEVANCE** The suggestions provided are intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provides information on potentially important issues related to the off-label treatment approach that should be considered to help ensure patient safety.

*JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2017.0080
Published online March 1, 2017.

Invited Commentary

Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

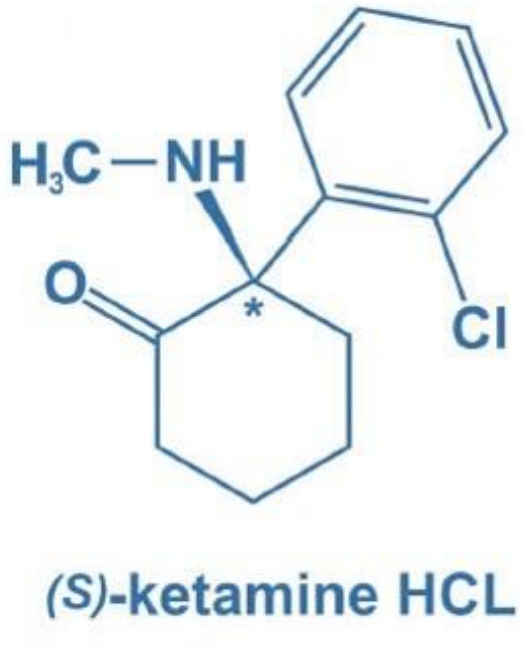
**Group Information:** The American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments members are listed at the end of this article.

**Corresponding Author:** Gerard Sanacora, MD, PhD, Yale University School of Medicine, 100 York St, Ste 2J, New Haven, CT 06511 (gerard.sanacora@yale.edu).

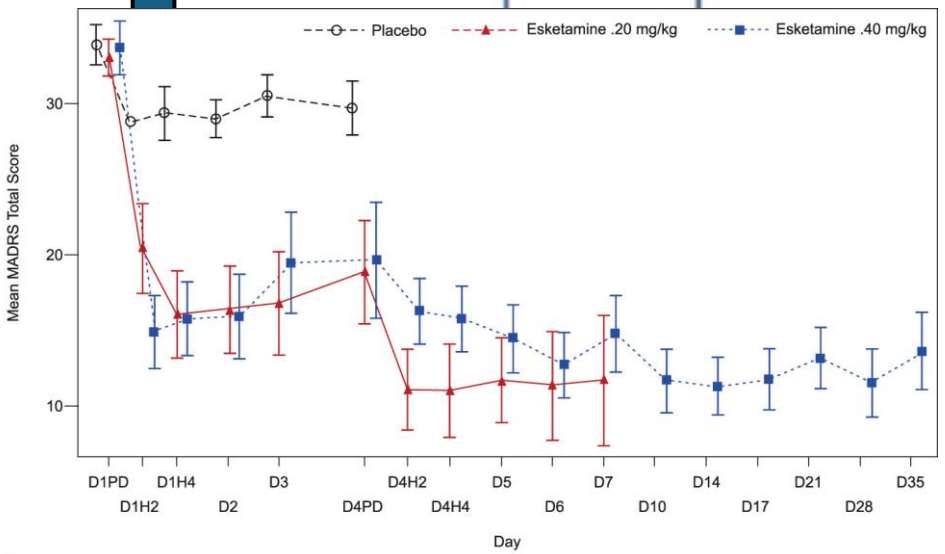
# Need to Address the Key, Clinically Relevant Questions Regarding Ketamine's Rapid Onset Antidepressant Effects

- **Immediate Clinical Relevance**
  - What is the Optimal Dosing Strategy for Ketamine (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?
    - Diagnoses, Subtypes, genetic, or endophenotypic differences in response
    - Drug-drug interactions (regarding both safety and efficacy)

# EsKetamine




The (S) enantiomer has a greater affinity for the NMDA glutamate receptor. This allows for a greater amount of NMDA receptor blocade with lower doses of the drug. (White et al.. (1980) Pharmacology of ketamine isomers in surgical patients. Anesthesiology 52: 231–239., Oye et al. . Effects of ketamine on sensory perception: evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther. 1992;260:1209–13)




| Number of Subjects | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 10 | 10 | 10 | 10 | 10 | 10 | | | | | | | | | | |
| Esketamine .20 mg/kg | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | | | | |
| Esketamine .40 mg/kg | 11 | 11 | 11 | 11 | 11 | 11 | 20 | 20 | 20 | 19 | 20 | 29 | 29 | 27 | 29 | 28 | 27 |

Singh et al. Biol Psychiatry. 2016 Sep 15;80(6):424-431

Antidepressant effects of esketamine delivered intravenously

# Esketamine Phase 3 Clinical Development Program in Treatment-Resistant Depression (TRD)

| Study | Design | n | Duration (wk) | Main endpoints |
|---|---|---|---|---|
| **Acute, fixed dose study (3001, TRANFORM-1)[1]** | Double-blind, active controlled | 346 | 4-week induction | MADRS change at 4 weeks |
| **Acute, flexible dose study (3002, TRANSFORM-2)[2]** | Double-blind, active controlled | 223 | 4-week induction | MADRS change at 4 weeks |
| **Elderly, acute, flexible dose study (3005, TRANSFORM-3)[5]** | Double-blind, active controlled | 138 | 4-week induction | MADRS change at 4 weeks |
| **Maintenance, relapse prevention study (3003, SUSTaIN 1)[3]** | Open-label or double-blind induction (4-wks) and optimization (12-wks), followed by double-blind, active-controlled maintenance | 705 | Variable duration, longer term | Time to relapse; relapse in stable remitters; relapse in stable responders |
| **Maintenance, safety study (3004, SUSTaIN 2)[4]** | Open-label | 802 | 52-weeks | Safety and tolerability |

**1.** Fedgchin M, et al. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX.;* Fedgchin M, et al. Int J Neuropsychopharmacol. 2019 Jul 10. [Epub ahead of print] **2.** Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. ; Popova et al. Am J Psychiatry. 2019 Jun 1;176(6):428-438 **3.** Daly EJ, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.; Daly et al. *JAMA Psychiatry.* 2019;76(9):893-903 **4.** Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. Wajs et al. J Clin Psychiatry. 2020 Apr 28;81(3):19 **5.** Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. Ochs-Ross et al. Am J Geriatr Psychiatry. 2020 Feb;28(2):121-141

# IN Esketamine (Spravato®) FDA Approval

**FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic, March 2019**

https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

**Expanded use of SPRAVATO esketamine CIII nasal spray for the treatment of major depressive disorder (MDD) with acute suicidal ideation or behavior, August 2020.**

https://onlinelibrary.wiley.com/doi/abs/10.1002/mhw.32471

# Esketamine (Spravato®) Guidance

| Treatment Phase | Administration | Adult dosing |
|---|---|---|
| **Induction phase** | | |
| Weeks 1-4: sessions 1-8 | Twice weekly | Day 1 starting dose: 56 mg<br>Subsequent doses: 56 or 84 mg |
| **Maintenance phase** | | |
| Weeks 5-8 (early maintenance): sessions 9-12 | Once weekly | 56 or 84 mg |
| Week 9 and later: sessions 13 and beyond | Every 2 weeks or once weekly[a] | 56 or 84 mg |

ESK, esketamine nasal spray; TRD, treatment-resistant depression.

[a]Dosing frequency should be individualized to the least-frequent dosing to maintain remission/response.

| | Outpatient HCSs | Inpatient HCSs | Pharmacies |
|---|---|---|---|
| Designate an authorized representative to review the ESK prescribing information and REMS Program Overview, complete an enrollment form and submit it to the REMS, and oversee implementation and coordinate activities of the REMS | X | X | X |
| Train all relevant staff involved in prescribing, dispensing, and/or administering ESK | X | X | X |
| Create processes and procedures to ensure ESK is administered under the direct supervision of a healthcare provider followed by at least 2 hours of monitoring | X | X | |
| Create processes and procedures to ensure ESK is dispensed only to REMS-certified HCSs and never directly to a patient | | | X |
| Submit all required patient enrollment and monitoring forms within the required time frames | X | | |
| Maintain all records of product received and dispensing information | X | X | X |
| Comply with all REMS audits | X | X | X |

ESK, esketamine nasal spray; HCS, healthcare setting; REMS, Risk Evaluation and Mitigation Strategy program. See enrollment form for a full list of requirements.

Spravato® (esketamine) nasal spray

## SPRAVATO® REMS

### Patient Monitoring Form - Outpatient Use Only

For Healthcare Setting Use Place Patient Label or Barcode Here

**INSTRUCTIONS:**

**This form is intended only for use by outpatient medical offices or clinics, excluding emergency departments.**

1. Complete all required fields on this form after **every** treatment session for **all outpatients** enrolled in the SPRAVATO® REMS.
2. Submit completed patient monitoring forms within **7 days**, online at www.SPRAVATOrems.com or by fax (1-877-778-0091).

** Indicates Required Field*

**Patient Information (PRINT)**

First Name*: | MI: | Last Name*: | Birthdate* (MM/DD/YYYY): | Sex*: ☐ Male ☐ Female ☐ Other

**Concomitant Medication**

Is the patient currently taking any of the following medication(s) that may cause sedation or blood pressure changes?

- Benzodiazepines* ☐ Yes ☐ No
- Non-benzodiazepine sedative hypnotics* ☐ Yes ☐ No
- Psychostimulants* ☐ Yes ☐ No
- Monoamine oxidase inhibitors (MAOIs)* ☐ Yes ☐ No

**Healthcare Provider Conducting Patient Monitoring (PRINT)**

First Name*: | Last Name*:

Telephone*: | Email*:

**Healthcare Setting Information (PRINT)**

Healthcare Setting Name*:

Healthcare Setting Address 1*: | Healthcare Setting Address 2:

City*: | State*: | ZIP*:

**Patient Treatment Session Information (Administration and Monitoring)**

| | |
|---|---|
| **Treatment Date*** | Date (MM/DD/YYYY): _____ |
| **Dose Administered*** | ☐ 56 mg ☐ 84 mg ☐ Other:_____ |
| **Treatment Duration*** | Total time _____minutes (from 1st device administration to completion of monitoring)<br>**Patient must be monitored for at least 2 hours** |
| **REMS Evaluation Question*** | *If there was not a 2-hour minimum monitoring requirement, when would this patient have been ready to leave/no longer require monitoring? _____ minutes from start of administration* |
| **Monitoring of Vital Signs*** | Vital signs were in acceptable range **prior** to:<br>• administration? ☐ Yes ☐ No<br>• treatment session completion? ☐ Yes ☐ No |
| **Monitoring of Blood Pressure*** | **Prior to administration** _____mmHg<br>**40 mins post-administration** _____mmHg<br>**Prior to treatment session completion** _____mmHg |

**Did the patient experience Sedation and/or Dissociation**

| **Sedation***: ☐ Yes ☐ No | **Dissociation***: ☐ Yes ☐ No |
|---|---|
| **Onset of symptoms** from start of administration*<br>☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins ☐ >120 mins | **Onset of symptoms** from start of administration*<br>☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins ☐ >120 mins |
| **Resolution of symptoms** within 2 hours?* ☐ Yes ☐ No<br>Specify total time to resolution*: _____min | **Resolution of symptoms** within 2 hours?* ☐ Yes ☐ No<br>Specify total time to resolution*: _____min |
| **Medication(s) given for sedation?*** ☐ Yes ☐ No<br>•If YES, name and dose of medication(s): _____ | **Medication(s) given for dissociation?*** ☐ Yes ☐ No<br>•If YES, name and dose of medication(s): _____ |

**Phone: 1-855-382-6022** **www.SPRAVATOrems.com** **Fax: 1-877-778-0091**

# Real-World Safety Profile of Esketamine Nasal Spray During the First 12 Treatment Sessions: An Analysis at 58 Months After Approval in the United States

Mai Himedan,[1] Ibrahim Turkoz,[2] Teodora Doherty,[2] Brianne Brown,[1] Phung Quach,[1] David M. Kern,[2] Gerard Sanacora[3]

[1]Janssen Scientific Affairs, LLC, a Johnson & Johnson company, Titusville, NJ; [2]Janssen Research & Development, LLC, Titusville, NJ; [3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT

## Introduction

- Esketamine nasal spray (ESK) was approved by the US Food and Drug Administration, in conjunction with an oral antidepressant, in March 2019 for the treatment of treatment-resistant depression (TRD) in adults and in July 2020 for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior[1]
- The recommended ESK dosing for TRD is shown in **Table 1**

**TABLE 1: Recommended ESK dosing for TRD**

| Treatment Phase | Administration | Adult dosing |
|---|---|---|
| **Induction phase** | | |
| Weeks 1-4: sessions 1-8 | Twice weekly | Day 1 starting dose: 56 mg<br>Subsequent doses: 56 or 84 mg |
| **Maintenance phase** | | |
| Weeks 5-8 (early maintenance): sessions 9-12 | Once weekly | 56 or 84 mg |
| Week 9 and later: sessions 13 and beyond | Every 2 weeks or once weekly[a] | 56 or 84 mg |

ESK, esketamine nasal spray; TRD, treatment-resistant depression.
[a]Dosing frequency should be individualized to the least-frequent dosing to maintain remission/response.

- Based on FDA requirements, Janssen developed and implemented a Risk Evaluation and Mitigation Strategy (REMS) program at the time of approval to mitigate the risks of serious adverse outcomes, including those resulting from sedation, dissociation, or from misuse and abuse, by ensuring the following
  - Healthcare settings (HCSs) that treat patients and pharmacies that dispense ESK are REMS certified
  - ESK is only dispensed and administered to patients in a medically supervised HCS that monitors these patients
  - Outpatients are enrolled in the REMS registry prior to treatment with ESK to further characterize risks and support safe use
  - All patients are informed about the potential for serious adverse outcomes resulting from sedation and dissociation and the need for monitoring
  - Patient administration is performed under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider in a healthcare setting for at least 2 hours after dosing for resolution of sedation and dissociation, and changes in vital signs
  - ESK is never dispensed directly to patients for home use
- To comply with the REMS, certified pharmacies and HCSs must follow specific requirements to receive, dispense, and treat patients with ESK (**Table 2**)

## Objective

- To examine and summarize real-world incidence of ESK treatment-emergent adverse events (TEAEs) of interest (i.e., actively solicited reports of sedation, dissociation, and increased blood pressure [BP]) and serious adverse events (SAEs) and to determine if the incidence of these events change between the induction and maintenance periods

## Methods

- Data from ESK REMS patient monitoring forms were evaluated to describe the key safety findings for the first 58 months (March 5, 2019, to January 5, 2024) after US product approval, with a focus on ESK TEAEs of interest (sedation, dissociation, and increased BP) and SAEs during the first 12 treatment sessions
- Results were summarized by first treatment session, sessions 1-8 (induction phase), and sessions 9-12 (early maintenance phase); the first 12 ESK treatment sessions were chosen for this analysis because most patients would have received ESK on similar schedules up to this point
  - TEAE rates reflect the percentage of patients who experienced ≥1 TEAE during the treatment phase
- Details of each outpatient treatment session, including the duration of monitoring after administration, BP values, TEAEs of interest (i.e., sedation and dissociation), and all SAEs observed, are documented in the REMS patient monitoring form, which is required to be submitted to the REMS administrator within 7 days after ESK administration. Healthcare providers in the outpatient setting are asked through solicited reporting to specifically record whether sedation, dissociation, and/or increased BP occurred at each treatment session
  - Post-administration BP increase, as measured at 40 min after dosing or at the time of discharge, was defined as BP post-administration increase of ≥20 mm Hg to a value ≥180 mm Hg for systolic pressure and/or ≥15 mm Hg to a value ≥105 mm Hg for diastolic pressure compared with values prior to administration
  - If pre-administration BP values were missing, systolic values ≥180 mm Hg and/or diastolic values ≥105 mm Hg after administration were also considered an increase
- SAEs for the ESK REMS were determined by the reporter and defined as any event occurring during or between sessions that results in
  - Hospitalization
  - Disability or permanent damage
  - Death
  - A life-threatening event
  - An important medical event (defined as any event that may jeopardize the patient or may require intervention to prevent any of the above outcomes)

**TABLE 2: ESK REMS certification requirements for HCSs and pharmacies**

| | Outpatient HCSs | Inpatient HCSs | Pharmacies |
|---|---|---|---|
| Designate an authorized representative to review the ESK prescribing information and REMS Program Overview, complete an enrollment form and submit it to the REMS, and oversee implementation and coordinate activities of the REMS | X | X | X |
| Train all relevant staff involved in prescribing, dispensing, and/or administering ESK | X | X | X |
| Create processes and procedures to ensure ESK is administered under the direct supervision of a healthcare provider followed by at least 2 hours of monitoring | X | X | |
| Create processes and procedures to ensure ESK is dispensed only to REMS-certified HCSs and never directly to a patient | | | X |
| Submit all required patient enrollment and monitoring forms within the required time frames | X | | |
| Maintain all records of product received and dispensing information | X | X | X |
| Comply with all REMS audits | X | X | X |

ESK, esketamine nasal spray; HCS, healthcare setting; REMS, Risk Evaluation and Mitigation Strategy program. See enrollment form for a full list of requirements.

## Results

### Baseline patient characteristics

- A total of 58,483 patients had ≥1 ESK treatment session during the evaluation period. At the first treatment session, most patients (65.2%) were aged between 18 and 49 years, and 61.1% were female (**Table 3**)

**TABLE 3: Patients with ≥1 ESK treatment session (March 5, 2019, to January 5, 2024)**

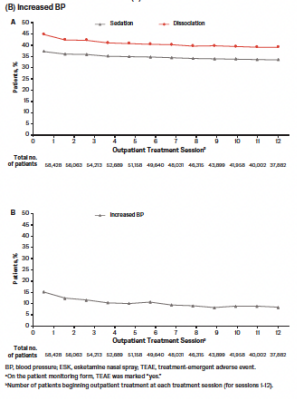
| n (%) | Patients with ≥1 ESK treatment session N = 58,483 |
|---|---|
| **Sex** | |
| Female | 35,762 (61.1) |
| Male | 22,300 (38.1) |
| Other/unknown | 421 (0.7) |
| **Age category** | |
| ≤12 years[a] | 1 (<0.1) |
| 13-17 years[a] | 55 (0.1) |
| 18-29 years | 11,758 (20.1) |
| 30-39 years | 13,577 (23.2) |
| 40-49 years | 12,774 (21.8) |
| 50-59 years | 10,895 (18.6) |
| 60-64 years | 4132 (7.1) |
| 65-74 years | 4359 (7.5) |
| ≥75 years | 932 (1.6) |
| **Region[b]** | |
| Southern United States | 20,844 (35.6) |
| Western United States | 14,453 (24.7) |
| Midwestern United States | 13,896 (23.8) |
| Northeastern United States | 9272 (15.9) |
| Other/unknown | 18 (<0.1) |

ESK, esketamine nasal spray.
[a]ESK is not approved for use in patients <18 years of age.
[b]According to 2010 US Census Bureau Geography Division guidelines.

### TEAEs of sedation, dissociation, and increased BP

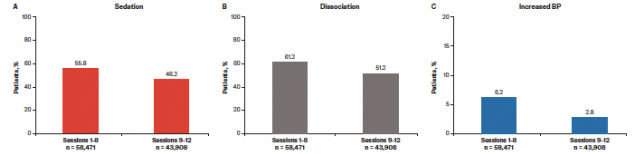
- Rates of TEAEs of sedation, dissociation, and increased BP showed a consistent trend over the course of treatment (**Figure 1**)
- Cumulative rates of solicited ESK TEAEs of interest in sessions 1-8 and sessions 9-12 were 55.8% and 46.2% for sedation, 61.2% and 51.2% for dissociation, and 6.2% and 2.8% for increased BP, respectively. Rates of TEAEs of interest generally decreased from induction to early maintenance (**Figure 2**)

**FIGURE 1: Incidence of solicited[a] reports of ESK TEAEs of interest over each of the first 12 treatment sessions: (A) sedation and dissociation and (B) increased BP**




BP, blood pressure; ESK, esketamine nasal spray; TEAE, treatment-emergent adverse event.
[a]On the patient monitoring form, TEAE was marked "yes."
[b]Number of patients beginning outpatient treatment at each treatment session (for sessions 1-12).

**FIGURE 2: Cumulative incidence of solicited[a] ESK TEAEs of interest by treatment phase: (A) sedation, (B) dissociation, and (C) increased BP**




BP, blood pressure; ESK, esketamine nasal spray; TEAE, treatment-emergent adverse events.
For sessions 1-8, n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment sessions 1 and 8 (these data are inclusive of the first treatment session).
For sessions 9-12, n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment sessions 9 and 12 (inclusive).
[a]On the patient monitoring form, TEAE was marked "yes."

- Rates of sedation, dissociation, and increased BP decreased from the induction phase to the early maintenance phase across all dose levels (**Table 4**)

**TABLE 4: TEAEs of interest by dose level and treatment session**

| | Sessions 1-8 | | Sessions 9-12 | |
|---|---|---|---|---|
| | Last session dose[a] | | Last session dose[a] | |
| n (%) | 56 mg n = 11,477 | 84 mg n = 46,397 | 56 mg n = 4073 | 84 mg n = 39,505 |
| Sedation[b] | 5864 (51.1) | 26,385 (56.9) | 1768 (43.4) | 18,336 (46.4) |
| Dissociation[c] | 6207 (54.1) | 29,153 (62.8) | 1732 (42.5) | 20,543 (52.0) |
| Increased BP[d] | 706 (6.2) | 2886 (6.2) | 126 (3.1) | 1095 (2.8) |

BP, blood pressure; TEAE, treatment-emergent adverse event.
Patients in the full analysis set had ≥1 treatment session.
[a]Last session with any dose.
[b]On the patient monitoring form, sedation was marked "yes."
[c]On the patient monitoring form, dissociation was marked "yes."
[d]A BP increase at 40 min or at the time of discharge was defined as post-administration BP increased ≥20 mm Hg to a value ≥180 mm Hg for systolic pressure or ≥15 mm Hg to a value ≥105 mm Hg for diastolic pressure compared with values prior to administration. If pre-administration blood pressure was missing, systolic values ≥180 mm Hg or diastolic values ≥105 mm Hg at 40 min after administration were also considered an increase.

### SAEs of sedation, dissociation, and increased BP

- At first treatment session, sessions 1-8, and sessions 9-12, SAE reports of sedation, dissociation, and increased BP were present in ≤0.1% of patients treated (**Table 5**)
- During the first 12 treatment sessions, the most common SAEs were dissociation, dizziness, hypertension, increased BP, nausea, and vomiting (each 0.1%) (**Table 6**)
- Using International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice criteria, SAEs resulting in hospitalization, death, a life-threatening event, or an important medical event occurred in ≤0.4% of patients across all studied treatment phases (**Table 7**)
- Respiratory depression was identified as a new event of interest; additional data collection from patient monitoring forms and analyses from the REMS program are planned

**TABLE 5: Summary of AEs of interest associated with reports of SAEs**

| | Treatment Session | | |
|---|---|---|---|
| n (%) | First session n = 58,483[a] | Sessions 1-8 n = 58,471[b] | Sessions 9-12 n = 43,908[b] |
| Patients with ≥1 SAE | 152 (0.3) | 485 (0.8) | 125 (0.3) |
| Sedation | 5 (<0.1) | 12 (<0.1) | 2 (<0.1) |
| Dissociation | 15 (<0.1) | 42 (0.1) | 5 (<0.1) |
| Increased BP[c] | 18 (<0.1) | 71 (0.1) | 14 (<0.1) |

BP, blood pressure; SAE, serious adverse event.
Patient SAEs were counted once per phase; therefore, it is possible that a patient had >1 SAE within each treatment phase.
[a]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[b]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (these data are inclusive of the first treatment session), or between treatment session 9 and 12 (inclusive), respectively.
[c]Includes blood pressure diastolic increase, BP increase, and BP systolic increase.

**TABLE 6: Summary of the most common REMS-PMF SAE descriptions (≥0.1% during the first 12 treatment sessions)**

| | Treatment session | | | |
|---|---|---|---|---|
| n (%) | First session n = 58,483[a] | Sessions 1-8 n = 58,471[b] | Sessions 9-12 n = 43,908[b] | Sessions 1-12 n = 58,474[c] |
| Dissociation | 15 (<0.1) | 42 (0.1) | 5 (<0.1) | 46 (0.1) |
| Dizziness | 19 (<0.1) | 45 (0.1) | 12 (<0.1) | 55 (0.1) |
| Hypertension | 15 (<0.1) | 37 (0.1) | 14 (<0.1) | 49 (0.1) |
| Increased BP[d] | 18 (<0.1) | 71 (0.1) | 14 (<0.1) | 82 (0.1) |
| Nausea | 26 (<0.1) | 68 (0.1) | 10 (<0.1) | 77 (0.1) |
| Vomiting | 29 (<0.1) | 69 (0.1) | 15 (<0.1) | 82 (0.1) |

ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals; BP, blood pressure; SAE, serious adverse event.
[a]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (these data are inclusive of the first treatment session).
[b]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[c]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 9 and 12 (inclusive).
[d]Of these patients, 9 had first sessions that occurred at ≥13 weeks; inpatient interactions were excluded.
[e]Includes BP diastolic increase, BP increase, and BP systolic increase.

**TABLE 7: SAEs by ICH-GCP criteria and treatment session**

| | Treatment session | | | |
|---|---|---|---|---|
| n (%) | First session n = 58,483[a] | Sessions 1-8 n = 58,471[b] | Sessions 9-12 n = 43,908[b] | |
| Hospitalization | 17 (<0.1) | 70 (0.1) | 30 (0.1) | |
| Disability or permanent damage | (0) | (0) | (0) | |
| Death | (0) | 1 (<0.1) | (0) | |
| Life threatening | 1 (<0.1) | 6 (<0.1) | 1 (<0.1) | |
| Important medical event[c] | 74 (0.1) | 237 (0.4) | 62 (0.1) | |

ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice.
[a]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[b]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (these data are inclusive of the first treatment session), or between treatment session 9 and 12 (inclusive), respectively.
[c]Any event that jeopardized the patient or required intervention to prevent an SAE. Some events reported under this category did not strictly meet the regulatory definition but were deemed serious at the time of assessment by the reporter's subjective judgment.

## Key takeaways

Actively solicited reports of sedation, dissociation, and increased blood pressure decreased over the course of ESK treatment and overall frequency of serious AEs was low

## Limitations

- The REMS Patient Monitoring Form only specifically solicited AEs of sedation, dissociation, and increased BP at each treatment session
- Repeated analyses at the patient level are needed to determine how predictably AEs change over the course of ESK treatment
- These data cannot be used to predict the likelihood of an AE occurrence for any individual patient
- AE severity is not captured on the REMS Patient Monitoring Form
- Based on other post-marketing sources, respiratory depression was identified as a new adverse reaction for ESK. Further analyses are currently underway to provide additional information regarding cases of respiratory depression

## Conclusions

- As anticipated, sedation and dissociation were commonly reported adverse events in the REMS program. Sedation, dissociation, and increased BP were more likely to occur during the first 8 treatment sessions compared with later sessions, and the likelihood of these events being associated with an SAE was rare
- Overall frequency of SAEs with esketamine nasal spray remains low and consistent with the safety profile described in the US prescribing information

### Acknowledgements

The authors thank Lynn Brown, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

### Disclosures

MH, GBL, and PQ are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company. IT, TD, and DK are employees of Janssen Research & Development, LLC. MH, IT, TD, BB, PQ, and DK hold stock in Johnson & Johnson. GS has served as a consultant for Allergan, Akarmes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Clasio, Denovo Biopharma, Engrail Therapeutics, Gilgamesh, Hoffman-La Roche, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Neuroo, Navitor Pharmaceuticals, Neurocrine, Novartis, Neven Pharmaceuticals, Otsuka, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Labs; has received research contracts from AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Johnson & Johnson, Hoffman-La Roche, Merck, Naurex, Servier, and Usona; holds equity in Biohaven Pharmaceuticals; and is a co-inventor on a US patent (#62/781,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (001154) filed on August 20, 2018, by the Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

Targeting Novel Pathways in Depression

Scan the QR code



Supported by Janssen Scientific Affairs, LLC, a Johnson & Johnson company

Presented at Psych Congress Elevate; May 30–June 2, 2024; Las Vegas, Nevada

References
1. SPRAVATO® (esketamine) nasal spray, CIII [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 10/2023.

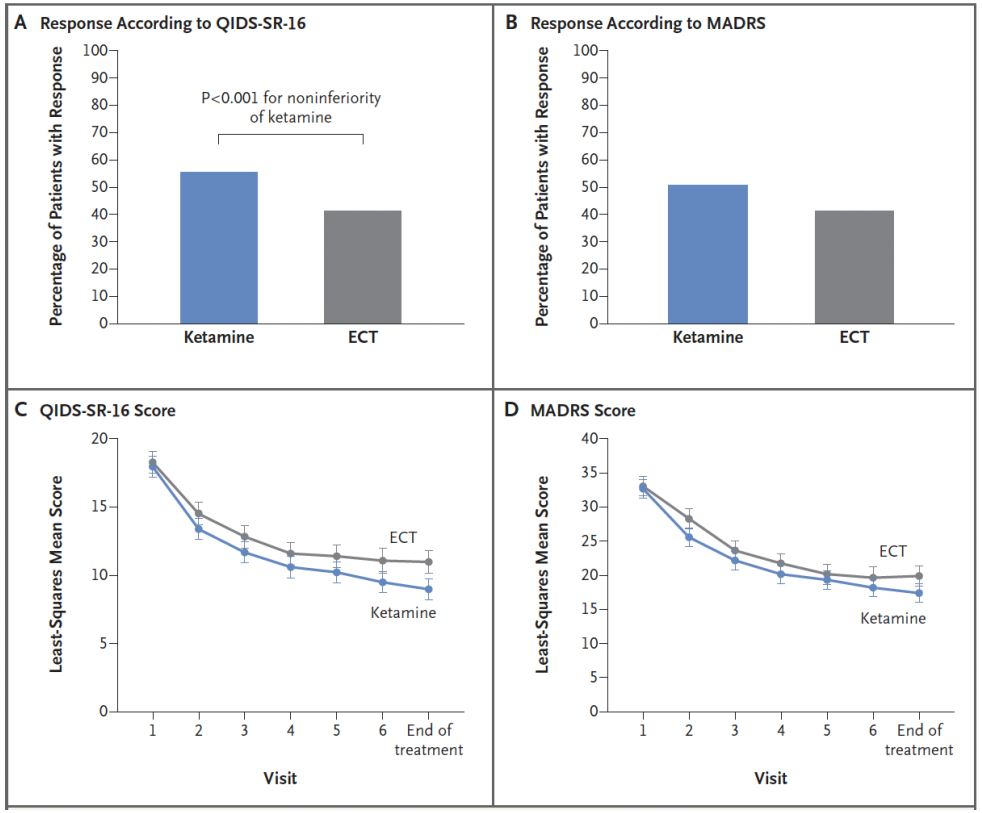
Data on > 58,000 patients and over 800,000 dose administrations

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 22, 2023 VOL. 388 NO. 25

# Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

A. Anand, S.J. Mathew, G. Sanacora, J.W. Murrough, F.S. Goes, M. Altinay, A.S. Aloysi, A.A. Asghar-Ali, B.S. Barnett, L.C. Chang, K.A. Collins, S. Costi, S. Iqbal, M.K. Jha, K. Krishnan, D.A. Malone, S. Nikayin, S.E. Nissen, R.B. Ostroff, I.M. Reti, S.T. Wilkinson, K. Wolski, and B. Hu




Ketamine provided at 0.5mg/kg/40mins 2X week for 3 weeks. ECT provided 3 X week for 3 Weeks.

Response:

Ket- 108/195 (55.4%)

ECT- 70/170 (41.2%)

Remission:

Ket- 63/195 (32.3%)

ECT- 34/170 (20.0%)

**Table 3. Moderate and Severe Adverse Events in the Modified Intention-to-Treat Population.***

| Adverse Event | Ketamine | ECT |
|---|---|---|
| | *no. of patients/total no. (%)* | |
| **Initial treatment phase** | | |
| ≥1 Adverse event | 49/195 (25.1) | 55/170 (32.4) |
| Gastrointestinal adverse event | 13/195 (6.7) | 9/170 (5.3) |
| Muscle pain or weakness | 1/195 (0.5) | 9/170 (5.3) |
| Headache | 16/195 (8.2) | 12/170 (7.1) |
| Severe or prolonged hypertension | 6/195 (3.1) | 4/170 (2.4) |
| Suicidal ideation | 4/195 (2.1) | 2/170 (1.2) |
| Suicide attempt | 0/195 | 0/170 |
| **Follow-up period** | | |
| ≥1 Adverse event | 17/108 (15.7) | 10/70 (14.3) |
| Severe or prolonged hypertension | 2/108 (1.9) | 0/70 |
| Suicidal ideation | 4/108 (3.7) | 1/70 (1.4) |
| Suicide attempt | 1/108 (0.9) | 0/70 |

* P>0.05 for all adverse events except muscle pain or weakness (P=0.01).

Median final KIT dose prior to exit: 0.85 mg/kg; range of dosing quantiles is 0.6 to 1.3 mg/kg

Alison McInnes presented at ASCP May 2024 in Miami FL

N Engl J Med 2023;388:2315-25.

nature mental health

Article

https://doi.org/10.1038/s44220-023-00140-x

# Randomized trial of ketamine masked by surgical anesthesia in patients with depression

Received: 31 May 2023

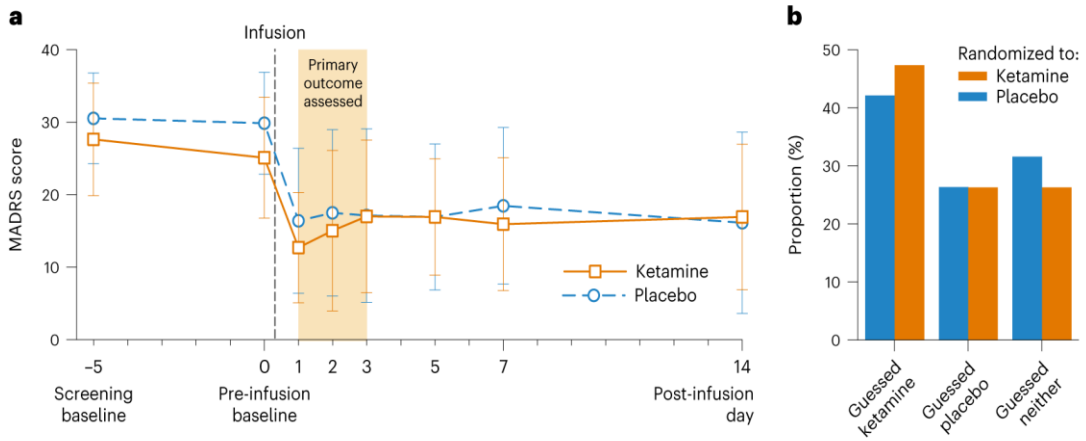
Accepted: 14 September 2023

Published online: 19 October 2023

Theresa R. Lii[1], Ashleigh E. Smith[1], Josephine R. Flohr[1], Robin L. Okada[1], Cynthia A. Nyongesa[1], Lisa J. Cianfichi[2], Laura M. Hack[3,4], Alan F. Schatzberg[3] & Boris D. Heifets[1,3]

*Remission occurred in 50% of the ketamine Group on post-infusion day 1 and 35% of participants in the placebo group.*

*By post-infusion day 3, 40% of both groups remained in remission.*




News & views

Neuropsychiatric disorders

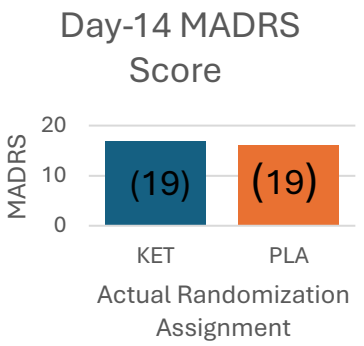
https://doi.org/10.1038/s44220-023-00141-w

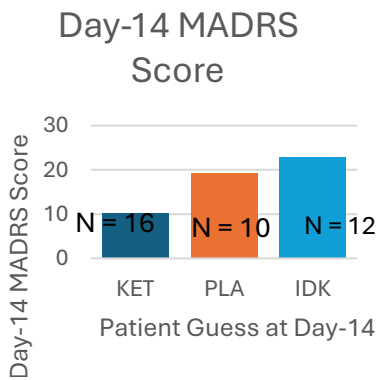
# Placebo's role in the rapid antidepressant effect

Gerard Sanacora & Luana Colloca

Check for updates

Numerous randomized placebo-controlled studies over the past two decades have shown that ketamine has a rapid antidepressant action. However, its acute transient effects on cognition and perception are likely to unmask study-arm assignment. Now, the use of surgical anesthesia to conceal treatment assignment finds high rates of rapid antidepressant response among participants, regardless of whether they are randomized to ketamine or placebo.




*Logistic regression suggested a significant inverse relationship between these two variables (odds ratio = 0.89 (95% CI 0.81 to 0.96); P = 0.001).*

VIEWPOINT

# The Rapidly Shifting Ketamine Landsca

**Samuel T. Wilkinson, MD**
Yale Depression Research Program, Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut; and Interventional Psychiatry Service, Yale–New Haven Hospital, New Haven, Connecticut.

**Joseph J. Palamar, PhD**
Department of Population Health, New York University Grossman School of Medicine, New York, New York.

**Gerard Sanacora, MD, PhD**
Yale Depression Research Program, Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut; and Interventional Psychiatry Service, Yale–New Haven Hospital, New Haven, Connecticut.

**Corresponding Author:** Samuel T. Wilkinson, MD, Yale Depression Research Program, Department of Psychiatry, Yale School of Medicine, 100 York St, Ste 2J, New Haven, CT 06511 (samuel.wilkinson@yale.edu).

**In recent years,** ketamine has been hailed as a miracle treatment for depression and related disorders. The US Food and Drug Administration (FDA) approved the S-enantiomer of ketamine, esketamine, as the first antidepressant in a new class for treatment-resistant depression in 2019.[1] Emerging evidence suggests that the landscape of ketamine both as a medical therapeutic and as a recreational substance is shifting. Herein, we highlight several key points that health care practitioners, policy makers, and patients and families should be aware of given this changing landscape.

## Tight Control for Esketamine But Not Ketamine

Ketamine was approved in 1970 as an anesthetic. Early research in the 1990s and 2000s demonstrated that subanesthetic doses of ketamine could lead to rapid and powerful antidepressant effects. Without any regulatory approval regarding treatment of psychiatric disorders, in the 2010s, a growing number of health care practitioners began offering subanesthetic doses of ketamine to patients with depression and other disorders, judging that existing evidence justified therapeutic use in some individuals.[2] Preliminary reports suggest that this practice of off-label ketamine use as a therapeutic in psychiatry has continued to grow in prevalence, largely without regulation.[3]

The protocol with the most evidence comprises 0.5 mg/kg of ketamine delivered intravenously over 40 minutes, which achieves plasma concentration levels of 70 to 200 ng/mL.[4] This is much lower than the plasma ketamine levels observed in patients awakening from ketamine anesthesia (500-1000 ng/mL) as well as the peak plasma levels used while patients are anesthetized (2000-3000 ng/mL).[4] Patients often experience perceptual disturbances and dissociative adverse effects during the infusion that subside approximately 30 to 60 minutes following the end of the infusion, which necessitates a period of posttreatment monitoring. While this is the most commonly used protocol, there is considerable variability among health care practitioners in the community with respect to the way ketamine is administered. A consensus statement from key stakeholders strongly advised that ketamine treatment be conducted in a medical facility (as opposed to in a home setting) to limit drug diversion and so that health care professionals can immediately respond to acute medical and behavioral changes.[4]

Following completion of registration trials, the FDA formally approved esketamine as a therapy for treatment-resistant depression in March 2019. Esketamine was approved with a strict treatment protocol enforced by a mandatory drug safety program (the Risk Evaluation and Mitigation Strategy). In contrast, physicians continue to have flexibility in how off-label ketamine is prescribed, for which no drug safety program

exists. It should
rigorous phase
of ketamine ar
tion (typically
ered to inform

The lack o
particularly rele
accompanied t
physicians to p
an in-person ex
ing ketamine lo
tients could ta
home administ
is explicitly fo
mented a healt
cal licenses in r
amine for at-h
patients; this cl
ment Administ
agency has reg

## Potential Con
## Widespread C

While some lea
approval of esk
imbursed by in
amine) would r
ketamine (whic
that clinics that
continue to exis
tempts to elicit
Medicare for ke
cessful. There
whether ketam
venously in clin
different (or s
esketamine. N
vantages to suc
including the ur
tential overus
doses (which c
and the potent

As ketamin
and with the ap
creased attenti
media and pop
reational ketar
other common
emerging evid
widely used as
may be associat
drug and adver
amount of ketar
medical setting
seems to be su





Journal of Affective Disorders 361 (2024) 198–208

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

# At-home, telehealth-supported ketamine treatment for depression: from longitudinal, machine learning and symptom network analy real-world data

David S. Mathai [a,b], Thomas D. Hull [c], Leonardo Vando [d], Matteo Malgaroli [e,*]

[a] The Johns Hopkins University School of Medicine, Center for Psychedelic and Consciousness Research, Department of Psychiatry and Behaviora MD, United States of America
[b] Sattva Medicine – Psychiatry/Psychotherapy Practice, Miami, FL, United States of America
[c] Institute for Psycholinguistics and Digital Health, United States of America
[d] Mindbloom, Orlando, FL, United States of America
[e] NYU Grossman School of Medicine, Department of Psychiatry, New York, NY, United States of America

ARTICLE INFO

*Keywords:*
Ketamine
Depression
Psychedelic
Network analysis
Machine learning
Telehealth

ABSTRACT

*Background:* Improving safe and effective access to ketamine therapy is of mental illness. Telehealth-supported administration of sublingual ket
*Methods:* In this longitudinal study, moderately-to-severely depressed p home over four weeks within a supportive digital health context. Treatr of therapeutic psychedelic trials. Patients receiving a second course of t were assessed using the Patient Health Questionnaire (PHQ-9) for machine learning and symptom network analyses to investigate outco
*Results:* A sample of 11,441 patients was analyzed, demonstrating a n non-severe ($n$ = 6384, 55.8 %) and severe ($n$ = 2070, 18.1 %) baselin detected in 3.0–4.8 % of participants and predominantly neurologic or treatment helped extend improvements in patients who responded fav was most strongly predicted by lower depression scores and age at bas Anhedonia sustained depression despite ongoing treatment.
*Limitations:* This study was limited by the absence of comparison or procedure for ketamine administration.
*Conclusions:* At-home, telehealth-supported ketamine administration w ciated with improvement in patients with depression. Strategies for c with rigorous telehealth models, as explored here, may uniquely addr

## 1. Introduction

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor-mediated dissociative drug, has received substantial attention in the last decade as a breakthrough mental health intervention (Sanacora et al., 2017). Though ketamine was approved for medical use by the United States Food and Drug Administration (FDA) as an anesthetic in 1970, its psychiatric value went largely unrecognized until 2000, when the first randomized controlled trial using a subanesthetic dose of ketamine for the treatment of depression indicated positive results (Berman et al., 2000). Numerous studies have sinc findings, providing evidence that depression and shows promise as of mental health disorders (Walsh

Despite interest in dissociative category of rapidly-acting mental 2023; Lepow et al., 2023; Nayak several issues have limited broader intervention. Most significantly, ke the FDA for use as an antidepre

* Corresponding author at: One Park Avenue, 8th Floor, New York, NY 10016, United States of America.
*E-mail address:* matteo.malgaroli@nyulangone.org (M. Malgaroli).

https://doi.org/10.1016/j.jad.2024.05.131
Received 22 January 2024; Received in revised form 30 April 2024; Accepted 25 May 2024
Available online 27 May 2024


nature medicine

Article

https://doi.org/10.1038/s41591-024-03063-x

# Extended-release ketamine tablets for treatment-resistant depression: a randomized placebo-controlled phase 2 trial

Received: 28 October 2023

Accepted: 8 May 2024

Published online: 24 June 2024

Check for updates

Paul Glue[1], Colleen Loo[2,3], Johnson Fam[4], Hsien-Yuan Lane[5,6], Allan H. Young[7], Peter Surman[8] & BEDROC study investigators*

Ketamine has rapid-onset antidepressant activity in patients with treatment-resistant major depression (TRD). The safety and tolerability of racemic ketamine may be improved if given orally, as an extended-release tablet (R-107), compared with other routes of administration. In this phase 2 multicenter clinical trial, male and female adult patients with TRD and Montgomery–Asberg Depression Rating Scale (MADRS) scores ≥20 received open-label R-107 tablets 120 mg per day for 5 days and were assessed on day 8 (enrichment phase). On day 8, responders (MADRS scores ≤12 and reduction ≥50%) were randomized on a 1:1:1:1:1 basis to receive double-blind R-107 doses of 30, 60, 120 or 180 mg, or placebo, twice weekly for a further 12 weeks. Nonresponders on day 8 exited the study. The primary endpoint was least square mean change in MADRS for each active treatment compared with placebo at 13 weeks, starting with the 180 mg dose, using a fixed sequence step-down closed test procedure. Between May 2019 and August 2021, 329 individuals were screened for eligibility, 231 entered the open-label enrichment phase (days 1–8) and 168 responders were randomized to double-blind treatment. The primary objective was met; the least square mean difference of MADRS score for the 180 mg tablet group and placebo was −6.1 (95% confidence interval 1.0 to 11.16, $P$ = 0.019) at 13 weeks. Relapse rates during double-blind treatment showed a dose response from 70.6% for placebo to 42.9% for 180 mg. Tolerability was excellent, with no changes in blood pressure, minimal reports of sedation and minimal dissociation. The most common adverse events were headache, dizziness and anxiety. During the randomized phase of the study, most patient dosing occurred at home. R-107 tablets were effective, safe and well tolerated in a patient population with TRD, enriched for initial response to R-107 tablets. ClinicalTrials.gov registration: ACTRN12618001042235.

[1]University of Otago, Dunedin, New Zealand. [2]Black Dog Institute & University of New South Wales, Sydney, New South Wales, Australia. [3]George Institute for Global Health, Sydney, New South Wales, Australia. [4]National University of Singapore, Singapore, Singapore. [5]China Medical University, Taichung, Taiwan. [6]China Medical University Hospital, Taichung, Taiwan. [7]Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK. [8]Douglas Pharmaceuticals, Auckland, New Zealand. *A list of authors and their affiliations appears at the end of the paper.
e-mail: Paul.glue@otago.ac.nz

# Where Do We Stand Today?

Considerations and challenges related to system-wide implementation of ketamine/esketamine for use beyond anesthesia

The American Journal of Psychiatry

# Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetal Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., Carlos Lopez Jaramillo, M.D., Ph.D., Siegfried Kasper, M.D., Kevin Kratiuk, B.Pharm., Jung Goo Lee, M.D., Ph.D., Yena Lee, H.B.Sc., Leanna M.W. Lui, Rodrigo B. Mansur, M.D., Ph.D., George I. Papakostas, M.D., Mehala Subramaniapillai, M.Sc., Michael Thase, M.D., Eduard Vieta, M.D., Ph.D., Allan H. Young, M.Phil., M.B.Ch.B., Carlos A. Zarate, Jr., M.D., Stephen Stahl, M.D., Ph.D.

**Published Online:**17 Mar 2021

**BOX 2. Esketamine and ketamine for treatment-resistant depression (TRD): Consensus**

- Evidence supports the rapid-onset (i.e., within 1–2 days) efficacy of esketamine and ketamine in TRD.
- Efficacy in TRD is best established for intranasal esketamine and intravenous ketamine; there is insufficient evidence for oral, subcutaneous, or intramuscular ketamine in TRD.
- Intranasal esketamine demonstrates efficacy, safety, and tolerability for up to 1 year in adults with TRD.
- Evidence for long-term efficacy, safety, and tolerability of intravenous ketamine in TRD is insufficient.
- Safety concerns with respect to ketamine and esketamine include, but are not limited to, psychiatric (e.g., dissociation, psychotomimetic), neurologic/cognitive, genitourinary, and hemodynamic effects.
- Esketamine is FDA approved for major depressive disorder with suicidal ideation or behavior but has not been proven to reduce suicide completion.
- Esketamine and ketamine should be administered only in settings with multidisciplinary personnel including, but not limited to, those with expertise in the assessment of mood disorders. A Risk Evaluation and Mitigation Strategy (REMS) is required in some countries administering esketamine (e.g., the United States).

# Collaborators

- **Yale PSYCHIATRY**
  - **Sam Wilkinson**
  - Sina Nikayin
  - Rachel Katz
  - Robert Ostroff
  - Sophie Holmes
  - **John Krystal**

**Janssen**

**Jaz Singh, Carla Canuso, Ella Daly, Ewa Wajs, Rachel Ochs, DJ Fu**

**PCORI ELKET-D A.Anand and Colleagues**
**PCORI EQIVALANCE study members**

**RAPID Study Group**
**MGH, Maurizio Fava, (RAPID Consortium)**

**APA, Council of Research Taskforce on Novel Biomarkers and Treatments**

**Joey Palamar**

**International Opinion Group, Roger McIntyre *et al***

**PCORI, NIMH, NARSAD, VA REAP, CT DMHAS, VA REAP,**

**Luana Colloca UMaryland**

**BOX 3. Esketamine and ketamine in TRD: Future research vistas**

- Comparative effectiveness data are needed (e.g., intravenous ketamine versus intranasal esketamine; esketamine or ketamine versus neurostimulation; esketamine or ketamine versus second-generation antipsychotics).
- A data commons and/or access to large public or private databases that provide the opportunity to assess serious but infrequent adverse events would provide a fuller understanding of the effectiveness and safety of esketamine and ketamine.
- Integrated measures (e.g., phenomenology, pharmacogenomics) should be used to identify ketamine response predictors as well as safety and tolerability predictors.
- Strategies to prolong the efficacy of esketamine and ketamine in adults with TRD are urgently needed (e.g., pharmacologic, manual-based psychosocial).
- More thorough characterization is needed of the long-term efficacy, safety, and tolerability of intravenous ketamine, as well as the possibility of withdrawal and/or tachyphylaxis/therapeutic tolerance.
- Characterization of the efficacy, tolerability, and safety of administration in less restrictive treatment environments (e.g., in physicians' offices or self-administration at home under certain conditions) is needed.
- Characterization of the relative efficacy, tolerability, and safety of oral, subcutaneous, and intramuscular formulations is needed.
- Further empirical study is needed on the risk for predisposing alcohol and other substance use disorders, as well as withdrawal-emergent suicidality, with esketamine and ketamine.
- Research is needed on the efficacy, safety, and tolerability of esketamine and ketamine in adults with non-treatment-resistant major depression as well as other mental disorders (e.g., major depressive disorder with psychosis, bipolar depression, posttraumatic stress disorder, substance use disorders).
- Integration of esketamine and ketamine with manual-based psychosocial treatments needs to be better characterized across mental disorders.
- The mechanism of action and tolerability of ketamine (e.g., role of opioidergic system), needs to be refined.
- The safety, tolerability, and efficacy of other ketamine derivatives (e.g., *R*-ketamine, *2R/6R*-hydroxynorketamine) remains to be characterized.
- Additional agents capable of rapid-onset antidepressant activity need to be identified.

# Scope of Ketamine Use Clinical Practice

**Steven P. Cohen, MD**
Northwestern University Feinberg School of Medicine
Uniformed Services University of Health Sciences

# Ketamine: ASRA, AAPM & ASA Guidelines for Chronic Pain

Steven P. Cohen

Edmund I. Eger Chair of Anesthesiology, Vice Chair of Research and Pain Medicine & Professor of Anesthesiology, Neurology, Physical Medicine & Rehabilitation, Psychiatry and Neurological Surgery, Northwestern University Feinberg School of Medicine

Director of Pain Research, Walter Reed National Military Medical Center

Professor of Anesthesiology and Physical Medicine & Rehabilitation

Uniformed Services University of the Health Sciences

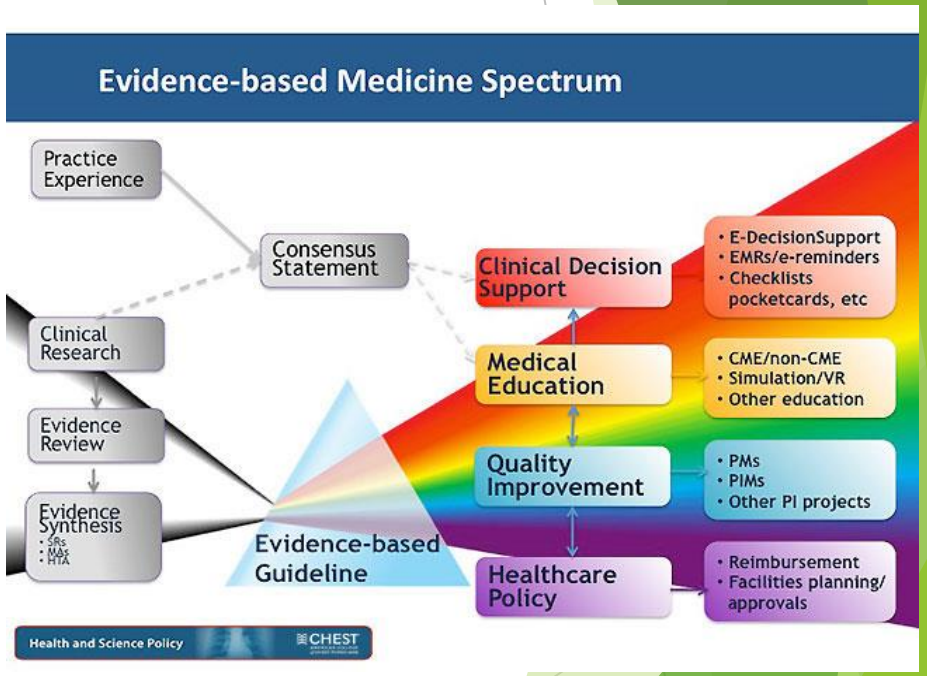
Colonel, U.S. Army (ret)

# Steven P. Cohen
# Financial Relationship Disclosure

- Consultant for Halyard, Scintilla, SPR, Boston Scientific & Abbott, Regeneron
- This presentation does discuss off-label usage

# Methods of Development

- Consensus guidelines approved in November 2016 by ASRA BoD, and developed into a joint effort between ASRA and AAPM
  - In early 2018, ASA signed on with minimal revisions
- 8 questions established for chronic pain section, and 5 for acute pain section, which were approved by the committee
  - Decision made on 1st conference call to separate the two and to have a comprehensive review on ketamine attached to the chronic pain section
- Pain questions separated into modules of 3 to 4 people who collaborated on answer with Committee Chair, which were then sent to the entire committee for approval or further revisions
- Used modified USPSTF guideline criteria
  - Used by numerous pain organizations



*Appendix Table 1.* **What the USPSTF Grades Mean and Suggestions for Practice**

| Grade | Definition | Suggestions for Practice |
|---|---|---|
| A | The USPSTF recommends the service. There is high certainty that the net benefit is substantial. | Offer/provide this service. |
| B | The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. | Offer/provide this service. |
| C | The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. | Offer/provide this service for selected patients depending on individual circumstances. |
| D | The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. | Discourage the use of this service. |
| I statement | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. | Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms. |

| **Initial quality of evidence** | **Study design** | **Lower if** | **Higher if** |
|---|---|---|---|
| **High** | **RCT, systematic review, meta-analysis** | Study limitations:<br>**1↓ Serious**<br>**2↓ Very serious**<br>Inconsistency:<br>**1↓ Serious**<br>**2↓ Very serious**<br>Indirectness:<br>**1↓Serious**<br>**2↓Very serious**<br>Impression:<br>**1↓Serious**<br>**2↓Very serious**<br>Publication bias<br>1 **likely**<br>**2↓Very likely** | Magnitude of effect:<br>**2↑ Very strong**<br>**1↑ Strong**<br><br>Dose-response gradient<br>**1↑**<br><br>All plausible confounders would have reduced the effect<br>**1↑** |
| **Moderate** | | | |
| **Low** | **Observational study (cohort study, case control study** | | |
| **Very low** | **Any other evidence (case series, case study)** | | |

Definition: Overall quality of evidence across studies for the outcome

level A :「High」 level B :「Moderate」 level C :「Low」 level D :「Very low」

# Acute & Chronic Pain Summary Guidelines

**TABLE 6.** Summary of ASRA/AAPM Recommendations for Subanesthetic Ketamine in Acute Pain

| Recommendation Category | Recommendation | Level of Evidence* |
|---|---|---|
| Indications for use | (1) Perioperative use in surgery with moderate to severe postoperative pain<br>(2) Perioperative use in patients with opioid tolerance<br>(3) As analgesic adjunct in opioid-tolerant patients with sickle cell crisis<br>(4) As analgesic adjunct in patients with OSA | (1) Grade B, moderate certainty<br>(2) Grade B, low certainty<br>(3) Grade C, low certainty<br>(4) Grade C, low certainty |
| Dosing range | Bolus: up to 0.35 mg/kg<br>Infusion: up to 1 mg/kg per hour | Grade C, moderate certainty |
| Relative contraindications | (1) Poorly controlled cardiovascular disease<br>(2) Pregnancy, psychosis<br>(3) Severe hepatic disease, ie, cirrhosis (avoid), moderate hepatic disease (caution)<br>(4) Elevated intracranial pressure, elevated intraocular pressure | (1) Grade C, moderate certainty<br>(2) Grade B, moderate<br>(3) Grade C, low certainty<br>(4) Grade C, low certainty |
| Personnel | Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician, emergency medicine physician) who is ACLS certified and trained in administering moderate sedation<br>Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation and is ACLS certified | Grade A, low certainty (see Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain from ASRA, AAPM, and ASA)[35] |

*Evidence was evaluated according to the USPSTF grading of evidence, which defined levels of evidence based on magnitude and certainty of benefit.[5]

**TABLE 6.** Summary of ASRA/AAPM/ASA Recommendations for Ketamine Infusions for Chronic Pain

| Recommendation Category | Recommendation | Level of Evidence* |
|---|---|---|
| Indications | (1) For spinal cord injury pain, there is weak evidence to support short-term improvement | (1) Grade C, low certainty |
| | (2) In CRPS, there is moderate evidence to support improvement for up to 12 wk | (2) Grade B, low to moderate certainty |
| | (3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement | (3) Grade D, low certainty |
| Dosing range and dose response | (1) Bolus: up to 0.35 mg/kg | (1) Grade C, low certainty |
| | (2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings | (2) Grade C, low certainty |
| | (3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h | (3) Grade C, low certainty |
| Relative contraindications | (1) Poorly controlled cardiovascular disease, pregnancy, active psychosis | (1) Grade B, low certainty |
| | (2) Severe hepatic disease (avoid), moderate hepatic disease (caution) | (2) Grade C, low certainty |
| | (3) Elevated intracranial pressure, elevated intraocular pressure | (3) Grade C, low certainty |
| | (4) Active substance abuse | (4) Grade C, low certainty |
| Role of oral NMDA receptor antagonist as follow-on treatment | (1) Oral ketamine or dextromethorphan, and intransal ketamine can be tried in lieu of serial infusions in responders | (1) Grade B, low certainty for oral preparations, moderate certainty for intranasal ketamine |
| Preinfusion tests | (1) No testing is necessary for healthy individuals | (1) Grade C, low certainty |
| | (2) In individuals with suspected or at high risk of cardiovascular disease, baseline ECG testing should be used to rule out poorly controlled ischemic heart disease. | (2) Grade C, low certainty |
| | (3) In individuals with baseline liver dysfunction or at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), and those who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis | (3) Grade C, low certainty |
| Positive response | (1) A positive response should include objective measures of benefit in addition to satisfaction such as ≥30% decrease in pain score or comparable validated measures for different conditions (eg, Oswestry Disability Index for back pain) | (1) Grade C , low-to-moderate certainty |
| Personnel and monitoring | (1) Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician) who is ACLS certified and trained in administering moderate sedation | (1) Grade A, low certainty |
| | (2) Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation | (2) Grade A, low certainty |
| | (3) Setting: at dosages exceeding 1 mg/kg per hour, a monitored setting containing resuscitative equipment and immediate access to rescue medications and personnel who can treat emergencies should be used, although this dose may vary based on individual characteristics | (3) Grade A, low certainty |

*Evidence was evaluated according to the US Preventive Services Task Force grading of evidence, which defined levels of evidence based on magnitude and certainty of benefit.[5]

ACLS indicates Advanced Cardiac Life Support; ICU, intensive care unit.

# Key Points, Differences, Explanations & Updates

| Question | Recommendations | Rationale |
|---|---|---|
| Who can give ketamine? | Physicians in charge of administration has DEA schedule 3 license (consistent with APA guidelines for depression treatment) but also be competent to administer moderate sedation (ACLS) b/c higher doses. The person who administers boluses can be an RN or physician with ACLS. For continuous infusions, a physician should be available to treat emergencies. | FDA classifies IV ketamine as indicated as an "anesthetic" agent for diagnostic and surgical procedures, ideally short-lasting; as an anesthetic induction agent; and to supplement low-potency agents such as $N_20$. First line of monograph asserts emergence reactions occur in 12% of people (may require trained personnel). |
| What are the best indications? | Chronic: CRPS (Grade B), SCI (Grade B for up to 2-wk benefit), (migraine) headache (Grade D; 2 of 5 studies in ED for migraine show benefit).<br>Acute: Pts undergoing painful surgeries; those with opioid tolerance or h/o OUD; severe acute pain including SSA; pts with sleep apnea. | Recommendations based on studies with different methodology; no conceptual basis for better response on CRPS & meta-analysis does not support superiority for any condition or pain category. Study from VA showed higher risk of relapse and overdose in pts with OUD in remission after surgery. |
| Contraindications | Poorly controlled cardiac dx or psychosis (Grade B), liver impairment & elevated IO and IC Pressure (Grade C). For chronic (not acute) pain, Grade C for active substance use disorder . | Weak evidence for elevated intraocular and ICP as contraindication; reports on cardiac cx infrequent. Difference for substance use disorder for acute vs. chronic pain based on stronger need for non-opioid analgesics for acute pain and higher doses needed for chronic pain. |
| Risk mitigation | No labs necessary for healthy individuals (c/w ASA recommendations for surgery). Baseline LFTs (and peri/post-infusion testing, and pre-testing EKG as needed. | Physician available who can address side effects (psychiatric, CV, GI, etc.). Short-acting BZD (midazolam) and/or alpha-2 agonist (clonidine) may prevent AEs. |
| Dosage | 0.35 mg/kg bolus, with up to 1 mg/kg/h for acute and up to 2 mg/kg/h for chronic pain. | The rationale for chronic pain (reverse central sensitization) may require higher doses, and dose-response relationship studied more for chronic pain. Effects may depend on total dose, peak blood levels and rate of rise to peak blood levels. |

# Is There Any Role For Oral ketamine Or Another NMDA Receptor Antagonist As A Follow-Up treatment In Lieu Of Repeat Infusions?

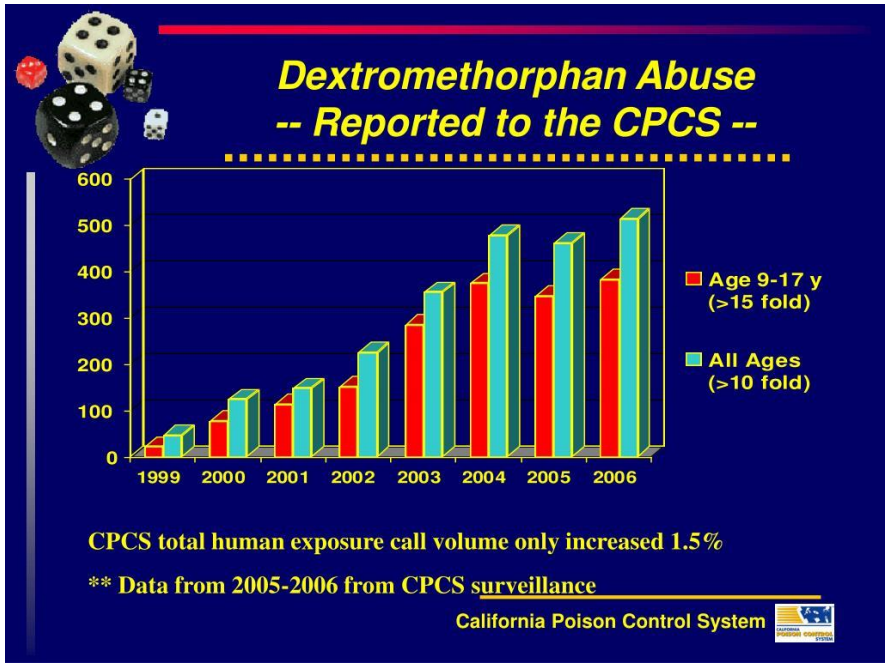
- Most placebo-controlled trials demonstrate no benefit from oral ketamine, though one showed an opioid-sparing effect
  - Oral ketamine has a bioavailability < 20% with wide variability
  - Contains abuse potential
- RCTs have demonstrated short but not long-term benefit from intranasal ketamine for acute & chronic pain, neuropathic pain and migraines
  - Bioavailability 40% with rapid on- and offset

- Cohen et al. (2004, 2006, 2009) found that IV ketamine predicts response to oral dextromethorphan for neuropathic pain, fibromyalgia and for opioid-tolerant people
  - Sensitivity 76%
  - Specificity 78%
  - PPV 67%
  - NPV 85%
  - Placebo response rate higher in ketamine responders (i.e. past (+) response predicts future (+) response

Jafarinia et al. 2016, Ishizuka et al. 2007, Lauretti et al. 1999, Haines et al. 1999; Carr et al. 2004; Huge et al. 2010; Afridi et al. 2013

# Use Of Non-Ketamine NMDA Receptor Antagonists Have Yielded Mixed Results for Neuropathic Pain

- Dextromethorphan, amantadine – conflicting results
- Memantine- negative
- Magnesium- positive, but few studies & small sample sizes
- Carbamazepine- positive





Collins et al. Pain Med 2010; Aiyer et al. Clin J Pain 2017

# Level of Evidence

- Considering the costs and resources involved, it is reasonable to provide a trial with follow-up oral or intranasal ketamine, or dextromethorphan, in lieu of serial treatments.
- Higher dose, repeat infusions should be provided to non-responders to other treatment regimens up to 8-12 per year.

- LOW LEVEL OF CERTAINTY FOR ORAL PREPARATIONS, MODERATE FOR INTRANASAL, GRADE B RECOMMENDATION

# Is There Any Evidence for a Dose-Response Curve or Therapeutic Cutoff

- All analgesic medications are associated with a therapeutic dose range
- For depression, a systematic review found that dosages above 0.5 mg/kg over 40 minutes were more effective than lower dosages
- Maher et al. found higher dosages and longer infusions were associated with longer durations of pain relief
- Noppers et al. found infusions < 2 h were likely to be ineffective
  - Infusions > 10 h were 95% likely to provide pain relief > 48 h, while those > 30 h were 99% likely
- In providing the rationale for anesthetic (> 7 mg/kg/h) doses of ketamine, Kiefer et al. found higher doses resulted in better relief
- Orhuru et al. Anesth Analg 2019: 2 of 3 RCTs that used > 400 mg cumulative dose reported benefit vs. 1 of 3 that used low-dose
- MD for high-dose −2.72 points; 95% CI, -3.18 to -2.27 points; P < 0.001 vs. MD for low-dose −1.20 points; 95% CI, −1.43 to -0.96 points; P <0.001
  - Likely cumulative dose, peak blood levels and rate of rise to peak blood levels that determine benefit
  - Weak correlation between psychomimetic & antidepressant effects\
  - Not all studies show dose response or correlation with blood levels (2 RCTs showed no correlation with serum levels)

Xu et al. 2016; Maher et al. 2017; Noppers et al. 2010 & 2011; Sigtermans et al. 2009; Schwartzman 2009; Amr 2010, Orhurhu et al. 2019; Kiefer et al. 2008

# Level of Evidence

- There is moderate evidence to support higher dosages of ketamine over longer time periods, and more frequent administration for chronic pain.
  - Higher doses also carry greater risks
- Similar to the strategy employed for opioids and other analgesic drugs with significant side effect profiles, it is reasonable to start dosing with a single, outpatient infusion lasting more than 2 hours, and reassess before initiating further treatments- similar to the strategy widely recommended for epidural steroid injections.

- LOW LEVEL OF CERTAINTY, GRADE C RECOMMENDATION

# What Constitutes a Positive Treatment Response?

- The threshold used to designate responders must consider risks and costs of treatment
- ≥30% decrease in pain considered "clinically meaningful"
  - ≥ 12.8% decrease in ODI clinically meaningful for back pain
  - Different than what is considered "statistically significant" in a placebo-controlled trial
- Should consider function, psychological and emotional well-being, sleep, medication use and satisfaction
- Among RCTs evaluating ketamine for chronic pain, 4 used ≥ 50% pain relief as the cutoff for a "responder"
  - 1 (-) study used ≥ 30% for cancer pain
- Studies evaluating patients for over 2 weeks did not designate a time frame for a "positive outcome"

Farrar et al. Pain 2001; Turk et al. Pain 2003; Noppers et al. Eur J Pain 2011; Kvarnstrom et al. Acta Anaesthesiol Scand 2003, 2004; Eichenberger et al. Anesth Analg 2008; Salas et al. J Palliat Med 2012

# Level of Evidence

- We consider > 30% decrease in pain, or a comparable improvement in function, coupled with patient satisfaction to be a positive outcome
- Single outpatient infusions should provide relief lasting > 3 weeks, while inpatient or serial outpatient infusions should provide relief lasting > 6weeks
  - Patient expectations and satisfaction should be considered
- Similar to guidelines for ESI, a “series” of infusions should not be administered by rote, 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
- **MODERATE LEVEL OF CERTAINTY, GRADE C RECOMMENDATION**

# Ketamine and Psychiatric Morbidity

- Co-prevalence rate of depression 30%-60%
- Ketamine makes people ‘feel good’
- Low-dose ketamine alleviates depression
  - IV ketamine, higher doses > Esketamine
  - Psychomimetic effects correlated with antidepressant effects in 37.5% of studies
- Evidence growing for PTSD & other psychiatric illnesses
- Growing rate of abuse
  - 2.3 million people in U.S. over 12 years old reported using ketamine
  - 3% of high school students
  - Increasingly implicated in MVCs
    - One study in Hong Kong found ketamine in 45% of subjects involved in non-fatal MVCs

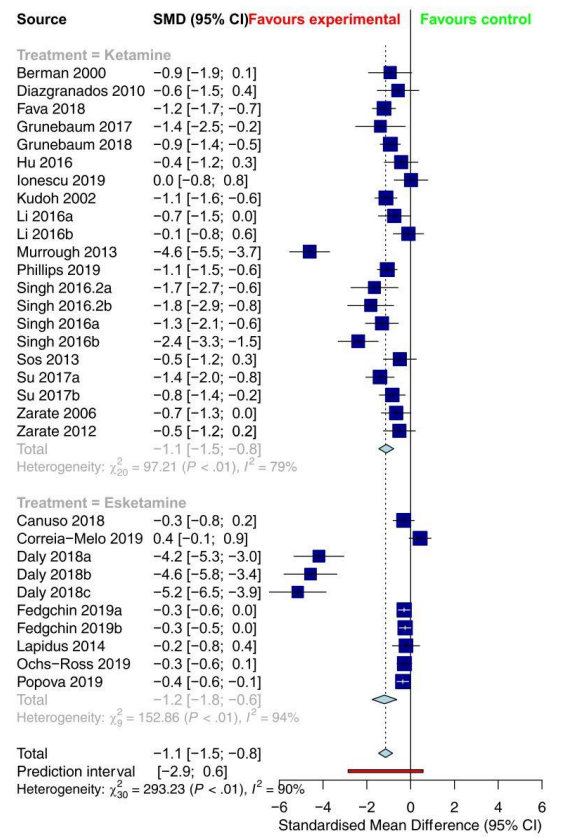
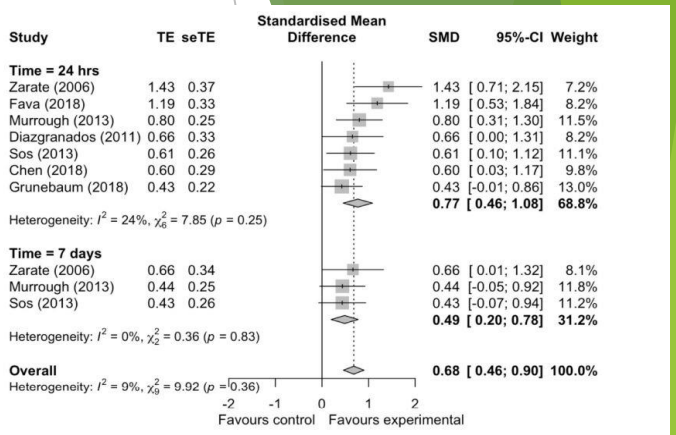
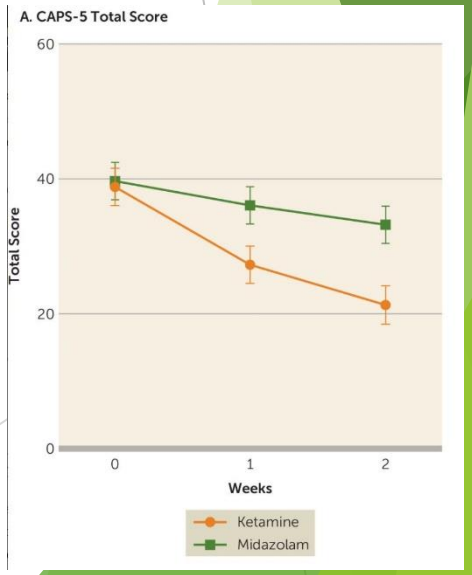



**Fig. 4.** Subgroup meta-analysis of depression rating scores in the treatment of depression with ketamine versus esketamine.

Bahji et al. 2021: IV Ketamine vs. s-Ketamine for Depression




Marcantoni et al. 2020: 0.5 mg/kg IV Ketamine vs. Placebo for Depression



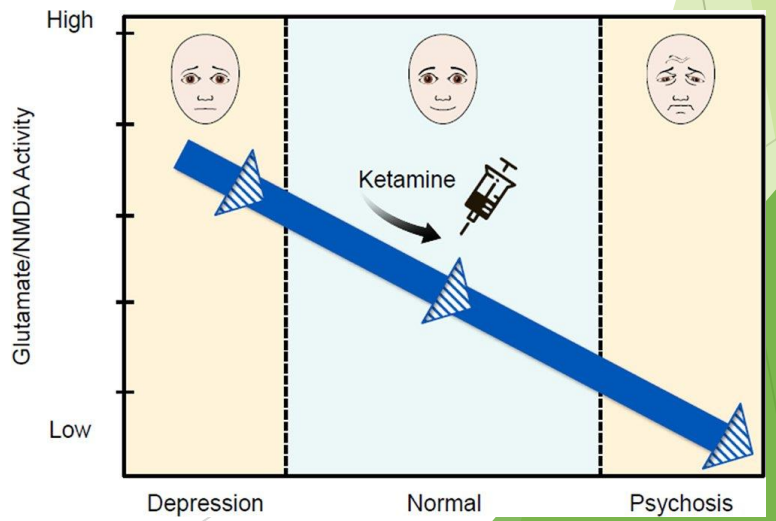

Feder et al. 2021: Repeat Ketamine vs. Versed for PTSD

2013 National Survey on Drug Use and Health in U.S.; Mathai et al. 2021; Wong et al. Hong Kong Med J

# Pain Dimensions: More Effective for Affective Component?

- Described in 1968 by Melzack & Casey
- Sensory-Discriminative- Based on nociceptive input, includes magnitude & location
  - Can be measured by QST
- Affective-Motivational- Evolutionary arousal & negative emotions (unpleasantness), from limbic & reticular structures
- Cognitive-Evaluative- Provides contextual info based on past experiences and likely outcomes (attitudes and beliefs), processed via higher CNS structures

- Large majority of studies have reported negative effects of ketamine on QST
- Schwartzman et al. RCT evaluating ketamine in 19 pts with CRPS: 31% reduction in S-D component vs. 46% in A-M component
- 2 studies reported better pain relief in obese pts, who have higher affective pain component

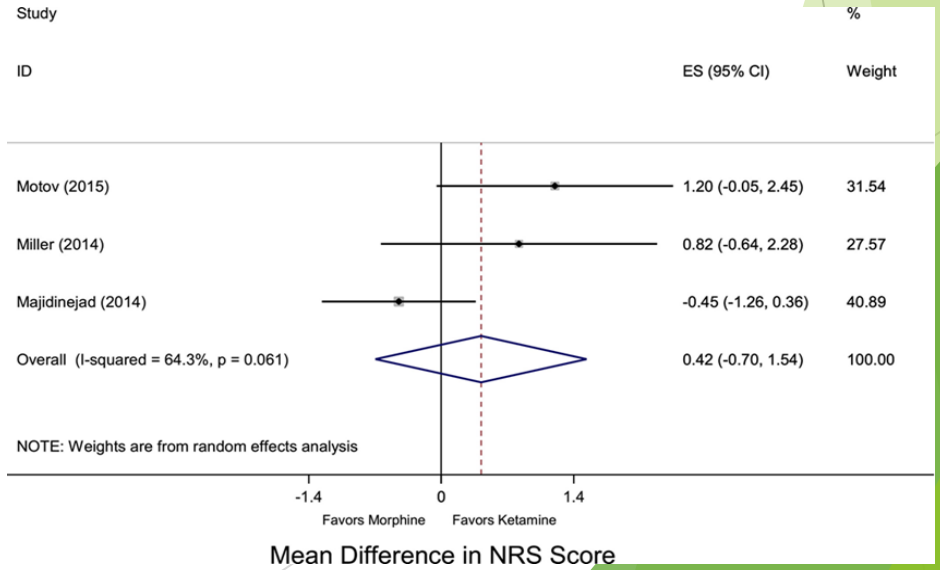



Eichenberger et al. A & A 2008, Schwartzman et al. Pain 2009; Noppers et al. EJP 2011; Cohen et al. Pain Med 2022

# Acute Pain Indications

- Moderate to severe postoperative pain, refractory to opioids or with limiting side effects
- Opioid tolerant patients
- Substance misuse disorder not a contraindication
  - Data suggest higher risk of relapse and overdose after surgery in pts with ho OUD
- Sickle cell anemia
- Patients with obstructive sleep apnea
- **Grade C evidence for ketamine PCA as sole analgesic for postoperative pain, Grade B for adjunct to opioids**

- Karlow et al. Ann Emerg Med 2018: Meta-analysis comparing low-dose (< 0.5 mg/kg) IV ketamine to opioids for acute pain in ED
- 3 studies, 251 patients
- Mean difference in pain scores 0.42 (95% CI = -0.70 to 1.54)
- Ketamine had more AEs (18 vs. 8) and requests for repeat dosing (4 vs. 0)



# Take Home Points

- The skyrocketing use of ketamine warrants the developed of consensus guidelines, which may improve patient care, inform regulatory guidelines, and enhance safety
- Considering the risks and resources involved in IV ketamine infusions, and their lack of long-term benefit, it is reasonable to trial an oral NMDA receptor antagonist, though the evidence supporting their effectiveness is mixed
- Indirect evidence, evidence-based reviews and extrapolation from clinical trials evaluating other analgesics support a dose-response relationship for subanesthetic dosages of ketamine for chronic pain
- Per IMMPACT guidelines, a positive treatment response must consider not only pain relief but also AE's, analgesic usage, patient expectations/ satisfaction, functional changes, sleep and psychological benefit
- Growing evidence for use in acute pain, even without opioids
- Compared to use for anesthesia (and even depression), research on ketamine for chronic pain is in its infancy, and should focus on indications, patient selection, long-term efficacy, and side effects

# Scope of Ketamine Use Clinical Practice

**Eric Hermes, MD**
Veterans Health Administration
Yale University School of Medicine

# Ketamine and Esketamine Delivery for Treatment Resistant Depression in the Veterans Health Administration

***Eric Hermes, M.D.***
*National Director, Psychopharmacology and Somatic Treatments*
*Office of Mental Health, Veterans Health Administration*
*27 June 2024*

VA | U.S. Department of Veterans Affairs

VA Connecticut Healthcare System, West Haven CT

810 Vermont Ave, Washington DC

# Ketamine & Esketamine ”National Protocol Guidance” for VA

**Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation**

**National Protocol Guidance**

**July 2022**

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, and Office of Mental Health Somatic Treatment Field Advisory Committee**

https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Ketamine_Infusion_for_Treatment_Resistant_Depression_Rev_Jul_2022.pdf

**Intranasal Esketamine for Depression**

**National Protocol Guidance**
**February 2022**

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, and Office of Mental Health and Suicide Prevention**

https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Intranasal_Esketamine_for_Depression_National_Protocol_Rev_FEB2022.pdf

Version 4.0 – 2022

# VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER

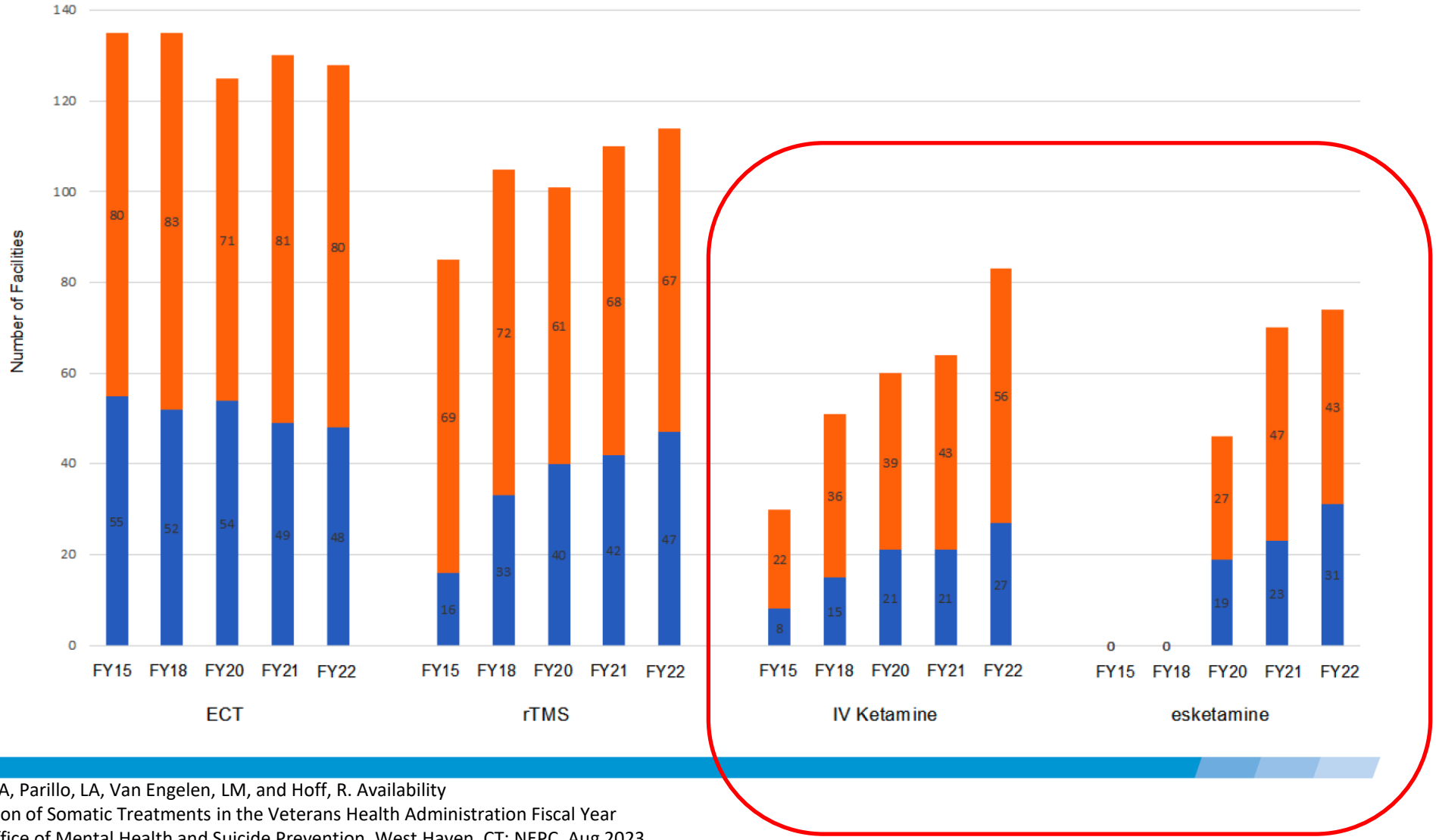
| | | | |
|---|---|---|---|
| 19. | For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation. | Weak for | Reviewed, New-replaced |

https://www.healthquality.va.gov/guidelines/MH/mdd/

# VA's Ketamine/Esketamine Dissemination Strategy

1. Community of Practice for "Somatic Treatments"
   - Email Group
   - Monthly Meeting
2. Ketamine/Esketamine Special Interest Group
3. National Training Program for ketamine/esketamine clinical teams
4. Information Hub
   - Policy, guidance, support documents
   - Data on Availability and Utilization
5. Technical Support for Implementation
6. Program Evaluation

# Ketamine and Esketamine Availability at VA Facilities



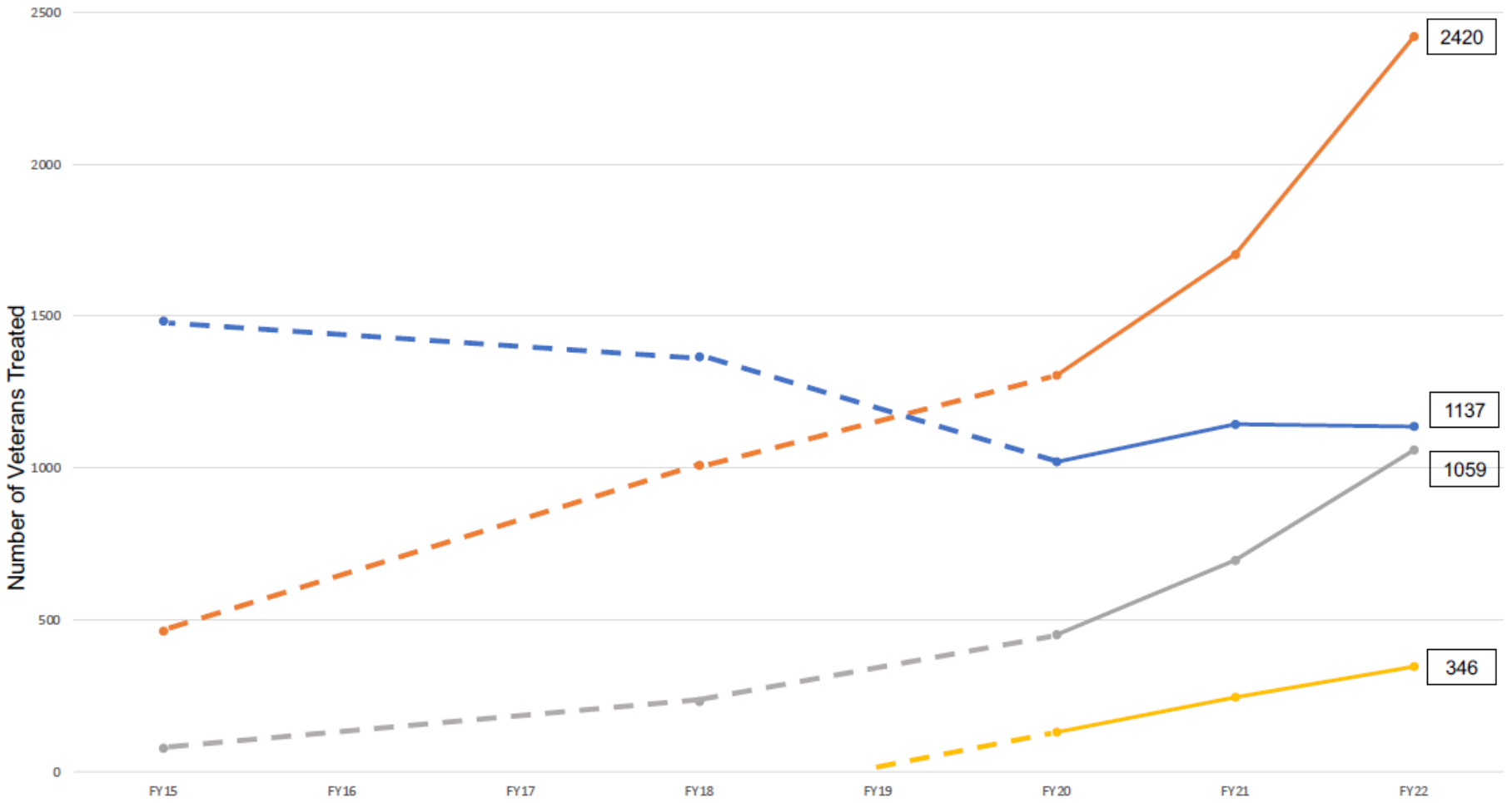

Available in a VA Facility

Available through Referral to the Community

Hermes, EDA, Parillo, LA, Van Engelen, LM, and Hoff, R. Availability and Utilization of Somatic Treatments in the Veterans Health Administration Fiscal Year 2022. VA Office of Mental Health and Suicide Prevention. West Haven, CT: NEPC. Aug 2023

VA | U.S. Department of Veterans Affairs

# Trends in ECT, rTMS, Ketamine, Esketamine Utilization Among Veterans




rTMS

ECT

Ketamine

esketamine

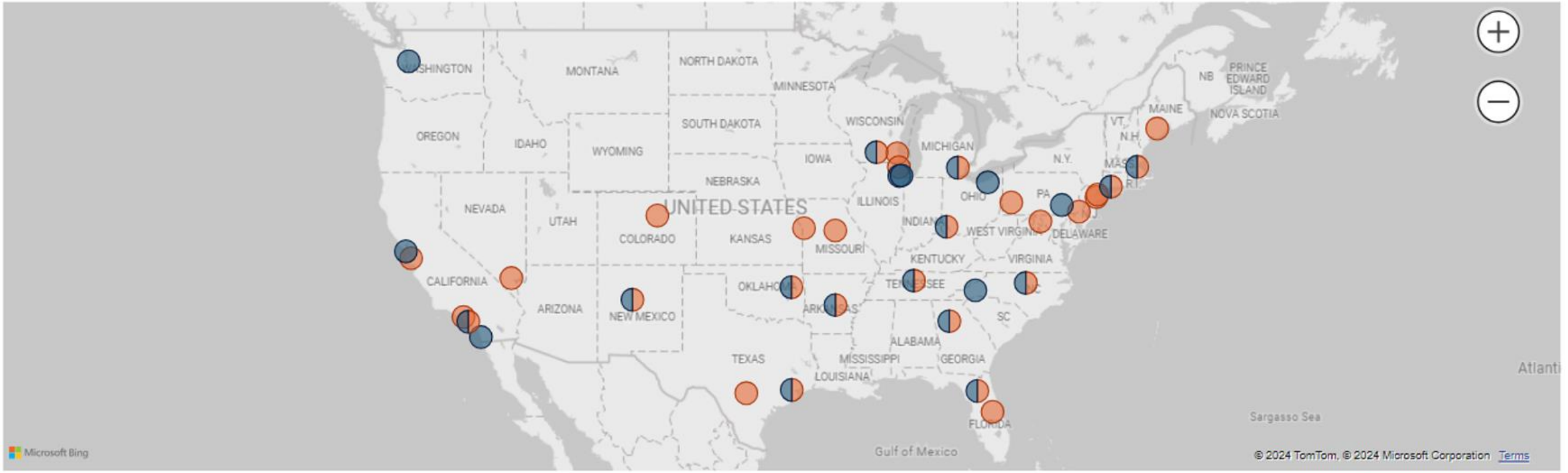
Hermes, EDA, Parillo, LA, Van Engelen, LM, and Hoff, R. Availability and Utilization of Somatic Treatments in the Veterans Health Administration Fiscal Year 2022. VA Office of Mental Health and Suicide Prevention. West Haven, CT: NEPC. Aug 2023

# Somatic Treatments Facility Utilization Dashboard

## *Ketamine and Esketamine Availability Map*

Introduction

**Treatment Type** ● Esketamine ● Ketamine




**Filter by Treatment Type**

- ☐ Esketamine
- ☐ Ketamine

| Esketamine Sites | Ketamine Sites |
|---|---|
| 30 | 22 |

# Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System

Paul N. Pfeiffer, MD; Jamarie Geller, MD; Dara Ganoczy, MPH; Jennifer Jagusch, MSW; John Carty, MD; Fe Erlita D. Festin, MD; William S. Gilmer, MD; Brian Martis, MD; Mohini Ranganathan, MD; Ilse R. Wiechers, MD; and Avinash Hosanagar, MD

*J Clin Psychiatry 2024;85(1):23m14984*

**Scan Now**

- See supplementary material for this article at Psychiatrist.com.
- Cite and share this article

- **Veterans who began treatment in 2020**
- **Population with Severe and Treatment Resistant Depression:**
  - Mean of 39 MH visits in the previous 6 months
  - 22% with inpatient stays
  - 13% prior rTMS
  - 18% prior ECT
- **Mean of 18 infusions** (about 3 months)
- **About 50% improved significantly**
- **26% reached response**

Table 1.

## Characteristics of Patients Treated With IV Ketamine for Depression (N = 215)

| Characteristic | n | % |
|---|---|---|
| **Age, y** | | |
| 18–25 | 1 | 0.5 |
| 26–45 | 93 | 43 |
| 46–65 | 89 | 41 |
| 66–75 | 27 | 13 |
| 76+ | 5 | 2 |
| **Gender** | | |
| Female | 38 | 18 |
| Male | 177 | 82 |
| **Race/ethnicity** | | |
| White | 178 | 83 |
| Black | 9 | 4 |
| Asian American, Pacific Islander | 4 | 2 |
| American Indian, Alaskan Native | 5 | 2 |
| Unknown/multiracial | 19 | 9 |
| Hispanic | 22 | 10 |
| **Comorbid diagnoses** | | |
| Posttraumatic stress disorder | 150 | 70 |
| Other anxiety disorder | 108 | 50 |
| Bipolar disorder | 37 | 17 |
| Major depressive disorder with psychotic features | 26 | 12 |
| Other psychotic disorder | 6 | 3 |
| Attention-deficit/hyperactivity disorder | 13 | 6 |
| Alcohol use disorder | 58 | 27 |
| Other substance use disorder | 59 | 27 |
| Personality disorder | 25 | 12 |
| Pain | 169 | 79 |

Abbreviation: IV = intravenous.

# Findings For Ketamine and Esketamine Deployment in VA

**Overall: Increasing AVAILABILITY at VA facilities and UTILIZATION by Veterans**

- Especially good as these are complex interventions requiring significant resources, care coordination, and presentation to a facility

**Challenges for VA**

- Rich Facilities getting Richer: Expansion is lead by facilities which already offer one intervention adding additional interventions
- Persisting Under-Treatment of Treatment Resistant Depression (TRD): Despite increasing utilization less than 2% of Veterans who may have TRD were treated in FY22 with any somatic treatment

# Next steps For VA

1. **Improve the Standardization of Delivery and Data Capture for Ketamine/Esketamine**
   - Recently Transitioned from retrospective report to real-time data capture
   - Institute templated procedure across the system
2. **Explore the Underutilization of Care for Veterans with TRD**
   - Identify barriers to specialized TRD evaluation and care.
3. **Prepare for the Future: Psychedelic Assisted Psychotherapy**
   - Nine VA facilities “formally” integrate psychotherapy as part of ketamine or esketamine delivery

# Contact

**Eric Hermes, M.D.**
National Director, Psychopharmacology and Somatic Treatments
Office of Mental Health, Veterans Health Administration

eric.Hermes@va.gov

# Scope of Ketamine Use Clinical Practice

Discussion:

- **Steven P. Cohen, MD,** Northwestern University Feinberg School of Medicine, Uniformed Services University of Health Sciences
- **Eric Hermes, MD,** Veterans Health Administration, Yale University School of Medicine
- **Mikhail Kogan, MD**, George Washington University Center Integrative Medicine
- **Brittany O'Brian, PhD**, Baylor College of Medicine
- **Jessica Poole, NDAP, CRNA**, Pennsylvania Association of Nurse Anesthetists
- **Sandhya Prashad, MD**, American Society of Ketamine Physicians

# Break

**The meeting will resume at 11:10 am ET**

REAGAN-UDALL FOUNDATION FOR THE FDA

# Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products

**Joseph Palamar, PhD, MPH**
New York University Langone Health

# Recreational Ketamine Use, Misuse of Prescribed Ketamine, and Associated Adverse Effects

**Joseph J. Palamar, PhD, MPH**

NYU Langone Health, Department of Population Health

June 27th, 2024

# Conflicts

I have consulted for the Baltimore-Washington High Intensity Drug Trafficking Area (HIDTA) program (funded by the ONDCP)

I declare no other potential conflicts of interest

# Current Funding

National Institute on Drug Abuse:

- R01DA060207 (PI: Palamar)
- R01DA057289 (PI: Palamar)
- U01DA051126 (PI: Cottler)

NYU Langone Health

# The History of Recreational Ketamine Use

NYU Langone Health

# Early recreational use and ‘abuse’

- Might have occurred as early as 1967
- Some reports suggest that available as pills and powder on the ‘street’ in the 1970s
- Abuse first reported by the FDA in 1979
- By the mid-1980s, instances of addiction were reported
- Appeared in the nightclub scene in the early 1990s as an adulterant in ecstasy
- Soon after, it became sold on its own
- Widespread diversion (veterinary clinics)
- Between 1992 and 1999, the DEA received ~800 reports of sales and possession
- Scheduled by the DEA (Schedule III) in 1999

Siegel RK. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. *NIDA Res Monogr.* 1978(21):119-147.
Jansen K. Ketamine: Dreams and Realities. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies; 2000.
Ketamine abuse. *FDA Drug Bull.* 1979;9(4):24. Kamaya H, Krishna PR. Ketamine addiction. *Anesthesiology.* 1987;67(5):861-862.
Jansen KL. Non-medical use of ketamine. *BMJ.* 1993;306(6878):601-602.
Mion G. History of anaesthesia: The ketamine story - past, present and future. *Eur J Anaesthesiol.* 2017;34(9):571-575.

NYU Langone Health

# Law enforcement seizures

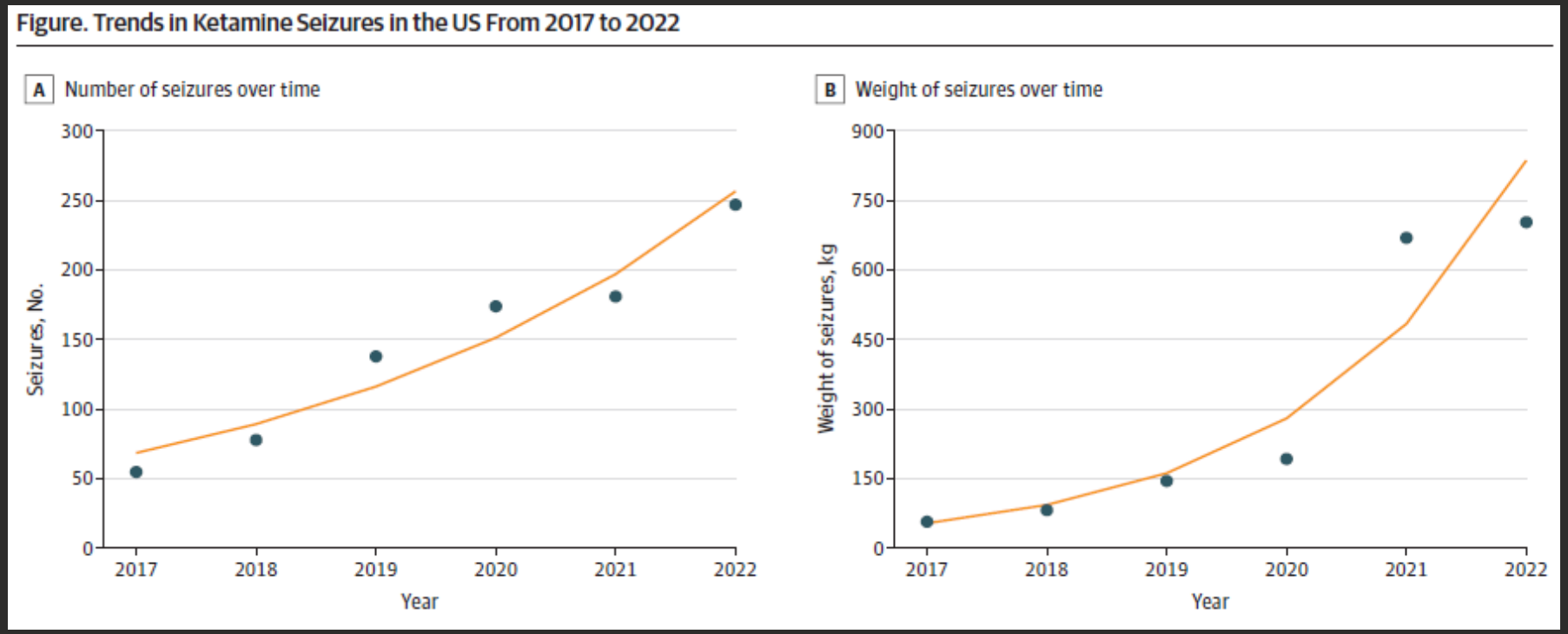
- Decades ago, most illicit ketamine was diverted from legitimate sources (e.g., veterinary clinics)
- Global production from clandestine laboratories in Southeast Asia (previously India)
- Most illicit product is now smuggled in through Mexico
- This version of ketamine is thus not pharmaceutical grade



National Drug Intelligence Center. Intelligence Bulletin: Ketamine. July 2004. Cloud J. Recreational Pharmaceuticals. *TIME* 2001.
Images: DEA. Ketamine. Erowid. Ttokkyo image. UNILAD. Hong Kong police seize record 13-ton haul of ketamine.

NYU Langone Health

# Ketamine law enforcement seizures in the US

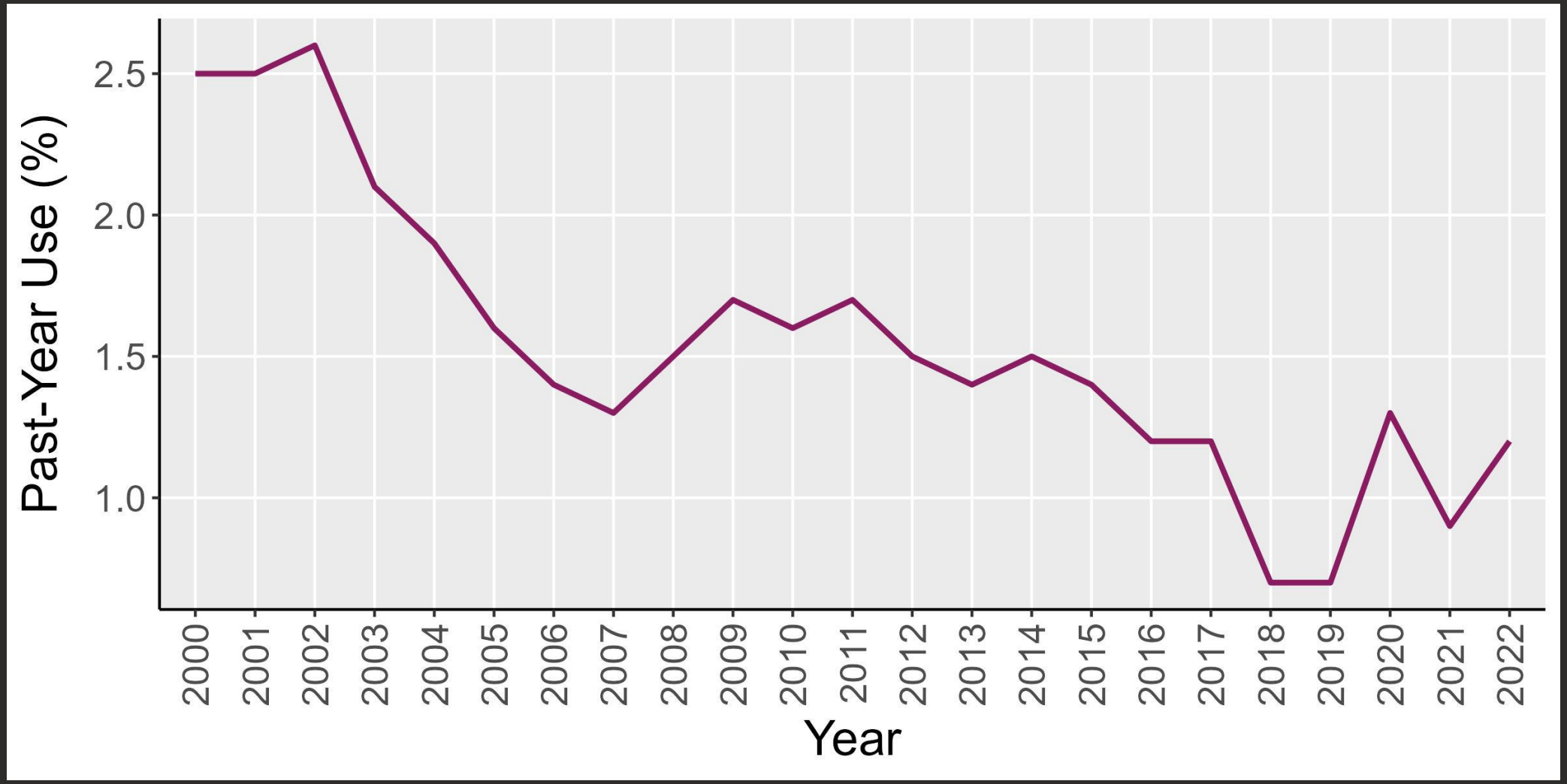



- The number of seizures increased 349% from 55 in 2017 to 247 in 2022
- 824 seizures in total weighing 4,084 lbs. (with one seizure weighing 1,591 lbs.)
- 99% in powder form
- Preliminary: in 2023, >350 seizures, >1,000 kg in powder

Palamar JJ, Wilkinson ST, Carr TH, Rutherford C, Cottler LB. Trends in Illicit Ketamine Seizures in the US From 2017 to 2022. JAMA Psychiatry. 2023;80(7):750-751.

NYU Langone Health

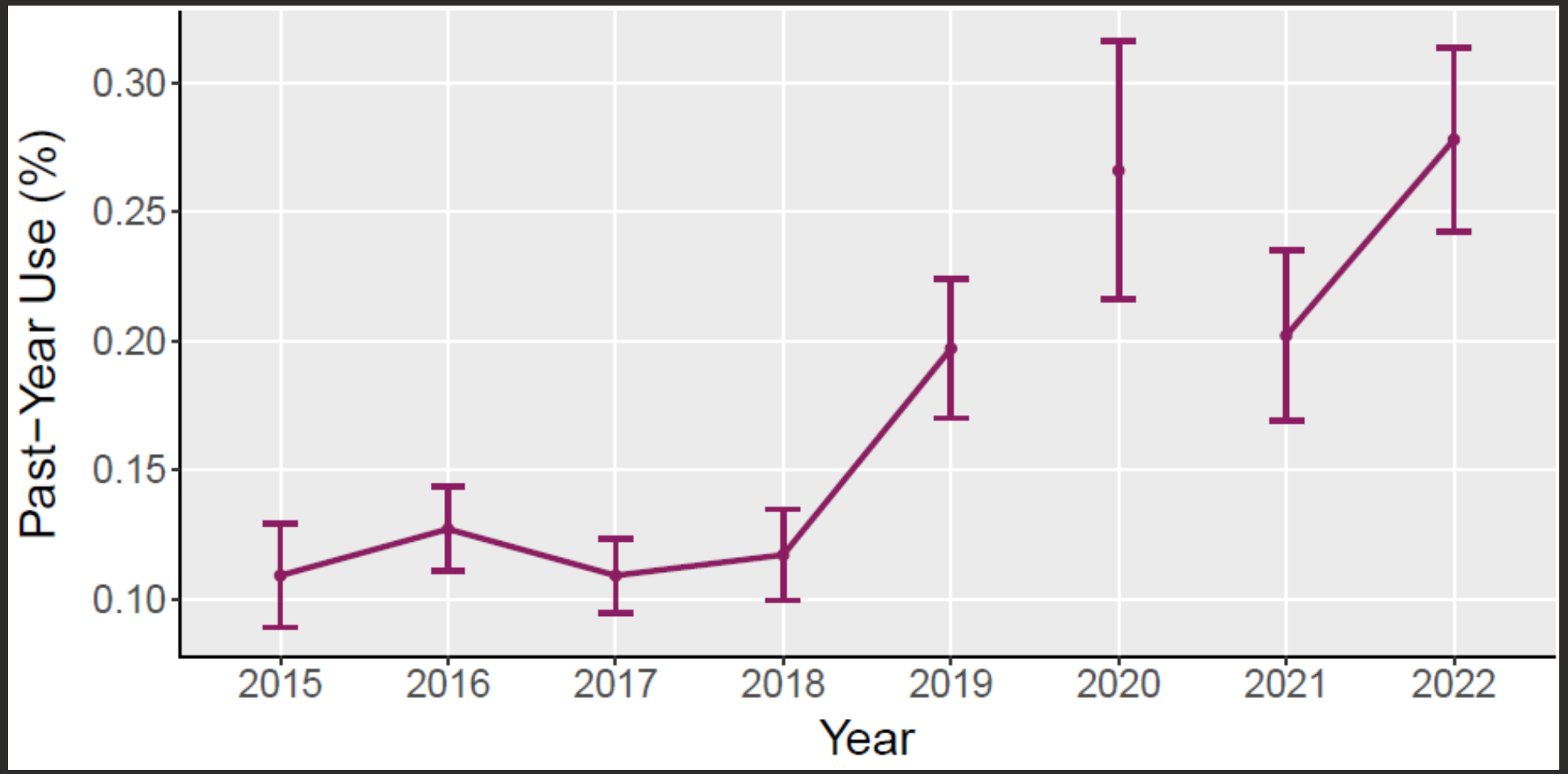
# Ketamine use among high school seniors in the US




Miech RA, Johnston LD, Patrick ME, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975–2022: Secondary school students. Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan. 2023.

NYU Langone Health

# Ketamine use among young adults (aged 18+) in the US



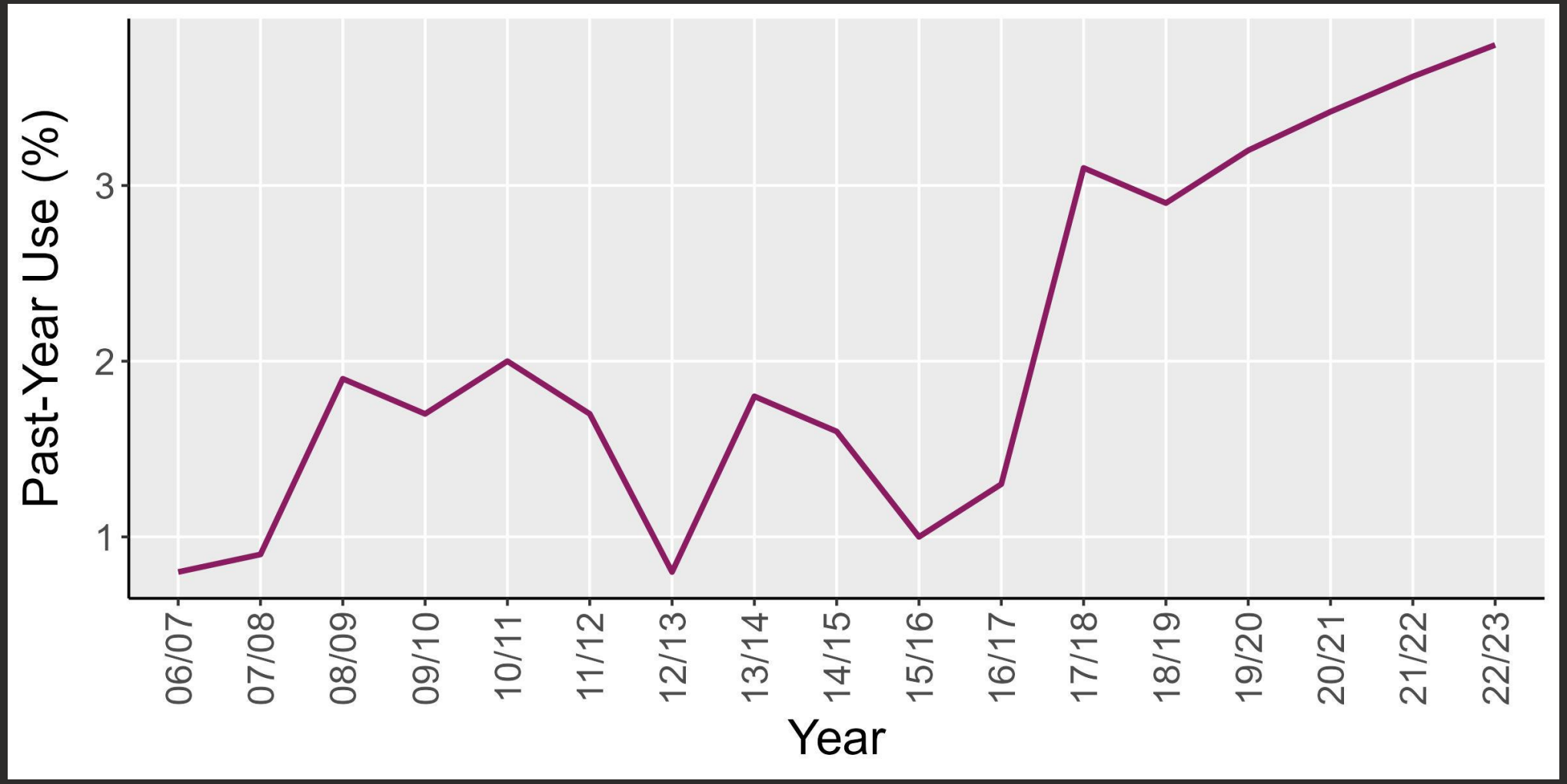

*Note:* Trend lines are plotted separately as trends are considered “broken” due to changes in the survey design

National Surveys on Drug Use and Health, 2015-2022

Palamar JJ, Rutherford C, Keyes KM. Trends in Ketamine Use, Exposures, and Seizures in the United States. Am J Public Health. 2021;111(11):2046-2049.

NYU Langone Health

# Ketamine use among young adults (aged 16-24) in the UK

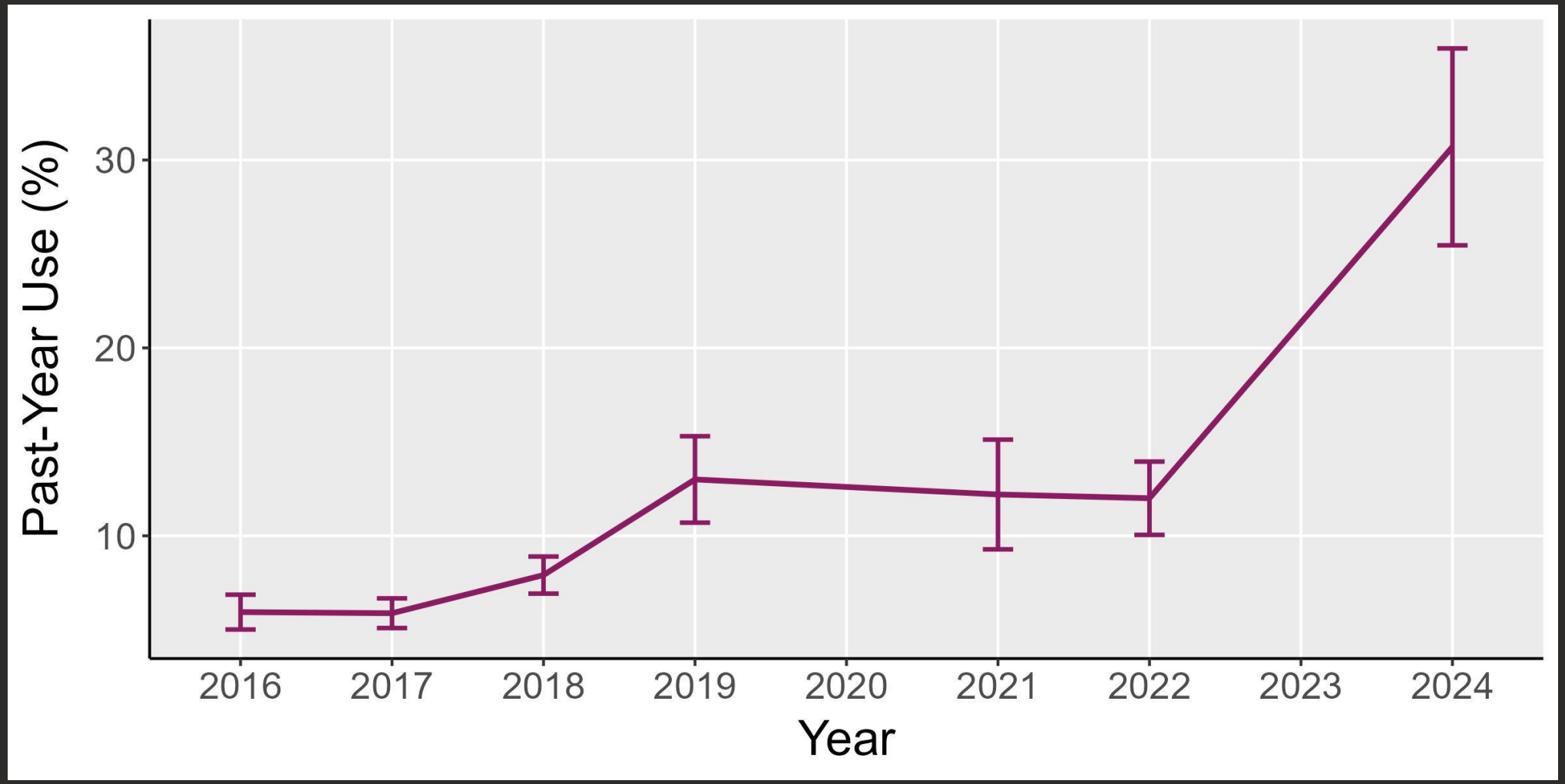



*Note:* Data were not collected during the COVID-19 pandemic

Crime Survey for England and Wales. Office for National Statistics. Drug misuse in England and Wales: year ending March 2023.

NYU Langone Health

# Ketamine use among NYC nightclub attendees

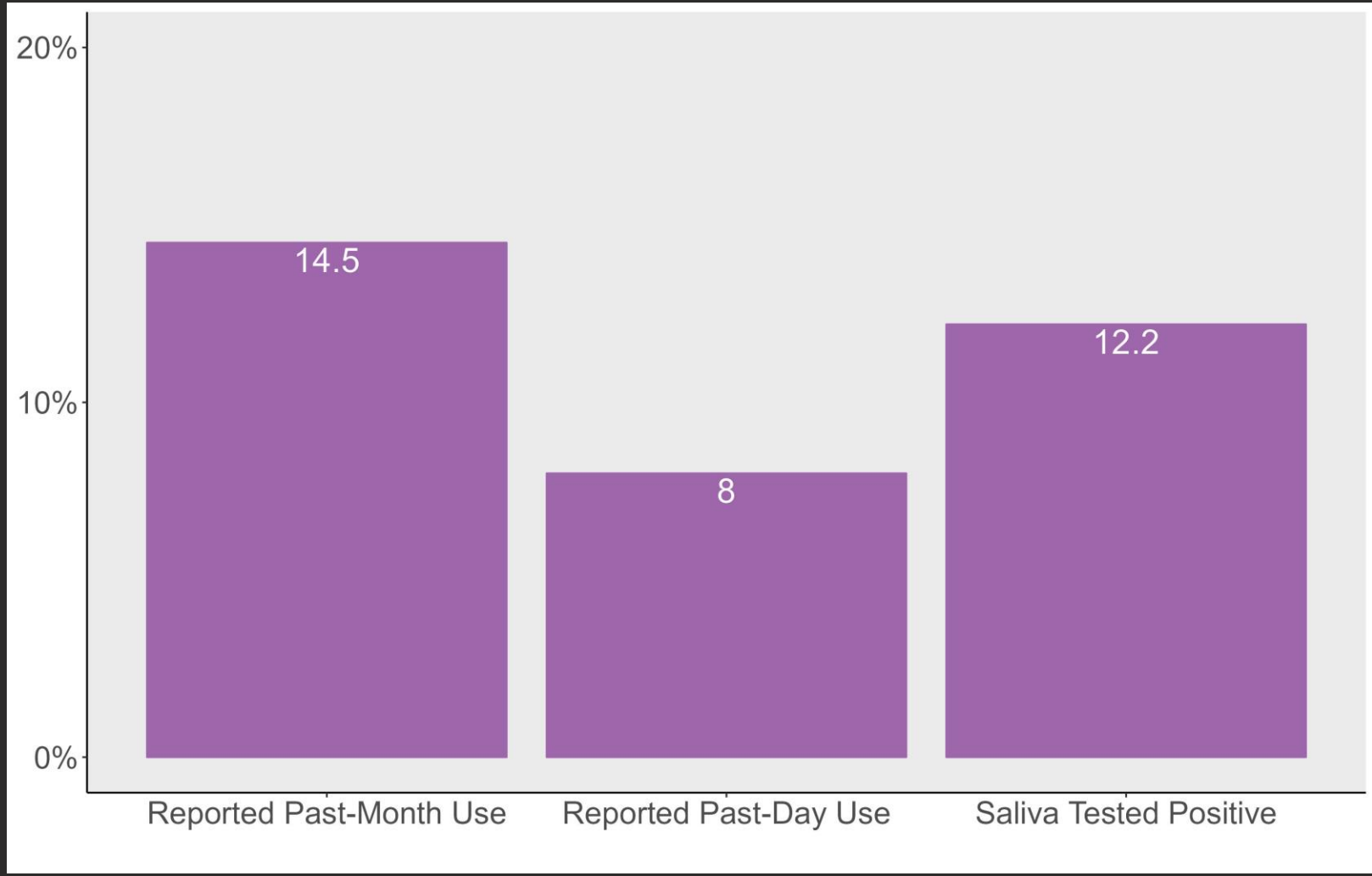



*Note:* 2024 represents Quarter 1 (January – March 2024)

Palamar JJ, Le A, Cleland CM, Keyes KM. Trends in drug use among nightclub and festival attendees in New York City, 2017-2022. Int J Drug Policy. 2023;115:104001.
Palamar JJ, Keyes KM. Trends in drug use among electronic dance music party attendees in New York City, 2016-2019. Drug Alcohol Depend. 2020;209:107889.

NYU Langone Health

# Ketamine use among NYC nightclub attendees




Data collected from 2024 Quarter 1 (n=200). Saliva testing conducted using liquid chromatography quadrupole time-of-flight mass spectrometry (LC–QTOF–MS).

NYU Langone Health

# Effects

NYU Langone Health

“It pretzels your thoughts into Mobius strips.”

“You see everything inside and out and curling all around itself…
There’s a lot of unfolding.”

James St. James, *Disco Bloodbath (Party Monster)*


NYU Langone Health

# General effects

- Numbness, passiveness, and perception that the world is not real
- Changed perception of body consistency or distortion of body parts
- Sensations of weightlessness or floating
- Absence or distortion of a sense of time or place
- Even small doses can lead to dissociation and hallucination
- Larger doses can lead to intense detachment from reality and perceived out-of-body experiences (“K-hole”)
- Effects can be seen as pleasurable or *horrific*
- Effects can thus impair judgment and impede functioning

Hansen G, Jensen SB, Chandresh L, Hilden T. The psychotropic effect of ketamine. *J Psychoactive Drugs.* 1988;20(4):419-425.
Jansen K. Ketamine: Dreams and Realities. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies; 2000.
Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993-2006). *J Clin Psychopharmacol.* 2008;28(1):114-116. Image: flowvella.com. Ketamine.

# Adverse effects

- A fifth (19%) of NYC nightclub attendees who used ketamine in the past year reported a “harmful or very unpleasant” effect after use in which they were concerned about their immediate safety
- In our more recent study, 13% had experienced such an effect after use in the past month
- Of these, 59% asked someone for help and 7% visited an emergency department (ED)
- Confusion and nausea/vomiting were the most common symptoms
- The last year of Drug Abuse Warning Network data in 2011 estimated 1,550 ketamine-related ED visits in the US (with 71.5% of cases involving alcohol co-use)
- We at NDEWS are receiving reports of deaths in Chicago and Florida (April 2024)

Palamar JJ, Acosta P, Le A, Cleland CM, Nelson LS. Adverse drug-related effects among electronic dance music party attendees. Int J Drug Policy. 2019;73:81-7. Palamar JJ, Le A. Prevalence of self-reported adverse effects associated with drug use among nightclub and festival attendees, 2019-2022. Drug Alcohol Depend Rep. 2023;7:100149. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: 2013. Chaves TV, Wilffert B, Sanchez ZM. Overdoses and deaths related to the use of ketamine and its analogues: A systematic review. Am J Drug Alcohol Abuse. 2023: 49(2):141-150.

NYU Langone Health

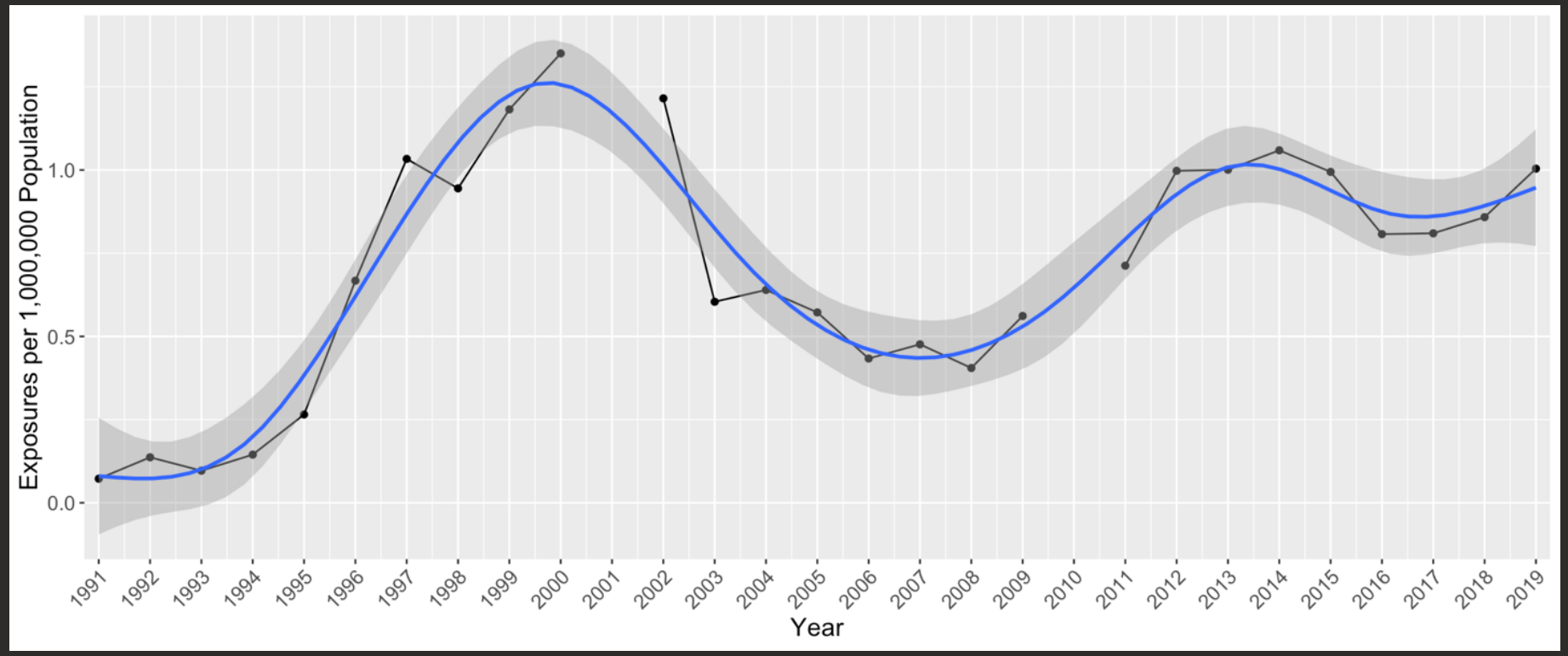
# Adverse effects

- In a study of ED presentations, the most common acute effects were impaired consciousness (45%), hypertension (40%), and tachycardia (39%)
- Acute risk of physical harm or death from accidents (e.g., drowning, car crashes)
- Vulnerable to physical and sexual assault
- Short- and long-term memory impairment
- Frequent ketamine use can lead to use disorder, driven by tolerance and craving
- Intense abdominal pain (“K-cramps”)
- Bladder issues such as ulcerative cystitis

Shbair MK, et al. Drugs involved in drug-facilitated crimes: Part I: alcohol, sedative-hypnotic drugs, gamma-hydroxybutyrate and ketamine. A review. Ann Pharm Fr. 2010;68(5):275-85. Fitzgerald ND, et al. Test-retest reliability and cross-cultural applicability of DSM-5 adopted diagnostic criteria for ketamine use disorders. Drug Alcohol Depend. 2021;228:109056. Morgan CJ, Curran HV. Ketamine use: a review. Addiction. 2012;107(1):27-38. Muetzelfeldt L, et al. Journey through the K-hole: Phenomenological aspects of ketamine use. Drug Alcohol Depend. 2008;95(3):219-29. Morgan CJ, et al. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. Addiction. 2010;105(1):121-33.

NYU Langone Health

# Ketamine-related poisonings in the US



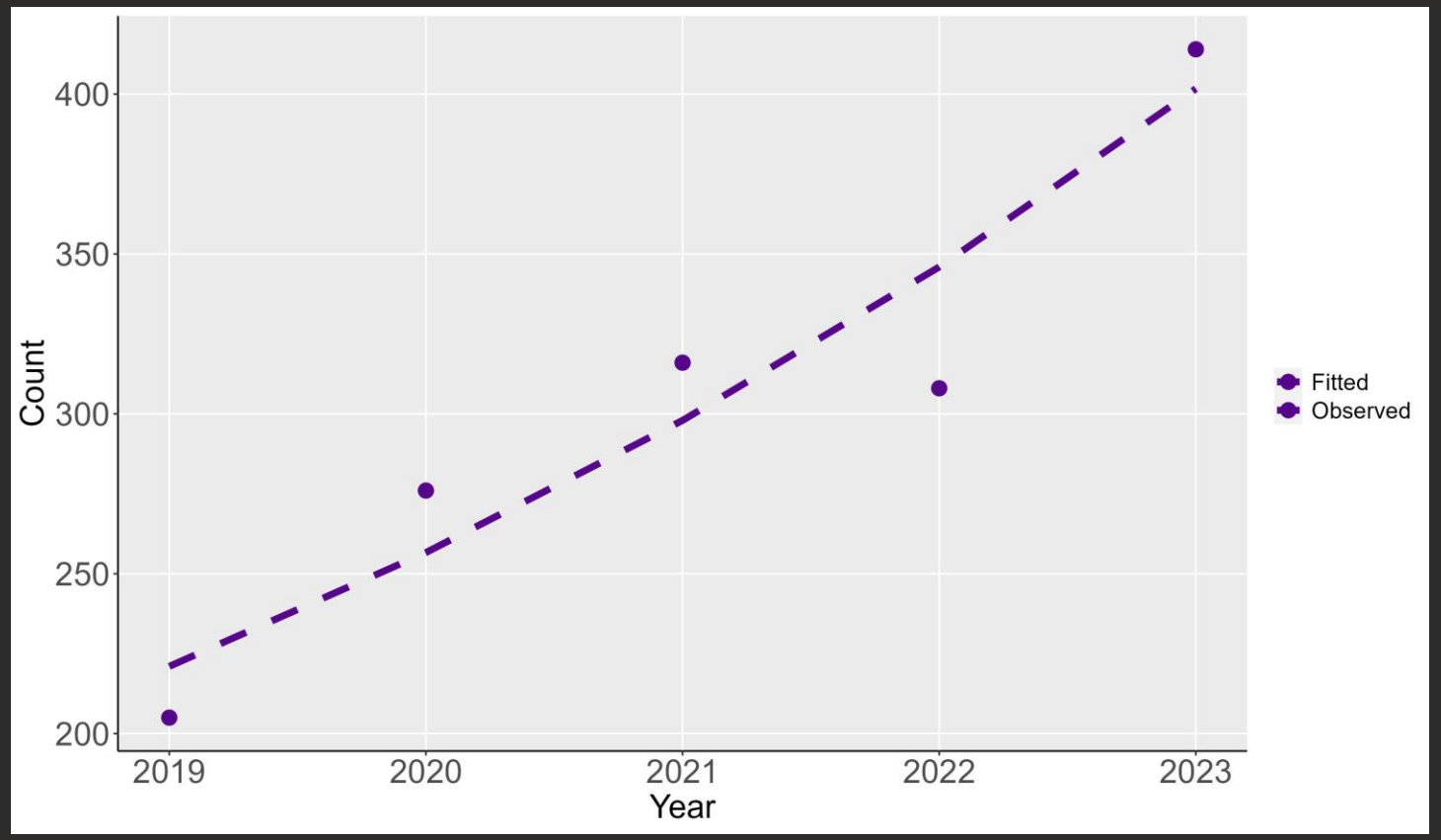

- 5% of cases reported to Poison Control in 2019-2021 were age ≤12 suggesting risk for childhood exposure

Palamar JJ, Rutherford C, Keyes KM. Trends in Ketamine Use, Exposures, and Seizures in the United States up to 2019. Am J Public Health. 2021;111(11):2046-2049.
Palamar JJ, Fitzgerald ND, Grundy DJ, Black JC, Jewell JS, Cottler LB. Characteristics of poisonings involving ketamine in the United States, 2019-2021. J Psychopharmacol. 2023;37(8):802-808.

NYU Langone Health

# Number of ketamine-related poisonings in the US

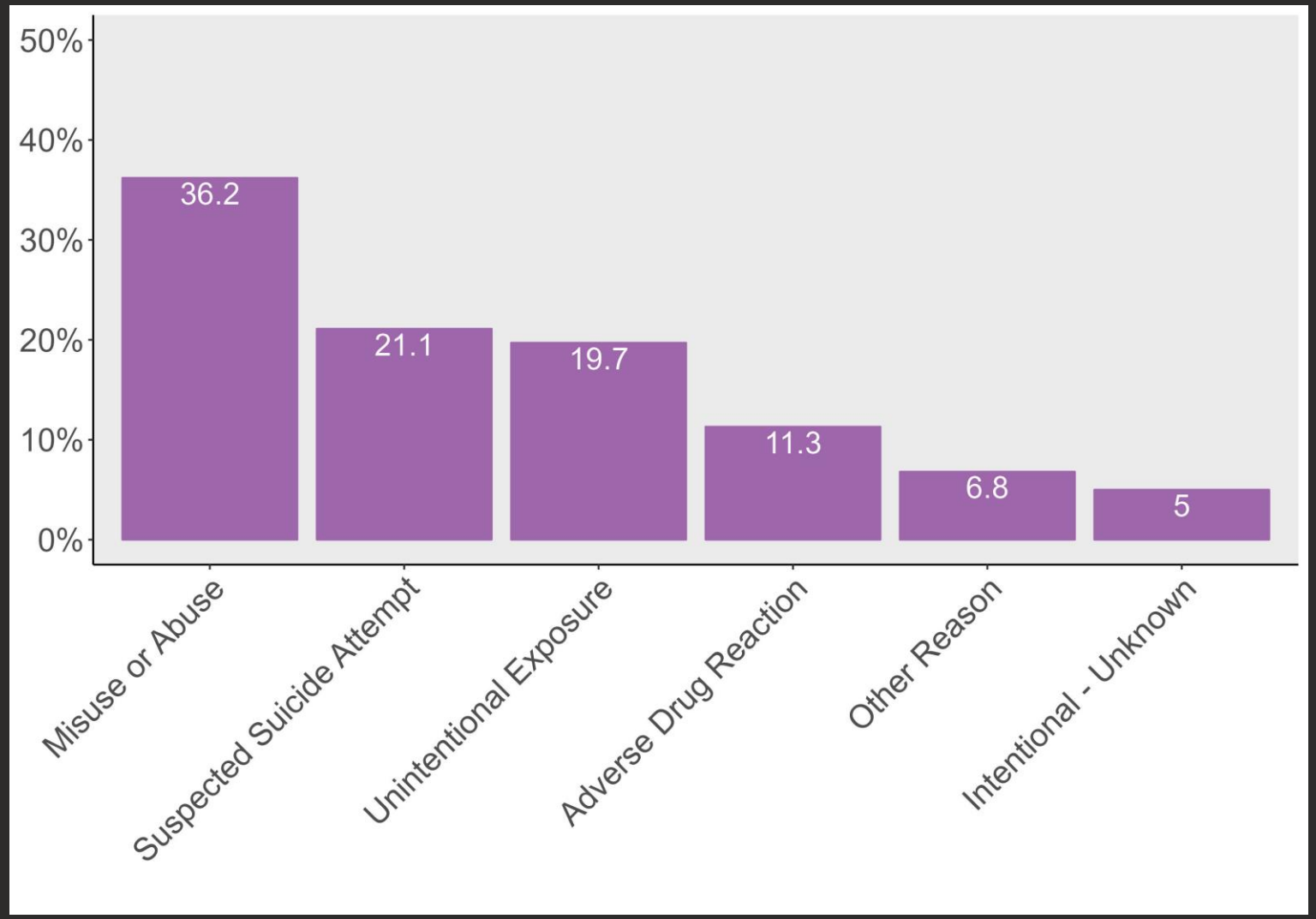
Preliminary analysis of data from 1,519 poisonings (“exposures”) reported to US poison centers, 2019-2023




Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Reasons for ketamine poisonings

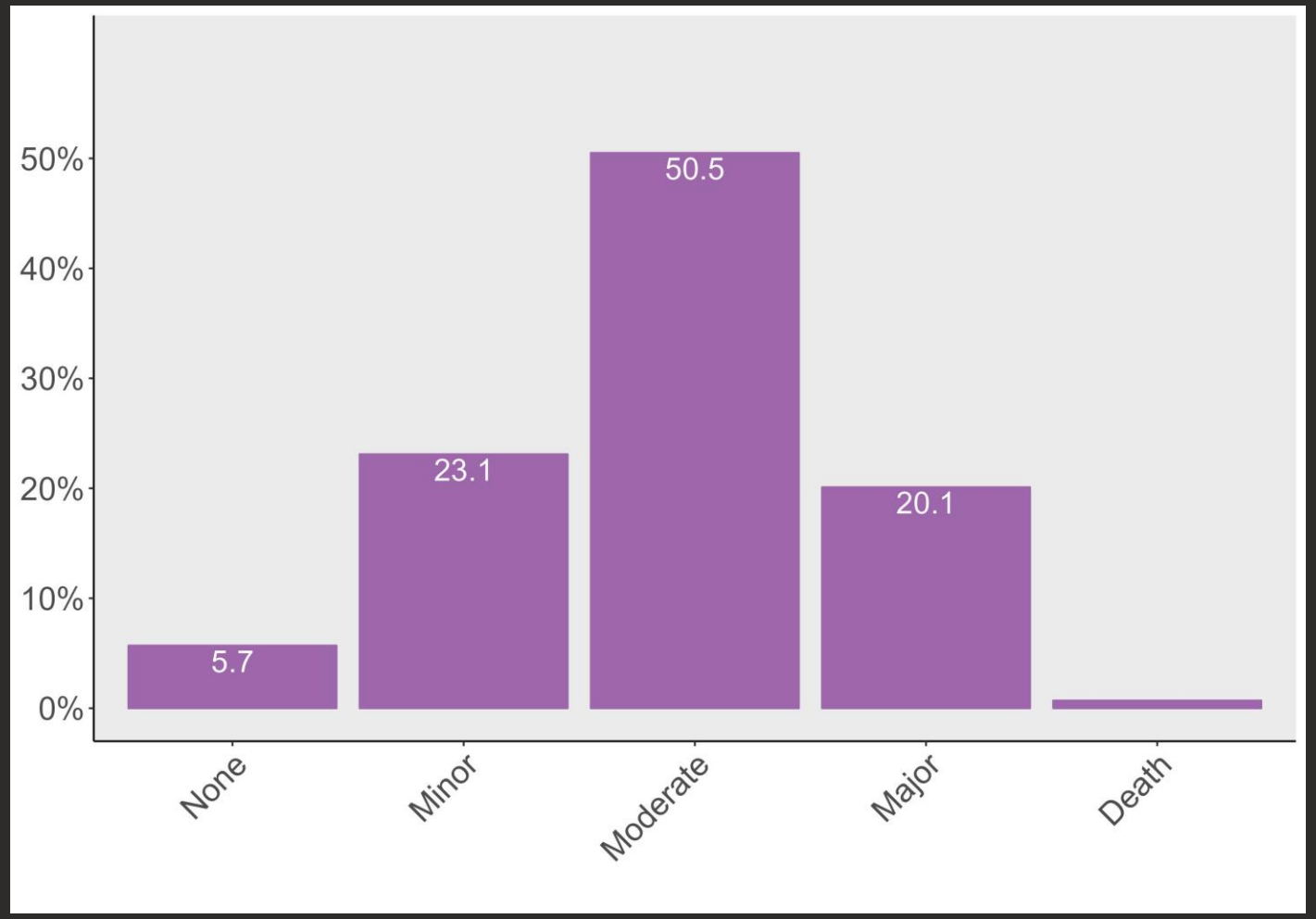



Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Severity of ketamine poisonings (misuse/abuse)

- **No effect:** no symptoms
- **Mild effect:** minimally bothersome
- **Moderate effect:** more pronounced or prolonged
- **Major effect:** life-threatening or permanently disabling
- **Death:** confirmed to have died in relation to use

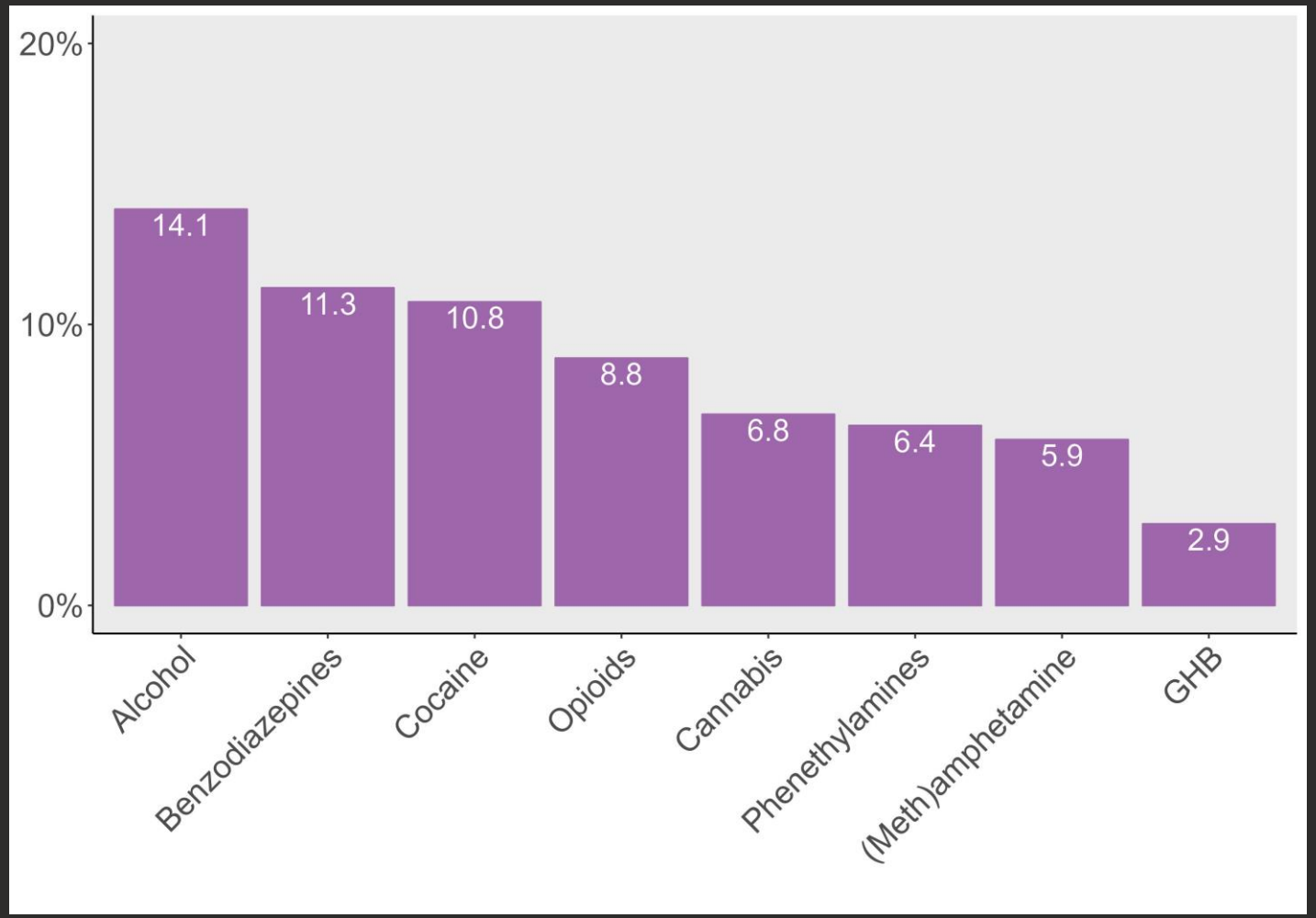



Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Co-drug use involved in ketamine poisonings

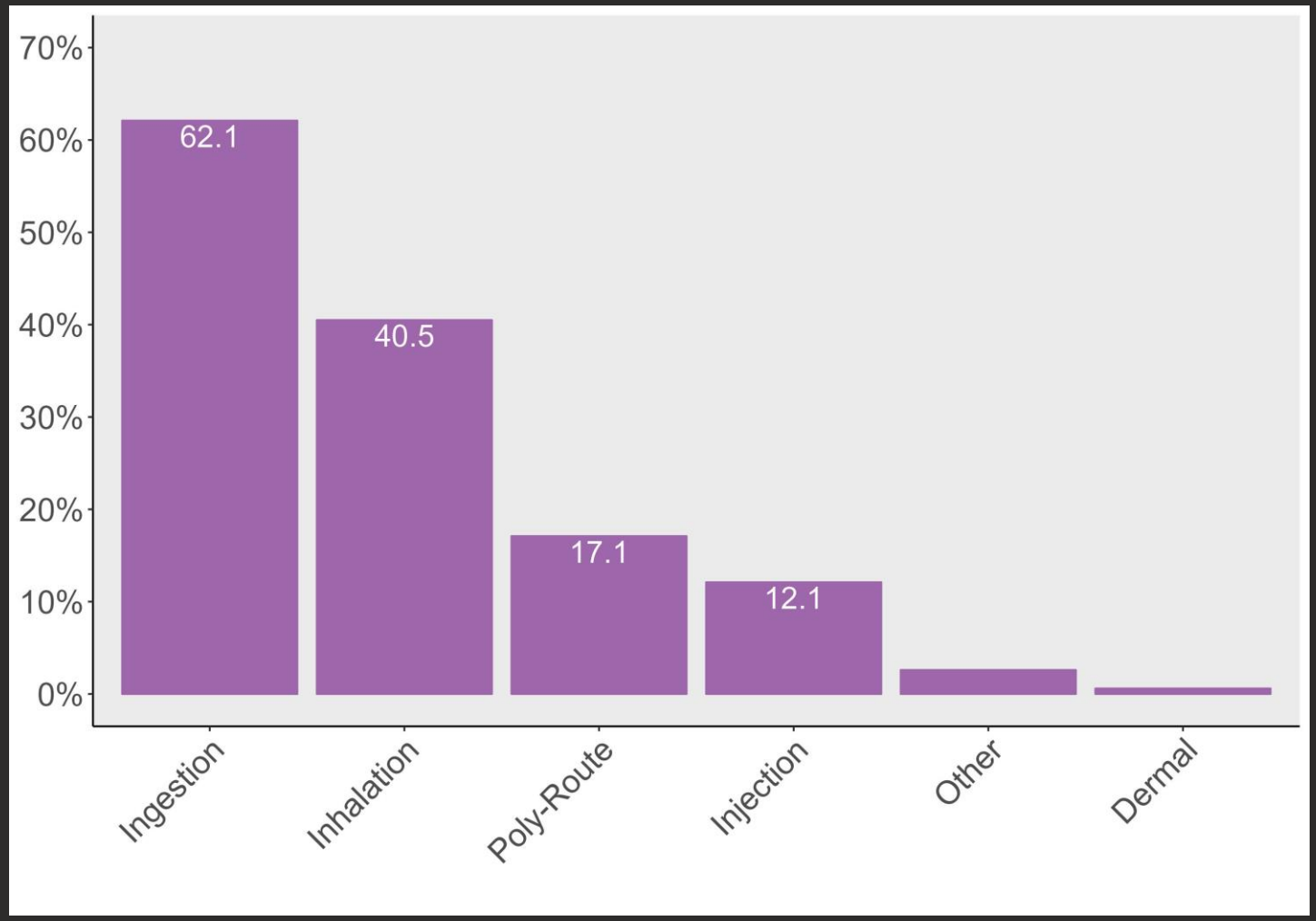
41% reported co-use of other drugs




Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Route of ketamine administration in poisonings

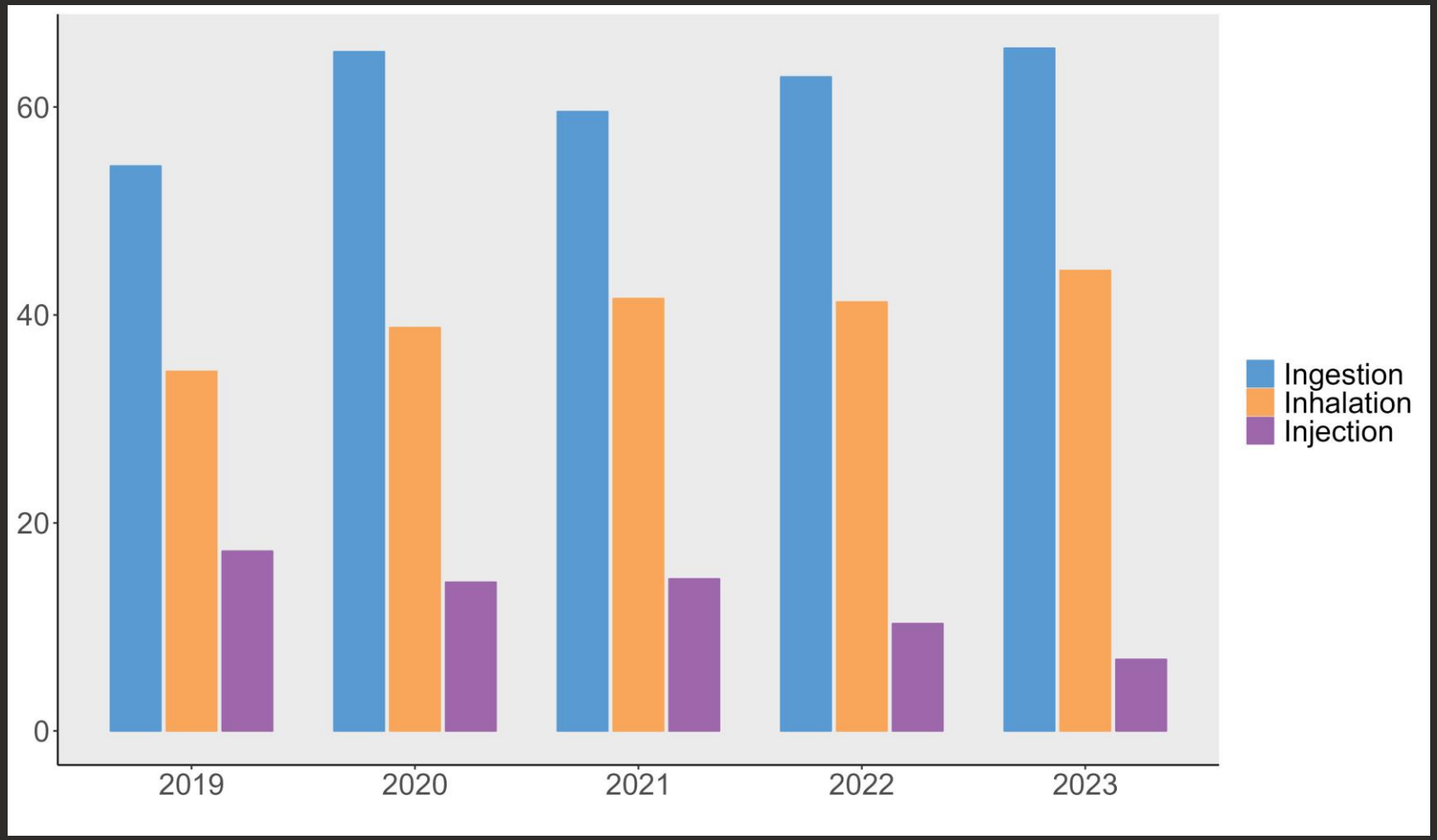



*Note:* 12.4% reported multiple routes of administration

Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Route of ketamine administration in poisonings

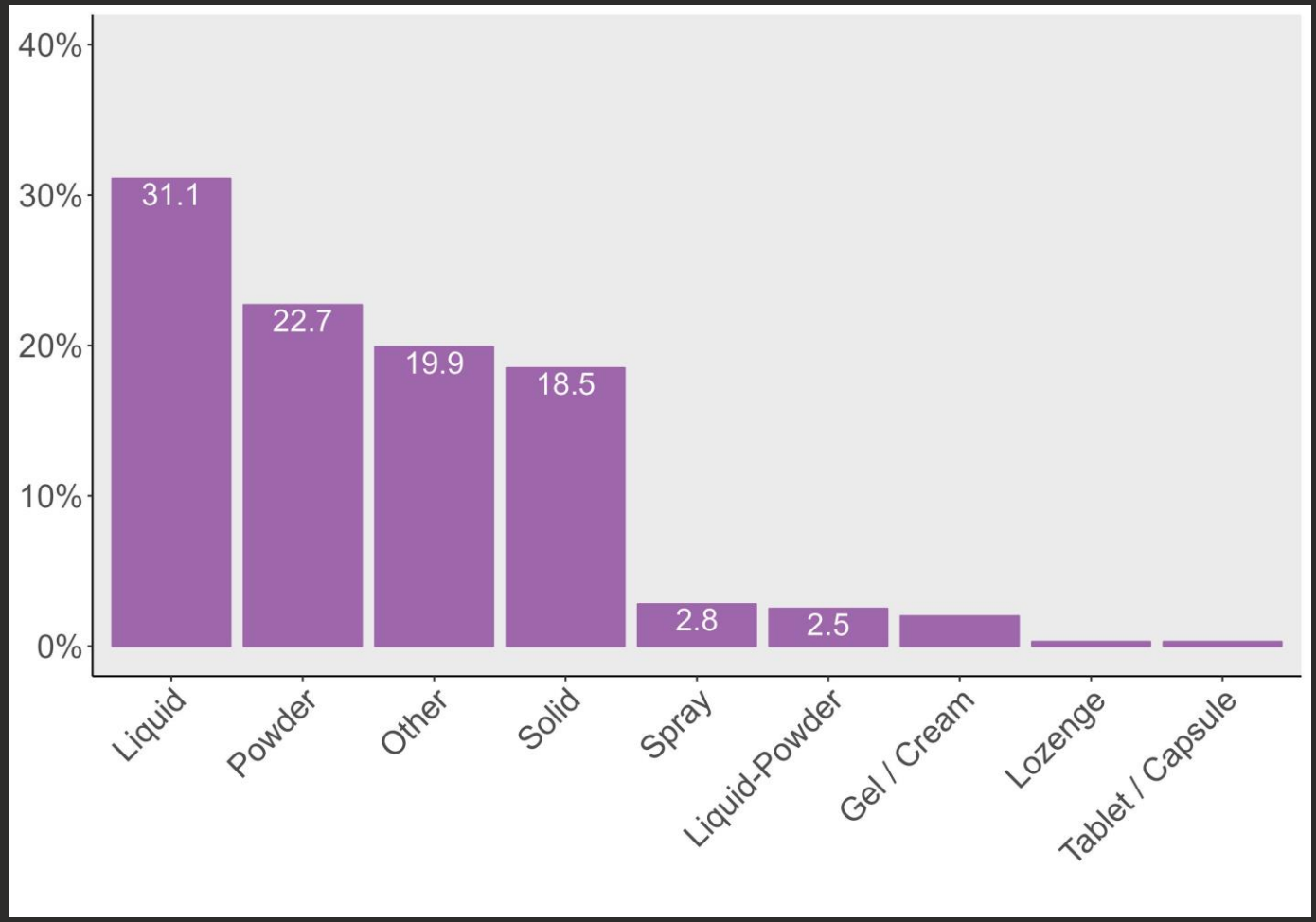



Injection decreased by 60% (p = .022)

Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Form of ketamine involved in poisonings

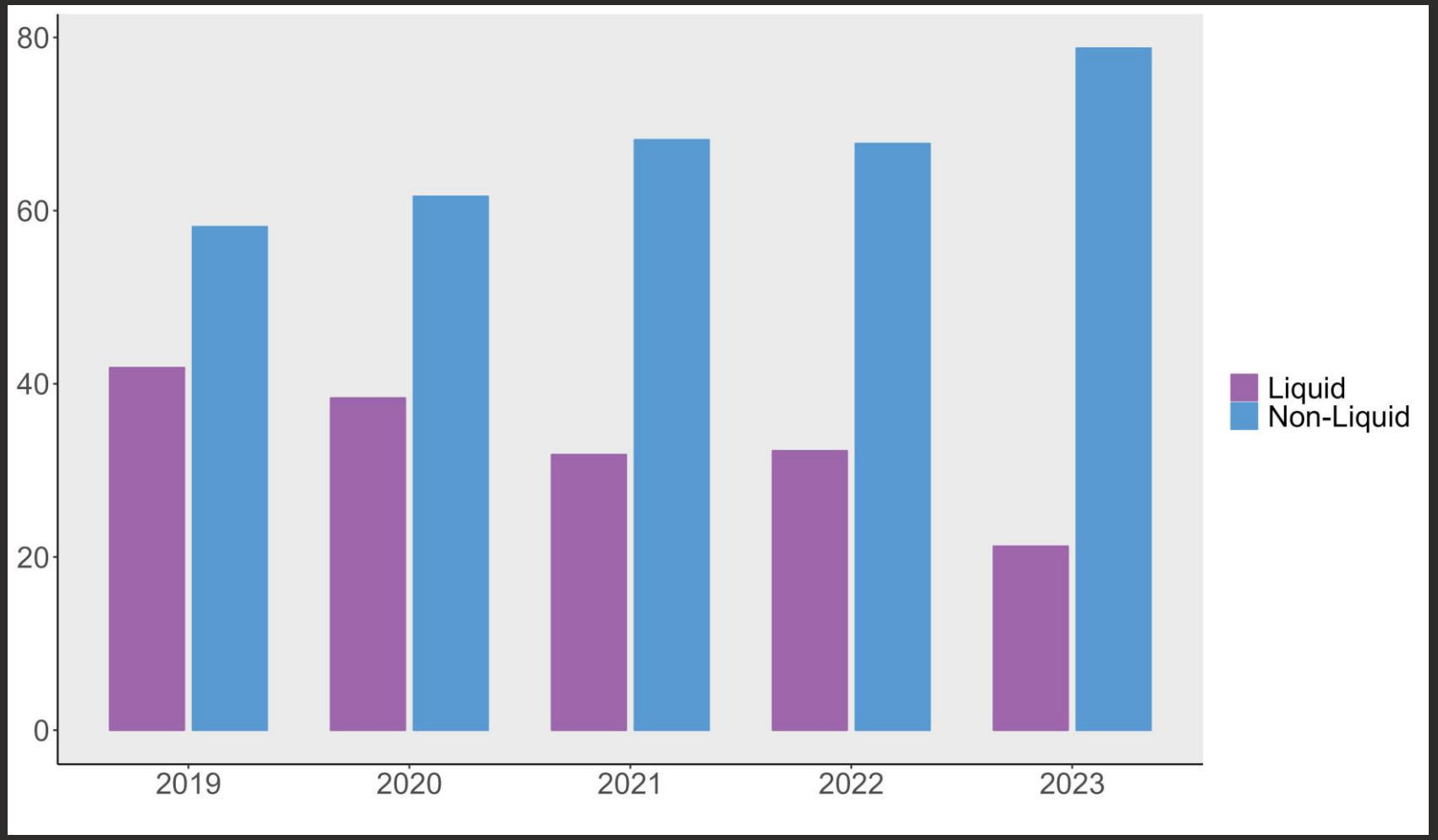



*Note:* "Solid" likely refers to powder or lozenges. "Liquid-powder" means that drug form was reported as liquid but subformulation was reported as powder.

Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# Form of ketamine involved in poisonings over time




Non-liquid ketamine use increased by 35% (p = .011)

Data obtained through with National Drug Early Warning System (NDEWS) collaboration with the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program

NYU Langone Health

# At-Home Psychiatric Treatment

NYU Langone Health

# Virtual prescribing

- Lozenges from compounding pharmacies
- Sometimes a “month supply” is prescribed
- In a few studies, very high dose (300-450 mg) rapid-dissolve tablets were mailed as a take-home treatment, with multiple tablets mailed to patients
- One doctor had prescribed ketamine to over 3,000 patients in 44 states in just three years. The DEA shut down his clinic in 2023

Hassan K, Struthers WM, Sankarabhotla A, Davis P. Safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety: A retrospective study of off-label, at-home use. Front Psychiatry. 2022;13:992624.
Hull TD, Malgaroli M, Gazzaley A, Akiki TJ, Madan A, Vando L, Arden K, Swain J, Klotz M, Paleos C. At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: Findings from a large, prospective, open-label effectiveness trial. J Affect Disord. 2022;314:59-67.
Gilbert D. This doctor prescribed ketamine from his home. DEA shut it down. Washington Post. May 10, 2023.
Image: balancedmentalwellness.com. Psychotherapy with Ketamine Troches: Age Guidelines

NYU Langone Health

# Risks Associated with Unsupervised Use

## Seven Concerns

NYU Langone Health

# Dysphoric Reactions With No Supervision

NYU Langone Health

# Patient Self-Harm or Harm to Others

NYU Langone Health

# Diversion

NYU Langone Health

# Stockpiling and Use of Large Doses

NYU Langone Health

# Alternate Routes of Administration

NYU Langone Health

# Ketamine Use Disorder

NYU Langone Health

# Seeking Illegal Supply After Introduced

**“Street” price is much cheaper than for other prescription drugs**

NYU Langone Health

# Continued Surveillance is Needed

- We need to better understand the drivers of ketamine misuse and adverse effects
- Research is needed to monitor the quickly changing legal *and* illegal ketamine landscape
- Research is needed to determine how much off-label prescribed ketamine has reached the black market

- We need this information to inform:
  - Policy decisions (regarding regulation, control, and advertising)
  - Prevention (to educate people about risks associated with use)
  - Treatment (for those experiencing problematic use)
  - Harm reduction (informing ketamine use in a safer manner)

NYU Langone Health

# Acknowledgments


- National Drug Early Warning System (NDEWS)
- Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program
- High Intensity Drug Trafficking Areas (HIDTA)
- NPS Discovery


# Funding


National Institute on Drug Abuse:

- R01DA060207 (PI: Palamar)
- R01DA057289 (PI: Palamar)
- U01DA051126 (PI: Cottler)


NYU Langone Health

NYU Langone Health

# Thank You

Please subscribe to the NDEWS Weekly Briefing:

NDEWS.ORG

# Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products

**Megan Ehret, PharmD, MS, BCPP**
University of Maryland Baltimore School of Pharmacy

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

# Patient Safety and Managing Adverse Effects of Ketamine

Megan J. Ehret, PharmD, MS, BCPP
Professor; Co-Director Mental Health Program
Department of Practice, Sciences, and Health Outcomes Research

# Tolerability and Safety

- Psychiatric
- Neurologic/Cognitive
- Hemodynamic
- Genitourinary
- Abuse liability

# Psychiatric

- Dissociation
  - Decreases with subsequent administration
  - Peaks within 40 minutes
  - Resolves in 1-2 hours
  - Clinician-Administered Dissociative States Scale (CADSS)
- Psychotomimetic
  - Pre-existing vulnerability

Short B, et al. Lancet Psychiatry 2018;5:65-78.
Malhotra AK, et al. Neuropsychopharmacology 1997;17:141-150.

# Neurologic/Cognitive

- Dizziness, drowsiness, light-headedness
- Long-term exposure: cellular or molecular evidence of neurotoxicity?

Zanos P, et al. Nature 2016;533:481-86.

# Hemodynamic

- Cardiac-stimulating effects
  - Increase in heart rate and blood pressure (10-50%)
    - Observed within 20-50 minutes of treatment
    - Resolve in 2-4 hours
    - 20-30% >180-100 mmHg and/or ≥110 b/min
    - ~20% may require pharmacologic treatment of hypertension
  - Palpitations, arrhythmias, chest pain, and hypotension

Szarmach J, Et al. Psychiatr Danub 2019;31:585-90.
Rodigues NB, et al. Expert Opin Drug Saf 2020;19:1031-40.
Short B, et al. Lancet Psychiatry 2018;5:65-78.
Correia-Melo FS, et al. J Affect Disord 2020;527-34.

# Genitourinary

- Lower urinary tract symptoms (20-40%; recreationally)
  - Nocturia
  - Painful hematuria
  - Dysuria
  - Urinary urgency
  - Incontinence
- Dose-dependent relationship: ketamine exposure and probability of experiencing symptoms

Winstock AR, et al. BJU Int 2012;110:1762-66.
Shahani R, e tal. Urology 2007;69:810-12.
Jhang J-F, et al. Int J Urol 2015;22:816-25.
Wei YB, et al. Hong Kong Med J 2013;19:341-

# Abuse Liability

- Healthy adults and recreational polydrug users: increased liking for ketamine
  - Concern for potential misuse and/or sensitization to other drugs of misuse
- Ketamine's effect on opioidergic systems- presage sensitization of drug reward substrates

George MS. Am J Psychiatry 2017;174:695-96.
Morgan CJA, et al. Psychol Med 2008;38:1331-40.

# Esketamine Vs. Ketamine- REMS?

- REMS- designed to help reduce the occurrence or severity of a particular serious adverse event for a single medication or class of medications
- Esketamine
  - Risk of sedation, dissociation, and respiratory depression after administration

# Identifying Safety Concerns and Potential Risks Associated with the Use of Ketamine Products

Discussion:

- **Francesca Cunningham, PharmD,** U.S. Department of Veterans Affairs
- **Megan Ehret, PharmD, MS, BCPP,** University of Maryland Baltimore School of Pharmacy
- **Joseph Palamar, PhD, MPH,** New York University Langone Health
- **Mark Rogge, PhD,** University of Florida School of Pharmacy
- **Eric Schwenk, MD,** Thomas Jefferson University

# Lunch

**The meeting will resume at 1:15 pm ET**

REAGAN-UDALL FOUNDATION FOR THE FDA