Advances in Treatment of Methamphetamine Use Disorder: Proposed CTN-0132 study

Manish Kumar Jha, MBBS

53rd Annual Meeting of ASAM on April 1, 2022

Disclosure Information (Required)

- Advances in Treatments for Methamphetamine Use Disorder
- Friday April 1, 2022; 10:30 – 11:30 AM

Manish Kumar Jha, MBBS

- Contract Research:
  - Acadia Pharmaceuticals
  - Janssen Research & Development
  - Supernus/Navitor
  - Neurocrine
- Honoraria for CME presentations
  - North American Center for Continuing Medical Education (NACCME)
  - Global Medical Education (GME)
- Educational Grant
  - Section Editor of the Psychiatry & Behavioral Health Learning Network
- Consultant Fees
  - Eleusis Therapeutics US, Inc
  - Janssen Global Services
  - Guidepoint Global

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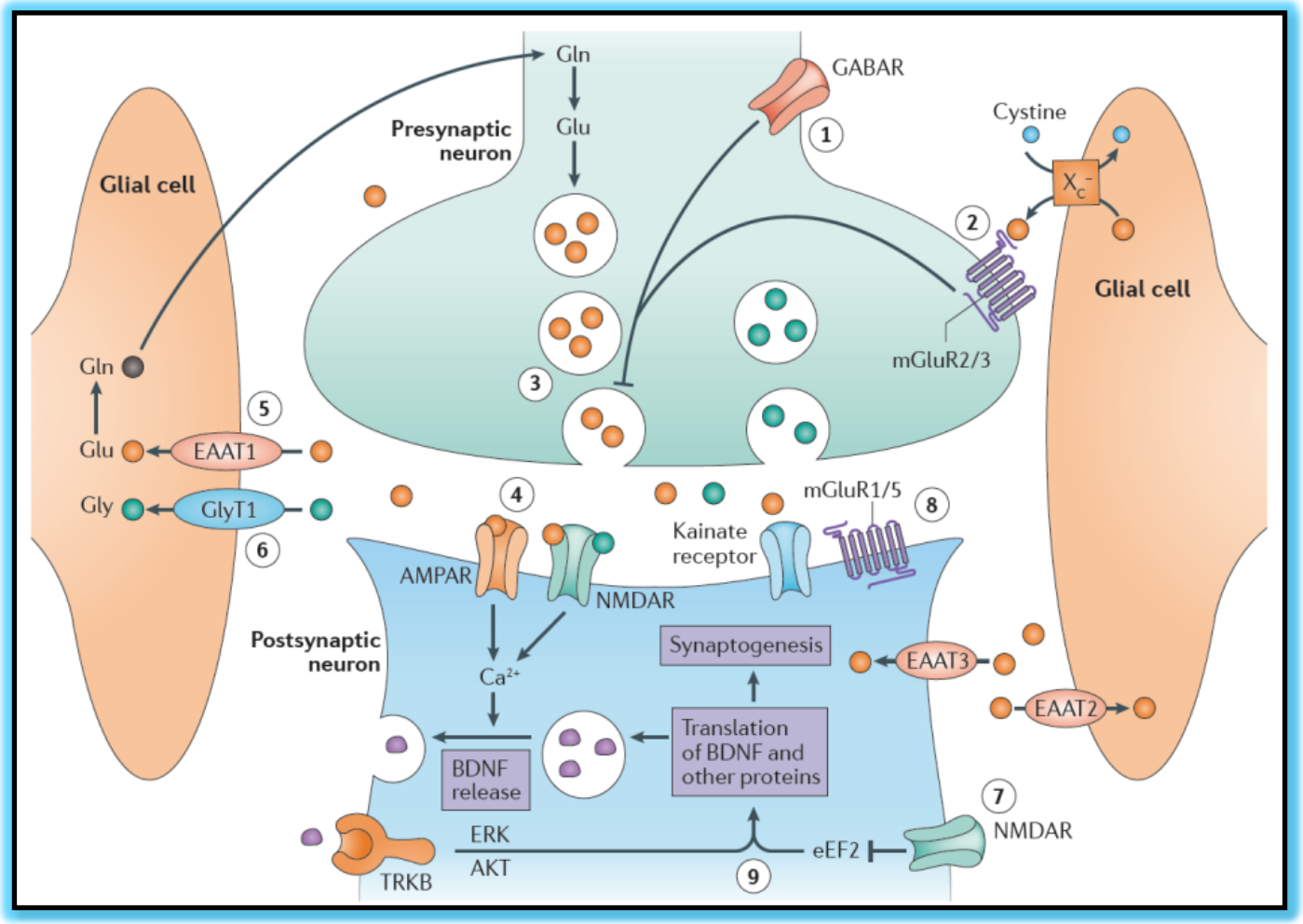
Learning Objectives

- Upon completion of the focus session, the participant will be able to articulate the role of glutamatergic dysregulation in methamphetamine use disorder, and potential therapeutic options to address this problem.

Glutamate Neurotransmission as Therapeutic Target



Murrough, Abdallah and Mathew. Nat Rev Drug Disc 2017

Overview of Glutamate Receptors

Ionotropic Receptors

Ligand-gated ion channels

- AMPA Receptors
  - GluR1-GluR4
- NMDA Receptors
  - NR1, NR2A-NR2D, NR3
- Kainate Receptors
  - KA1-KA5

Metabotropic Receptors

G protein-coupled receptors (GPCRs)

- Group I
  - mGluR1, mGluR5
- Group II
  - mGluR2, mGluR3
- Group III
  - mGluR4, mGluR6, mGluR7, mGluR8

Ketamine

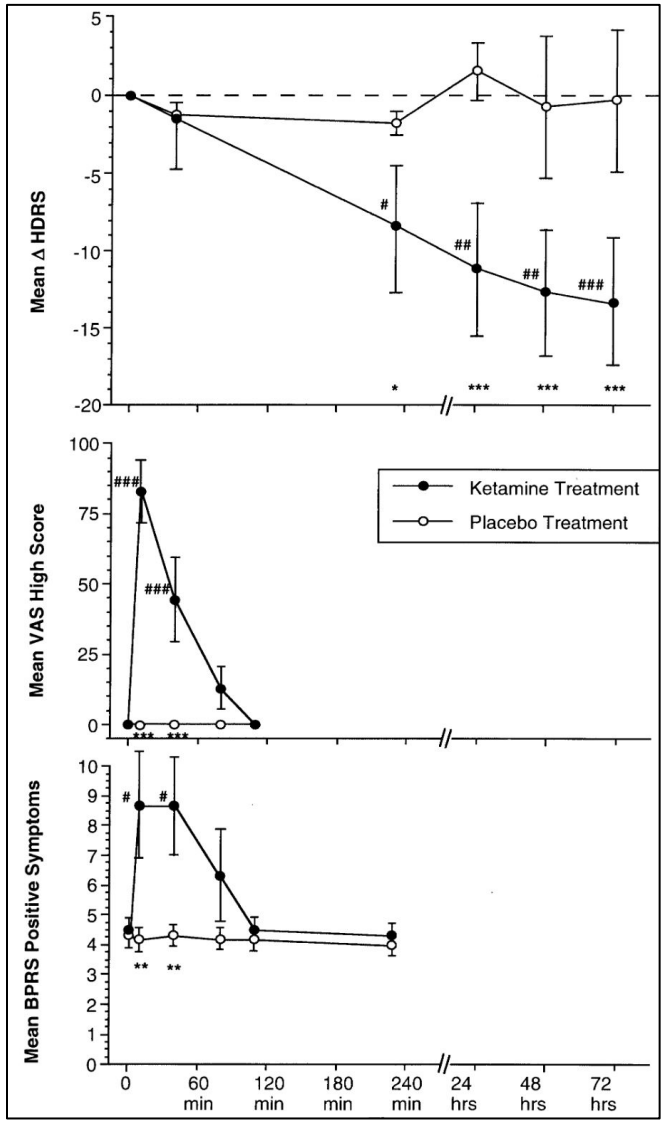
- Used as an anesthetic agent
  - *In kids*
  - *In emergency or*
  - *In patients at high risk of respiratory depression*
- Anesthetic use limited due to side effects of psychosis
- Also used in management of chronic pain
- Occasionally misused for its dissociative effects
- Cognitive impairment associated with chronic misuse

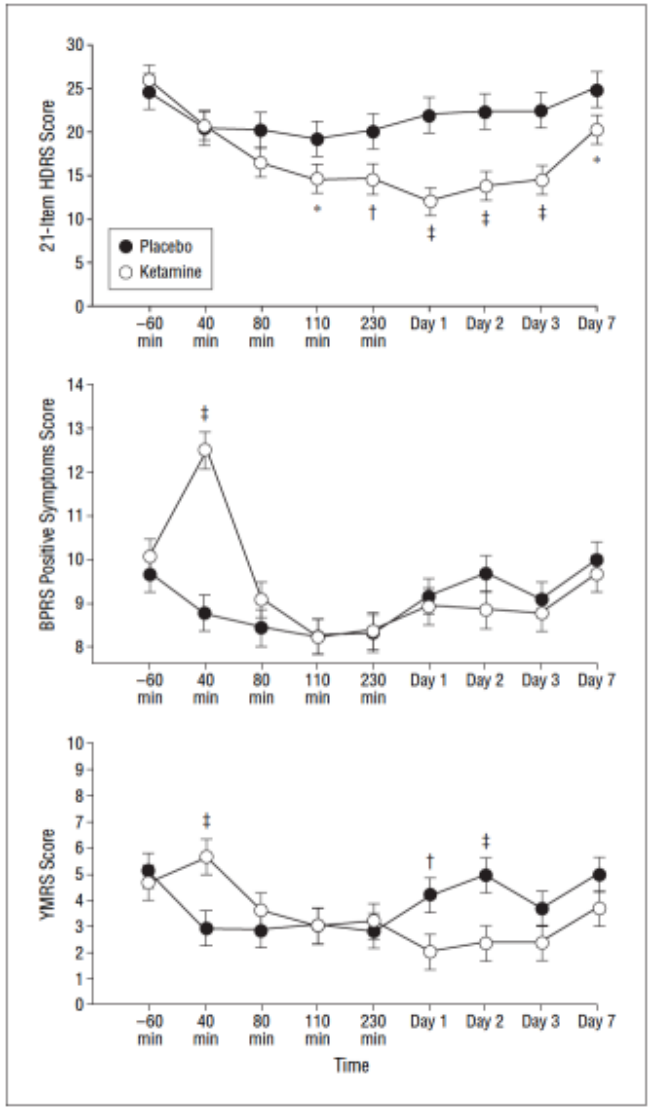
Ketamine in treatment of depression

- Rapid onset
- Subanesthetic (0.5 mg/kg) dose
- Non-competitive antagonist of NMDA receptor
- Route – IV mostly (also intranasal, IM and oral)
- Bioavailability – 90% IM or IV, 16% orally
- Low plasma protein binding (10-30%)
- Mostly (80%) metabolized to norketamine ➔ Hydroxynorketamine (HNK)
- Elimination half-life of ketamine is 2-3 hours

Rapid Antidepressant Effects of a Single IV Dose of Racemic Ketamine

Berman et al. Biological Psychiatry 2000



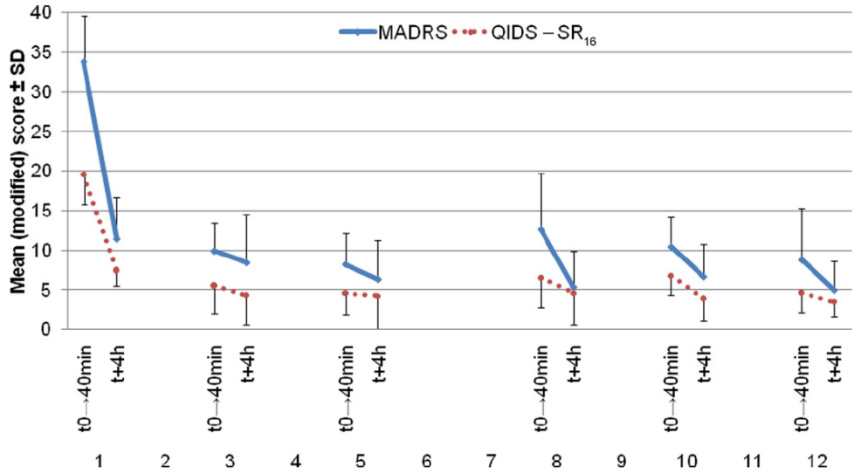


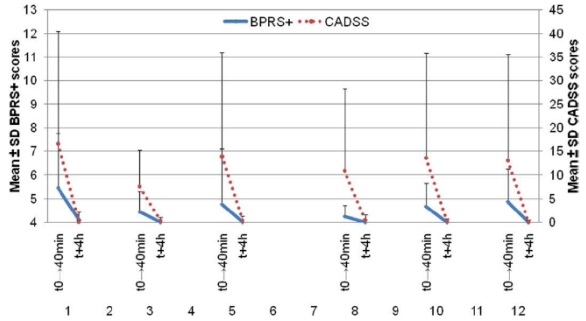
Zarate et al, Arch Gen Psych 2006.

Repeated Ketamine Infusions for Depression

Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression

Marije aan het Rot, Katherine A. Collins, James W. Murrough, Andrew M. Perez, David L. Reich, Dennis S. Charney, and Sanjay J. Mathew



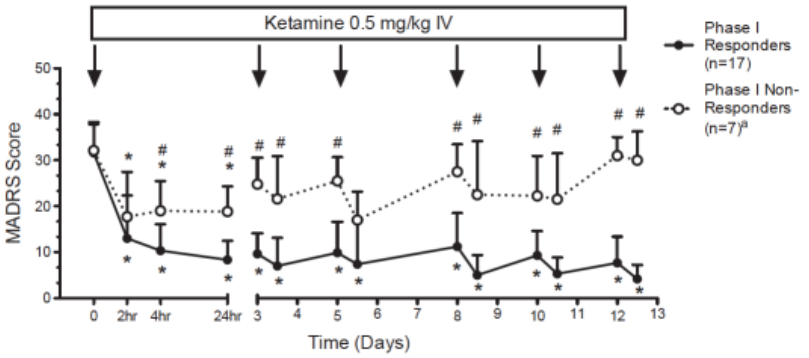


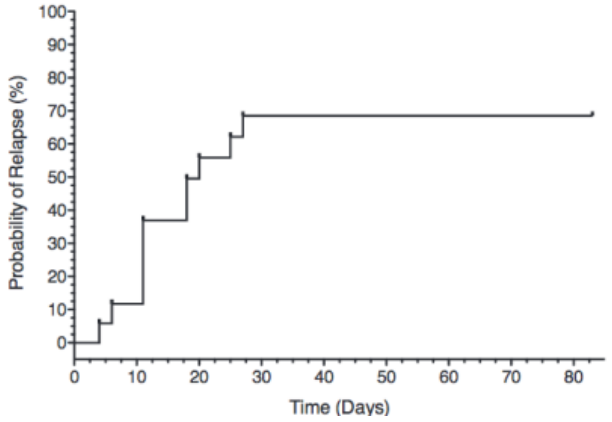
aan het Rot et al, Biol Psychiatry, 2010.

ARCHIVAL REPORT

Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression

James W. Murrough, Andrew M. Perez, Sarah Pillemer, Jessica Stern, Michael K. Parides, Marije aan het Rot, Katherine A. Collins, Sanjay J. Mathew, Dennis S. Charney, and Dan V. Iosifescu





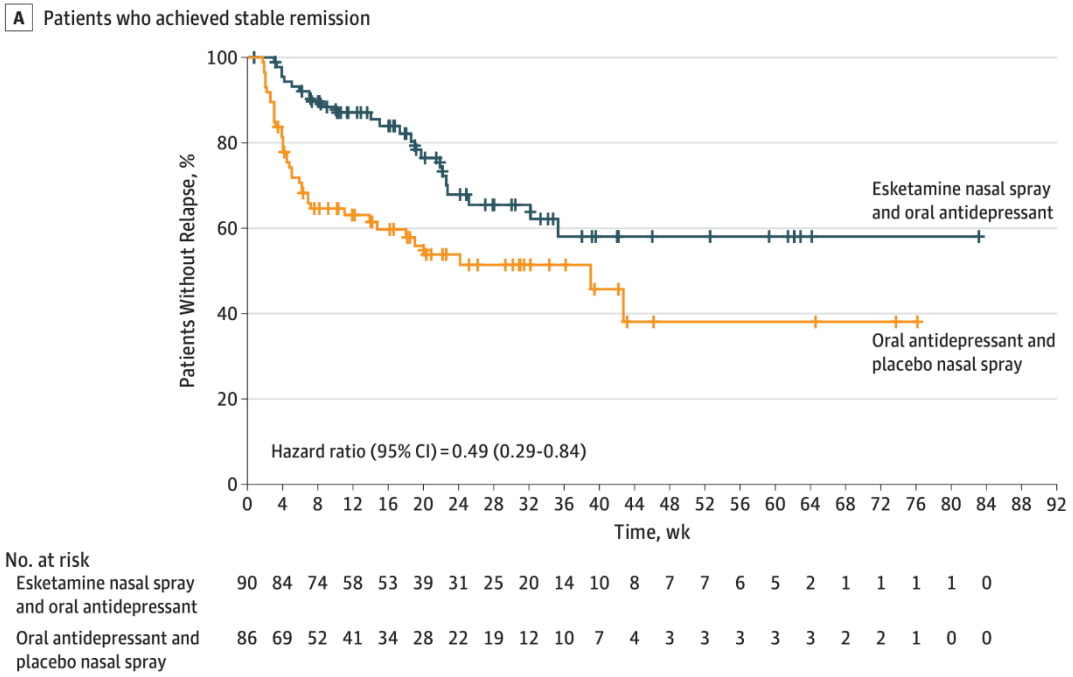
Murrough et al, Biol Psychiatry, 2013.

Intranasal esketamine for TRD

Results of Short-Term Studies of Esketamine.*

Study and Treatment Group	No. of Patients	Primary Efficacy Measure: MADRS Total Score			
		Baseline Score	Least Squares Mean Change from Baseline (95% CI)	Least Squares Mean Difference from Placebo (95% CI)	One-Sided P Value†
3001					
ESK, 56 mg	115	37.4±4.8	−18.9 (−21.4 to −16.4)	−4.1 (−7.7 to −0.6)	0.013
ESK, 84 mg	114	37.8±5.6	−18.2 (−20.9 to −15.6)	−3.2 (−6.9 to 0.5)	0.044
Placebo	113	37.5±6.2	−14.9 (−17.4 to −12.4)	—	—
3002					
ESK, 56 or 84 mg	114	37.0±5.7	−20.8 (−23.3 to −18.4)	−4.0 (−7.3 to −0.6)	0.010
Placebo	109	37.3±5.7	−16.8 (−19.3 to −14.4)	—	—
3005					
ESK, 28, 56, or 84 mg	72	35.5±5.9	−10.1 (−13.1 to −7.1)	−3.6 (−7.2 to 0.07)	0.029
Placebo	65	34.8±6.4	−6.5 (−9.4 to −3.6)	—	—

* In Study 3001, the lower dose could not be tested for statistical significance because the higher dose failed. CI denotes confidence interval, ESK esketamine, and MADRS Montgomery–Åsberg Depression Rating Scale (scores range from 0 to 60, with higher scores indicating more severe depression). Data are from the Food and Drug Administration. Plus–minus values are means ±SD.
† One-sided P values are compared with P=0.025.

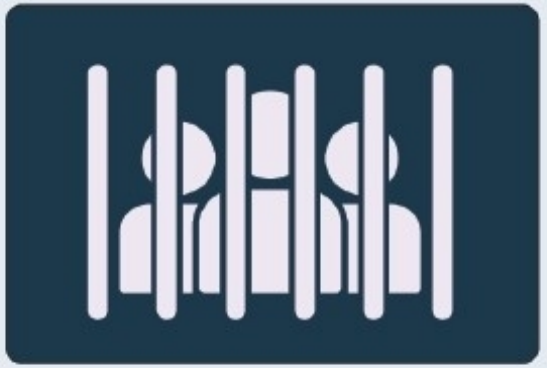


Kim et al. NEJM 2019; Daly et al. JAMA Psychiatry 2019

Burden of Stimulant Misuse

COST OF STIMULANT MISUSE TO SOCIETY

In 2018, there were **27,342 stimulant overdose deaths** – roughly **40%** of all overdose deaths in the United States.



Stimulant-related offenses accounted for more than of all federal drug offenses. **75%**

Amphetamine-related hospital costs totaled **$436 million** in 2003, and increased to **$2.17 billion** by 2015.

Substance Abuse and Mental Health Services Administration (SAMHSA): Treatment of Stimulant Use Disorders. SAMHSA Publication No. PEP20-06-01-001 Rockville, MD: National Mental Health and Substance Use Policy Laboratory. Substance Abuse and Mental Health Services Administration, 2020.

Ketamine for substance use disorders

A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial

Elias Dakwar, M.D., Edward V. Nunes, M.D., Carl L. Hart, Ph.D., Richard W. Foltin, Ph.D., Sanjay J. Mathew, M.D., Kenneth M. Carpenter, Ph.D., C.J. "Jean" Choi, M.S., Cale N. Basaraba, M.P.H., Martina Pavlicova, Ph.D., Frances R. Levin, M.D.

Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder

Meryem Grabski, Ph.D., Amy McAndrew, Ph.D., Will Lawn, Ph.D., Beth Marsh, B.Sc., Laura Raymen, M.Sc., Tobias Stevens, Ph.D., Lorna Hardy, Ph.D., Fiona Warren, Ph.D., Michael Bloomfield, Ph.D., Anya Borissova, M.D., Emily Maschauer, M.Sc., Rupert Broomby, M.D., Robert Price, M.D., Rachel Coathup, M.D., David Gilhooly, M.D., Edward Palmer, M.D., Richard Gordon-Williams, M.D., Robert Hill, Ph.D., Jen Harris, D.Clin.Psych., O. Merve Mollaahmetoglu, M.Sc., H. Valerie Curran, D.Clin.Psych., Brigitta Brandner, M.D., Anne Lingford-Hughes, M.D., Ph.D., Celia J.A. Morgan, Ph.D.

Dakwar et al. Am J Psychiatry 2019; Grabski et al. Am J Psychiatry 2022

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- 5-day inpatient stay
- Ketamine (0.5 mg/kg) or midazolam (0.025 mg/kg) single infusion over 40 minutes
- 5-week course of mindfulness-based relapse prevention
  - Daily from day 2 through 5 during inpatient stay
  - Once a week during weeks 2 through 5

Dakwar et al. Am J Psychiatry 2019

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FIGURE 2. Time to first use or dropout, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence

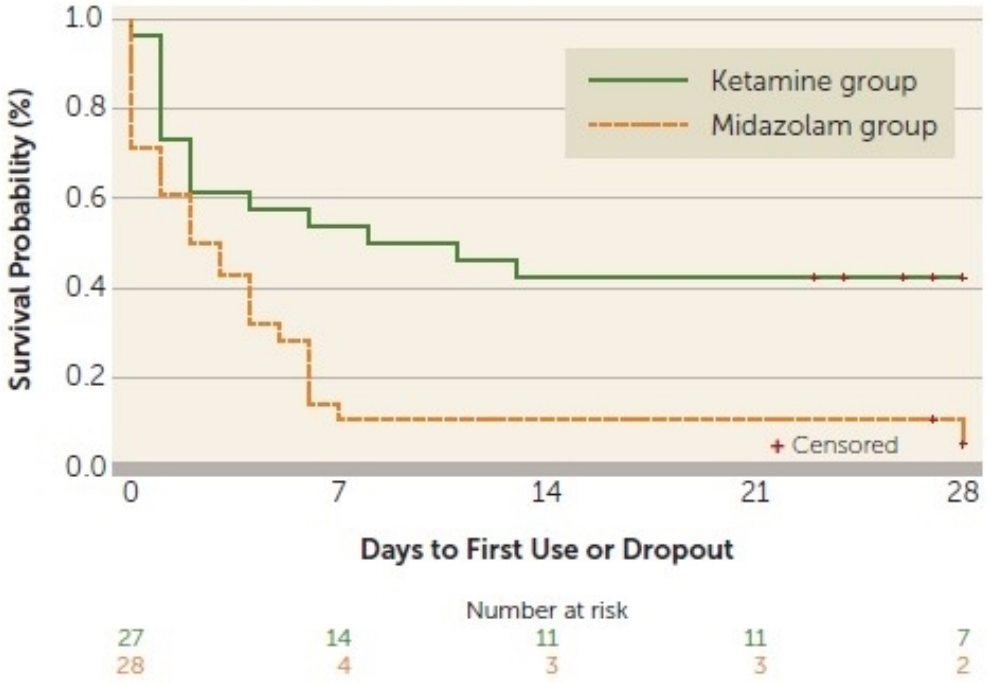
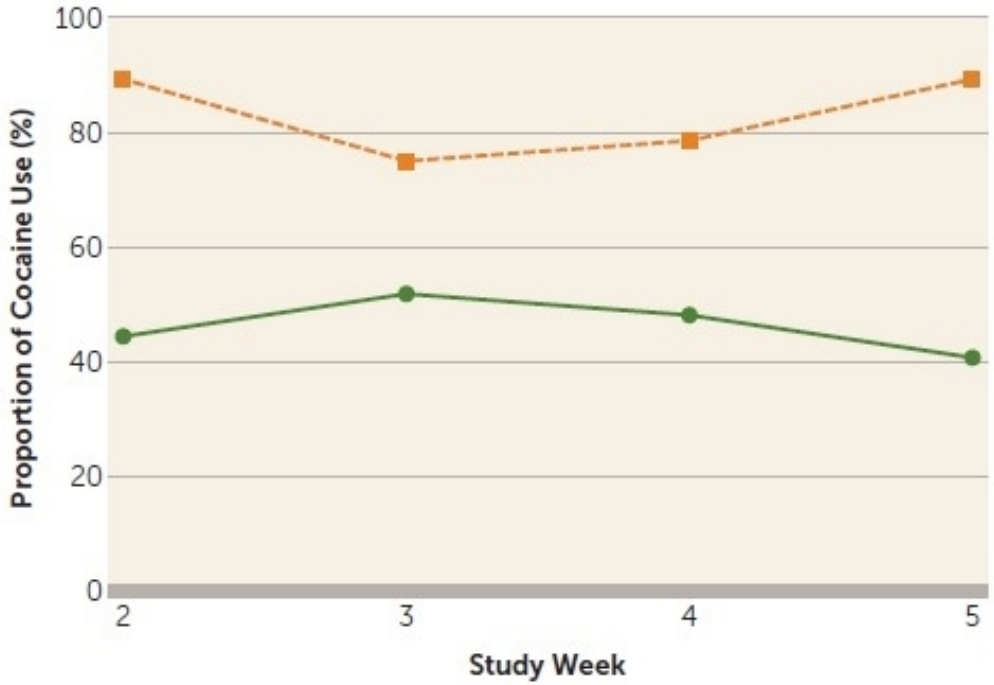


FIGURE 3. Observed proportion of cocaine use over time, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence

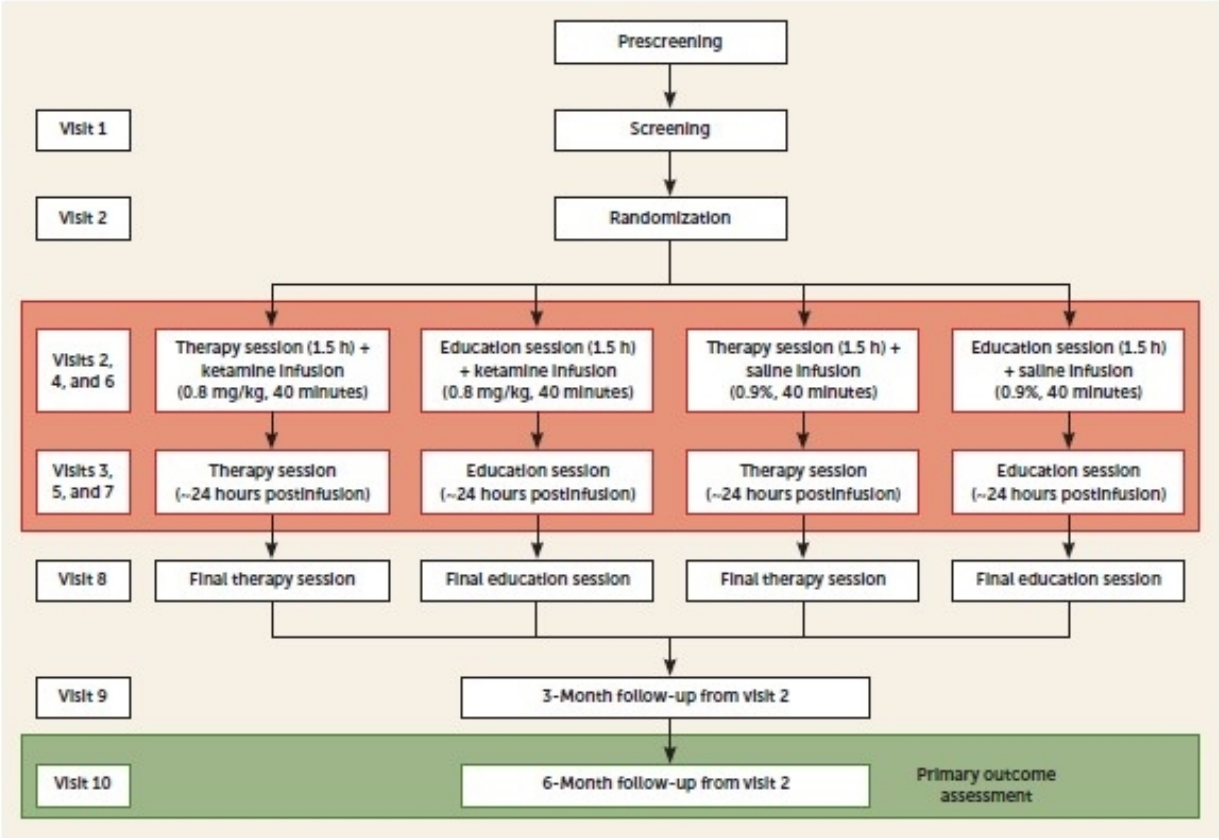


Dakwar et al. Am J Psychiatry 2019

Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder

- Individuals with alcohol use disorder who had completed detox
- Ketamine (0.8 mg/kg) or saline three 40-min infusion over three weeks
- 90-minute long sessions, also mindfulness during infusion experience

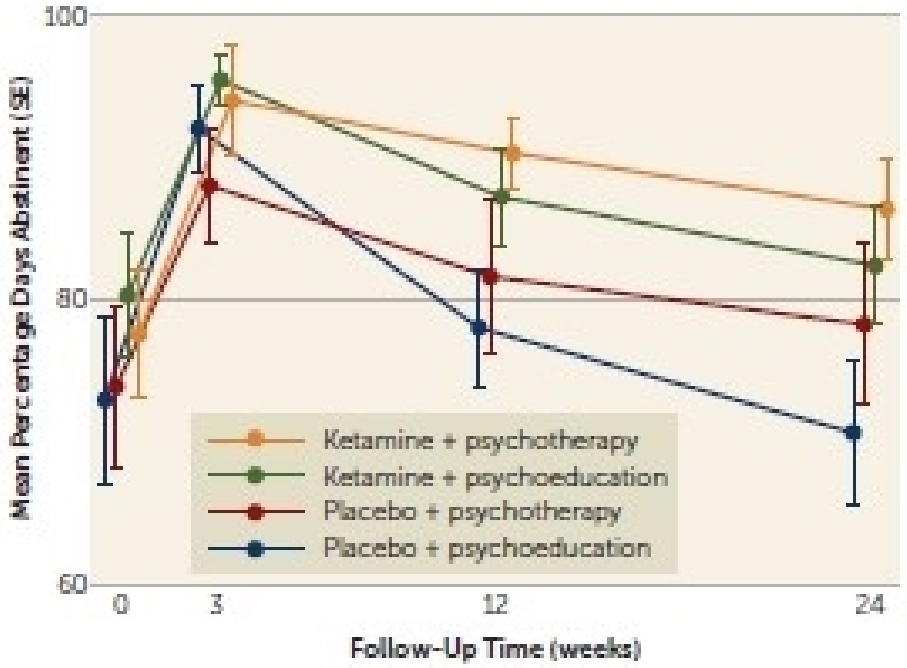
FIGURE 1. Schematic of the trial design in a study of ketamine and psychological therapy in the treatment of alcohol use disorder[a]



Grabski et al. Am J Psychiatry 2022

Results

FIGURE 3. Percentage days abstinent across the four treatment conditions in a study of ketamine and psychological therapy in the treatment of alcohol use disorder[a]



Grabski et al. Am J Psychiatry 2022

Proposed study design of CTN-0132

- Double-blind RCT of ketamine vs. midazolam
- Patients with moderate or severe methamphetamine use disorder.
- Ketamine: 0.71 mg/kg; Midazolam: 0.02 mg/kg
- Thrice-weekly infusions (total of 18 infusions)
- Acute-phase and follow-up of 6 weeks each
- N=120, four sites
- Treatment outcome of response: 3 out of 4 negative UDS in weeks 6 and 7 (for acute-phase).

Final Takeaways/Summary

- Targeting glutamate neurotransmission may offer new treatments
- Studies of depression show that ketamine and its s-enantiomer (esketamine) lead to rapid and robust improvement.
- Initial studies in adults with cocaine use disorder suggest that ketamine is associated with lower likelihood of subsequent relapse.
- Studies in methamphetamine use disorder have not been conducted. Additionally, repeated treatments with ketamine have not been studied for treatment of stimulant use disorder.

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