Ketamine: A New Way to Change Your Mind

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Founder and Medical Director, Reset Ketamine

August 15, 2018

OUTLINE OF PRESENTATION

Review history of ketamine

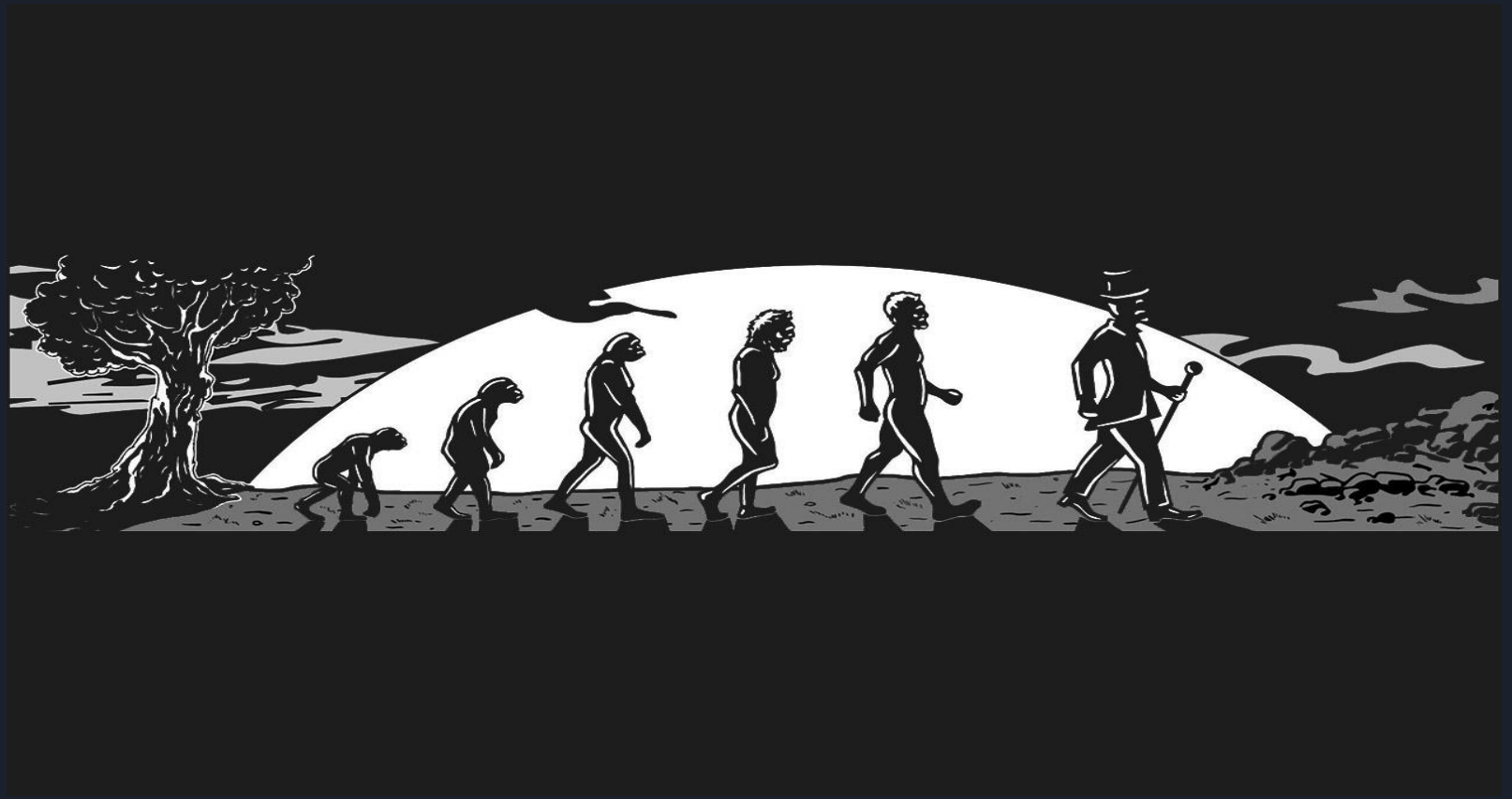
Learn about the mechanism of action for ketamine

Review the latest evidence for ketamine

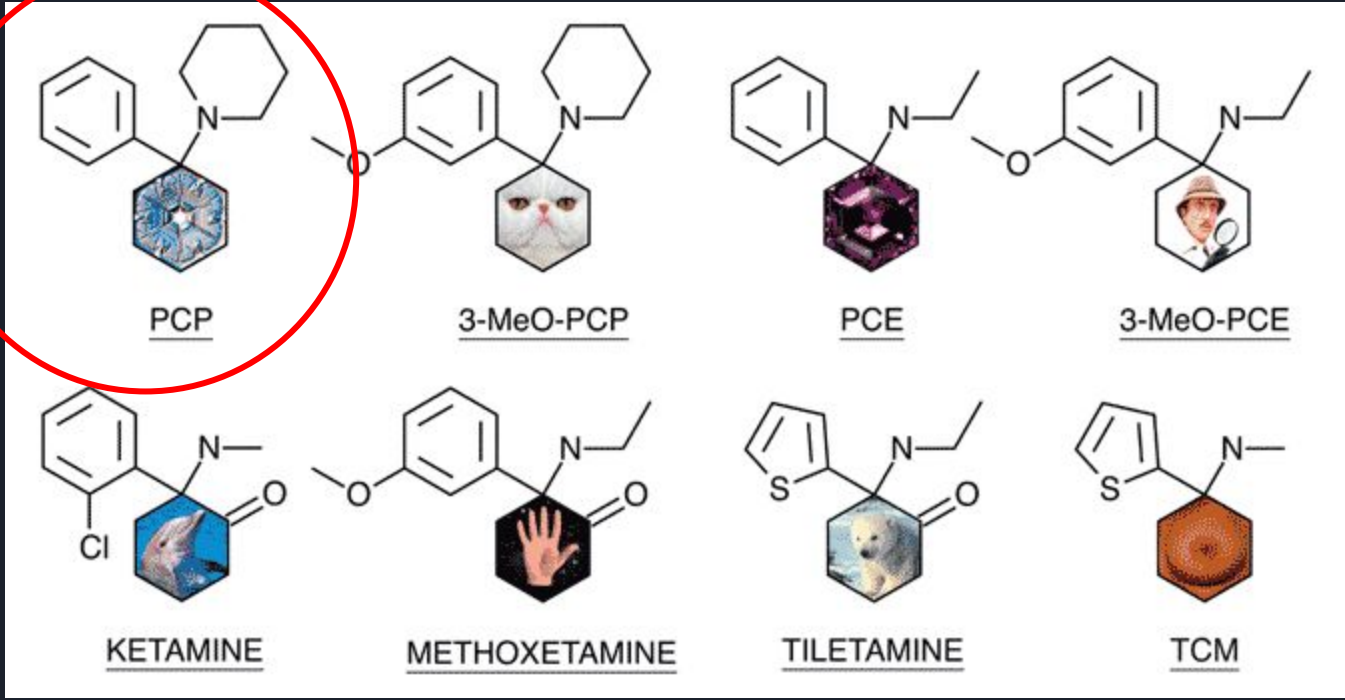
- Depression
- PTSD
- Suicidal Ideation
- Addiction

Case Reports of Patients from Reset Ketamine

A Short History of Ketamine



Member of the **arylcyclohexylamine** group



Phencyclidine

First made in 1926

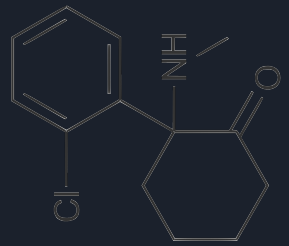
In 1956, patented by Parke-Davis Pharmaceutical company for general anesthesia

In 1965, use discontinued because of prolonged psychotic symptoms

However, became a drug of abuse and made in underground labs

Street Name = “Angel Dust” and PCP

Ketamine

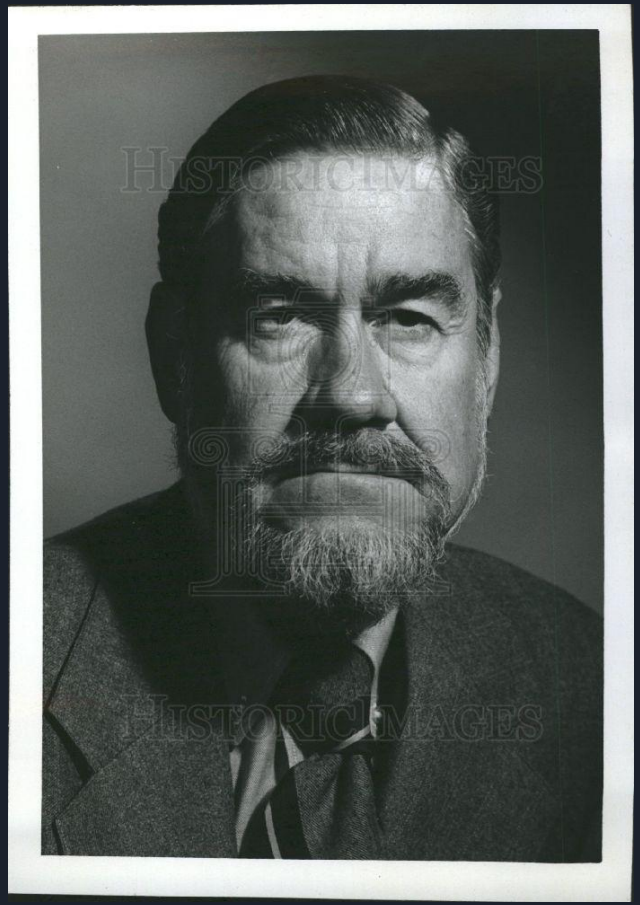


In 1962, Calvin L. Stevens, PhD, organic chemist at Wayne State University, was consulting for Parke Davis pharmaceuticals.

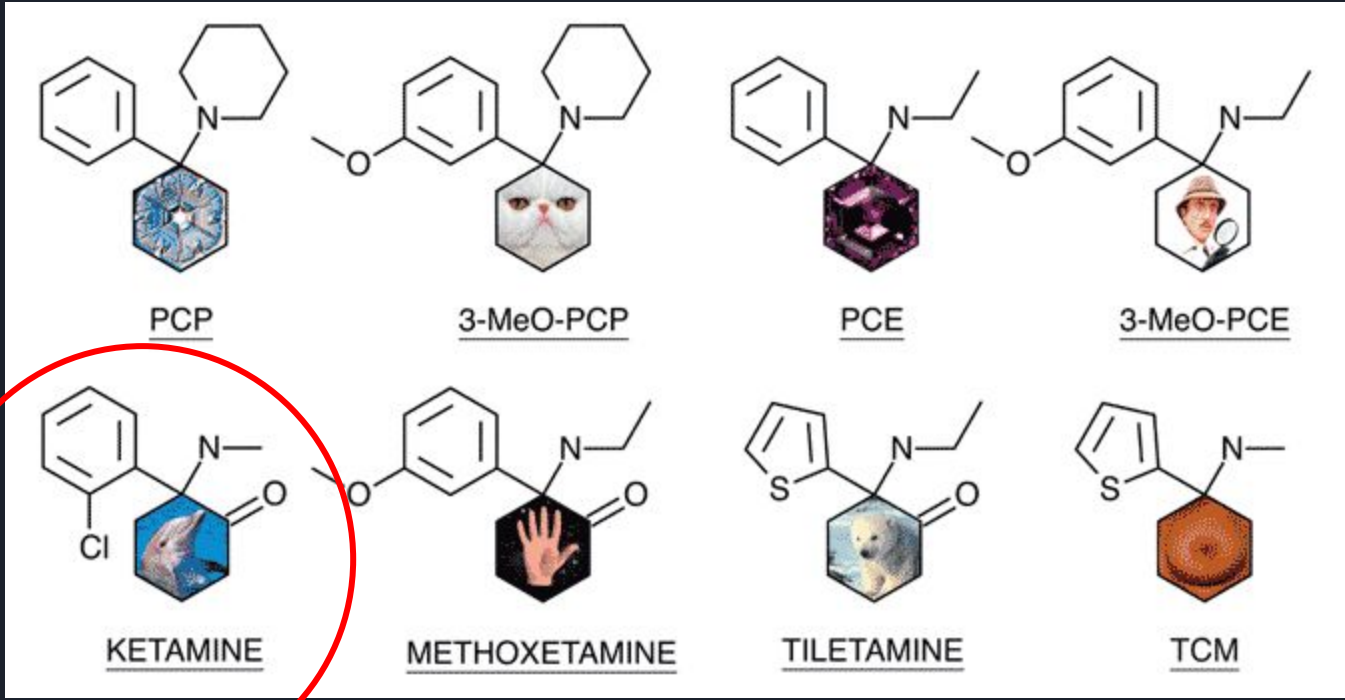
Requested to make a safer anesthetic than phencyclidine

He synthesized a phencyclidine derivative, called CI-581

Later renamed it **ketamine**.



Member of the **arylcyclohexylamine** group



First use in humans - 1964

Dr. Edward Domino tested ketamine at Jackson Prison in Michigan.

20 inmates volunteered

Described transient hallucinations and dream-like states

“Spaced out” and “Floating”

At higher doses was found to be induce profound anesthesia

DISSOCIATIVE ANESTHETIC


Most widely used battlefield anesthetic agent, sedative, & analgesic agent in Vietnam

In 1970, FDA approved ketamine for use as anesthesia for children, adults, and elderly.

20 years....

Annals of Emergency Medicine
An International Journal

Ketamine Sedation for Pediatric Procedures: Part 1, A Prospective Series

Emergency physicians frequently perform painful but necessary procedures on frightened children. We conducted a prospective, uncontrolled clinical trial of ketamine sedation (4 mg/kg IM) to facilitate a variety of procedures in 108 children aged 14 months to 13 years. Acceptable conditions were achieved with a single injection in 97% of the patients, and adjunctive restraint or local anesthesia was not required in 86%. Full sedation was produced within five minutes in 83%. Mean duration from injection to dischargeable recovery was 82 minutes (range, 30 to 175 minutes). One 18-month-old child vomited shortly after injection and experienced transient laryngospasm with cyanosis; intubation was not required, and there were no adverse sequelae. Airway patency and independent respirations were fully maintained in all other patients; no hemodynamic instability occurred at any time. There were no other clinically significant complications. Emesis well into the recovery phase was noted in 6% of the patients. Nightmares were not observed. Response from parents and physicians was strongly positive. Ketamine can be effectively used by emergency physicians to facilitate procedural sedation, yet equipment and expertise for advanced airway management are mandatory due to the rare occurrence of laryngospasm. [Green SM, Nakamura R, Johnson NE: Ketamine sedation for pediatric procedures: Part 1, a prospective series. Ann Emerg Med September 1990;19:1024-1032.]

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Received for publication May 1, 1989. Revision received September 7, 1989. Accepted for publication November 14, 1989.

Presented at the Society for Academic Emergency Medicine Annual Meeting in San Diego, May 1989.

INTRODUCTION

Not used in EDs until this landmark study, Annals of EM, Sept. 1990

Ketamine Sedation for Pediatric Procedures: Part 2, Review and Implications

[Green SM, Johnson NE: Ketamine sedation for pediatric procedures: Part 2, review and implications. Ann Emerg Med September 1990;19:1033-1046.]

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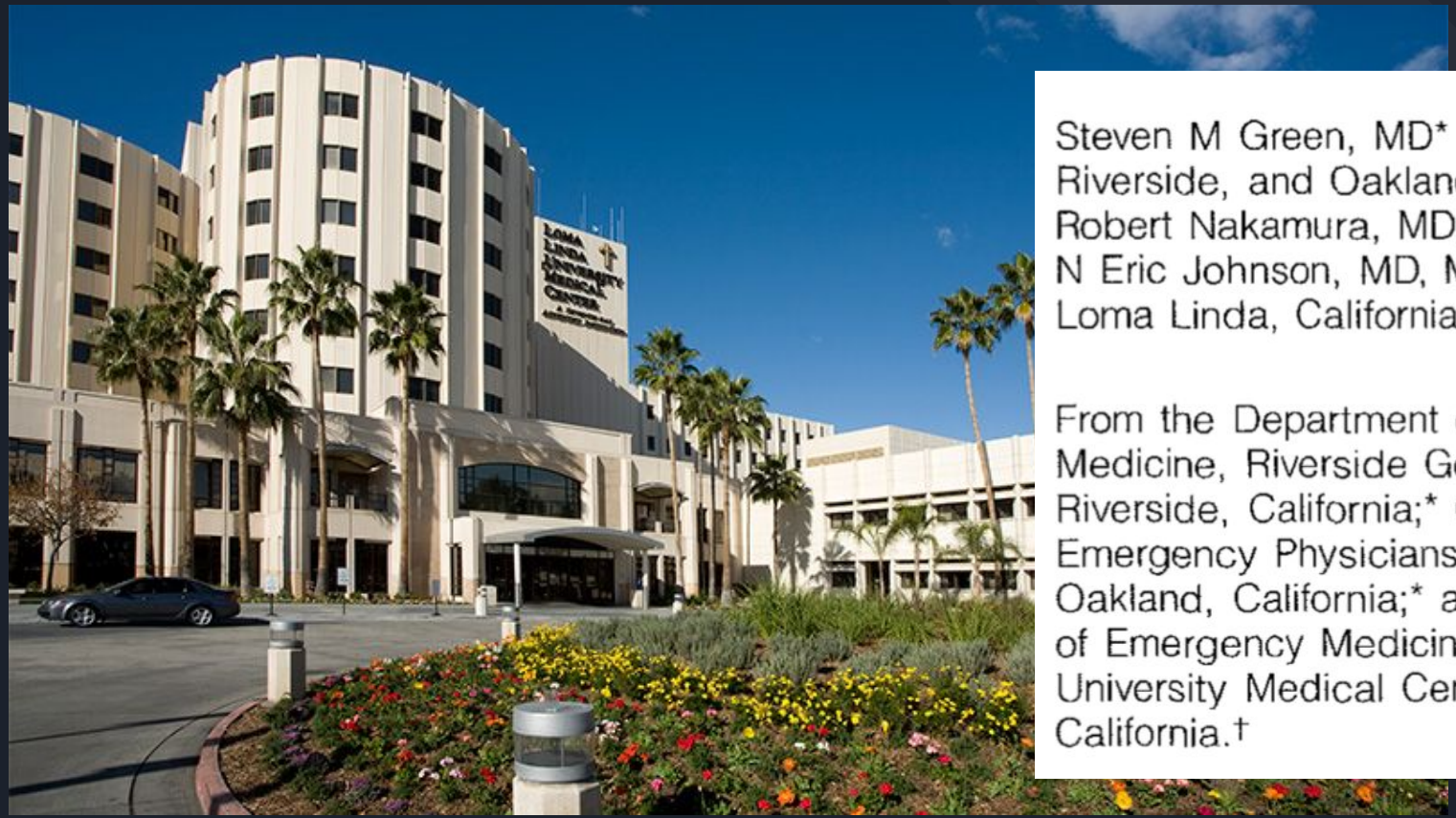
Received for publication May 1, 1989. Revisions received September 7, 1989, and April 9, 1990. Accepted for publication May 2, 1990.

INTRODUCTION

Emergency physicians frequently perform procedures that can be painful. Ketamine hydrochloride can be valuable in these circumstances; when administered IV or IM, it rapidly produces profound sedation and analgesia, allowing performance of procedures under optimum conditions. Spontaneous breathing and protective airway reflexes are maintained without intubation, and recovery to a degree suitable for emergency department discharge typically occurs in 30 to 120 minutes.

Use of ketamine for various pediatric applications has been extensively documented in numerous studies of more than 11,000 children as having outstanding safety and efficacy.[1-97] Despite frequent recommendations for use of this agent in the ED,[35,98-100] reports of ED applications are few and of limited scope.[31-34]

Structurally derived from the street drug phencyclidine in 1963 and introduced into general clinical practice in 1970, ketamine is a unique com-



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Now, ketamine has been used in humans for over 50 years.

It is on the WHO “List of Essential Medicines”

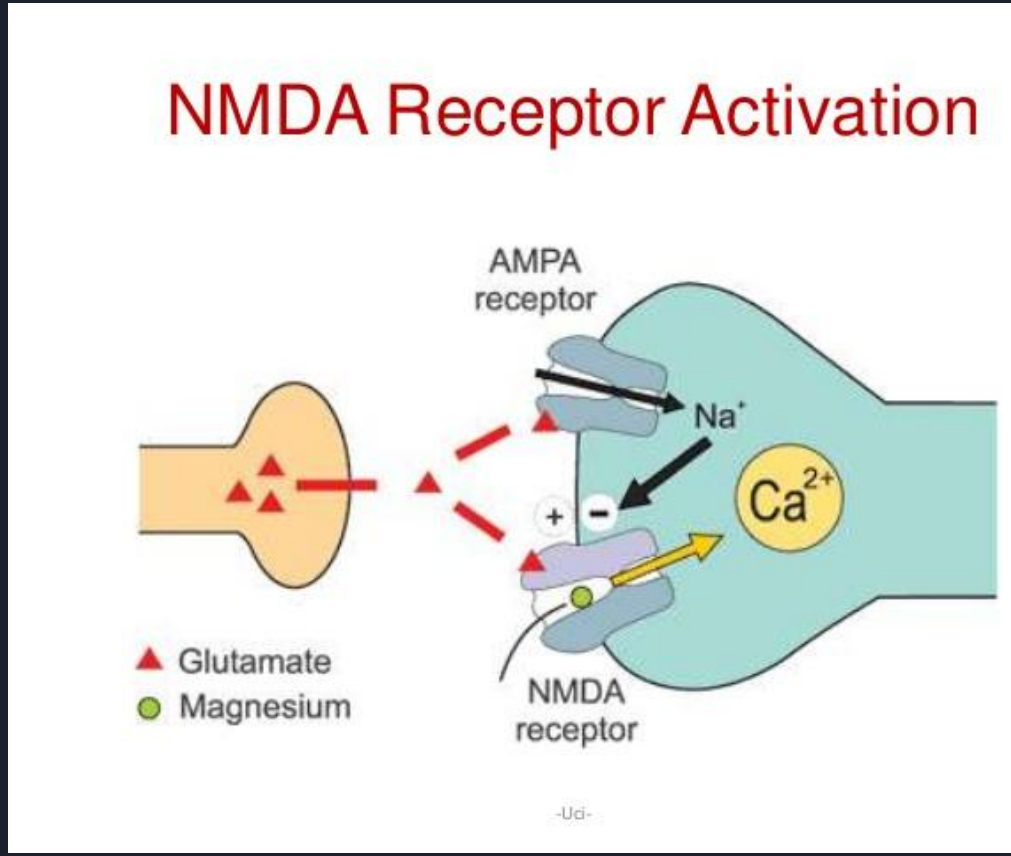
HOW DOES IT WORK - HYPOTHESIS

Targets glutamate (excitatory messenger)

Ketamine blocks the N-methyl-D-Aspartate receptor

Prevents the NMDA receptor from being activated by glutamate

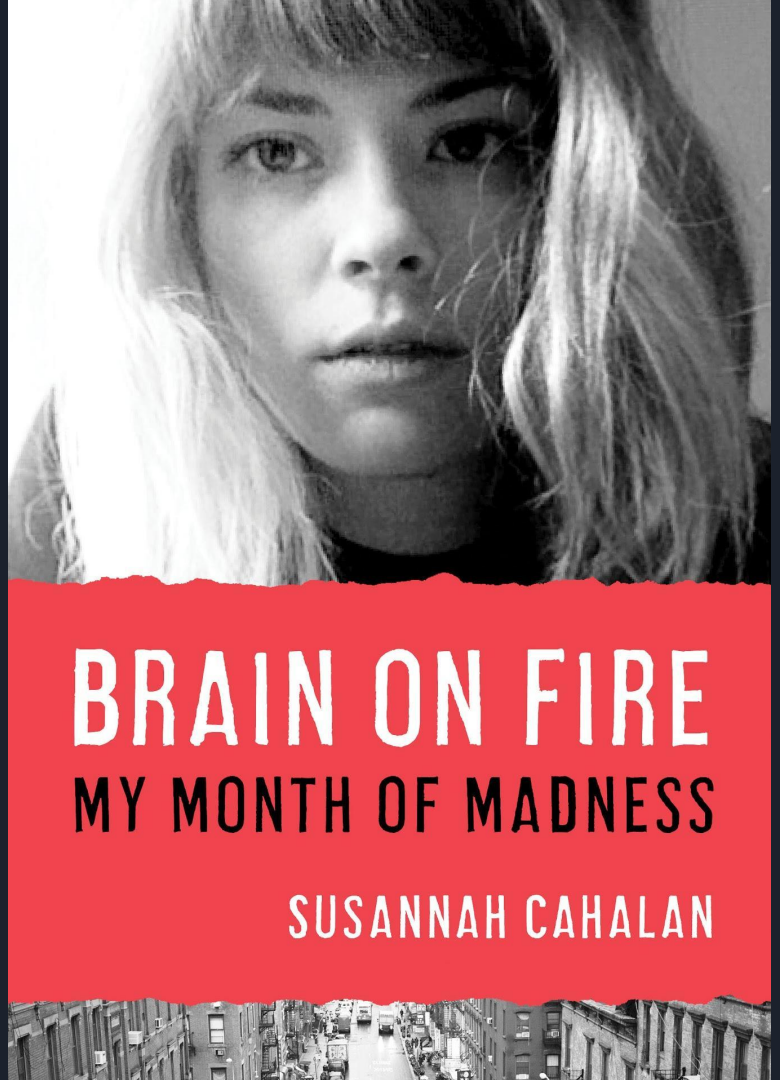
Belief that this is what allows for analgesic and anesthetic effects.



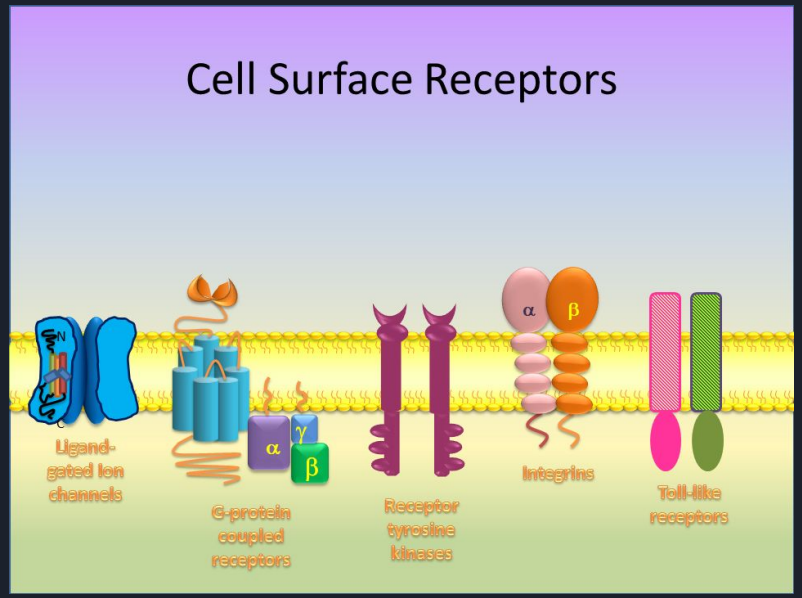
Anti NMDA receptor encephalitis:

Rapid progression of psychiatric and neuropsychiatric symptoms.

75% presents with seizures



Also has some direct and indirect effects on:



Mu, kappa, delta opioid receptor

Dopamine D2 receptors

Serotonin

Acetylcholine

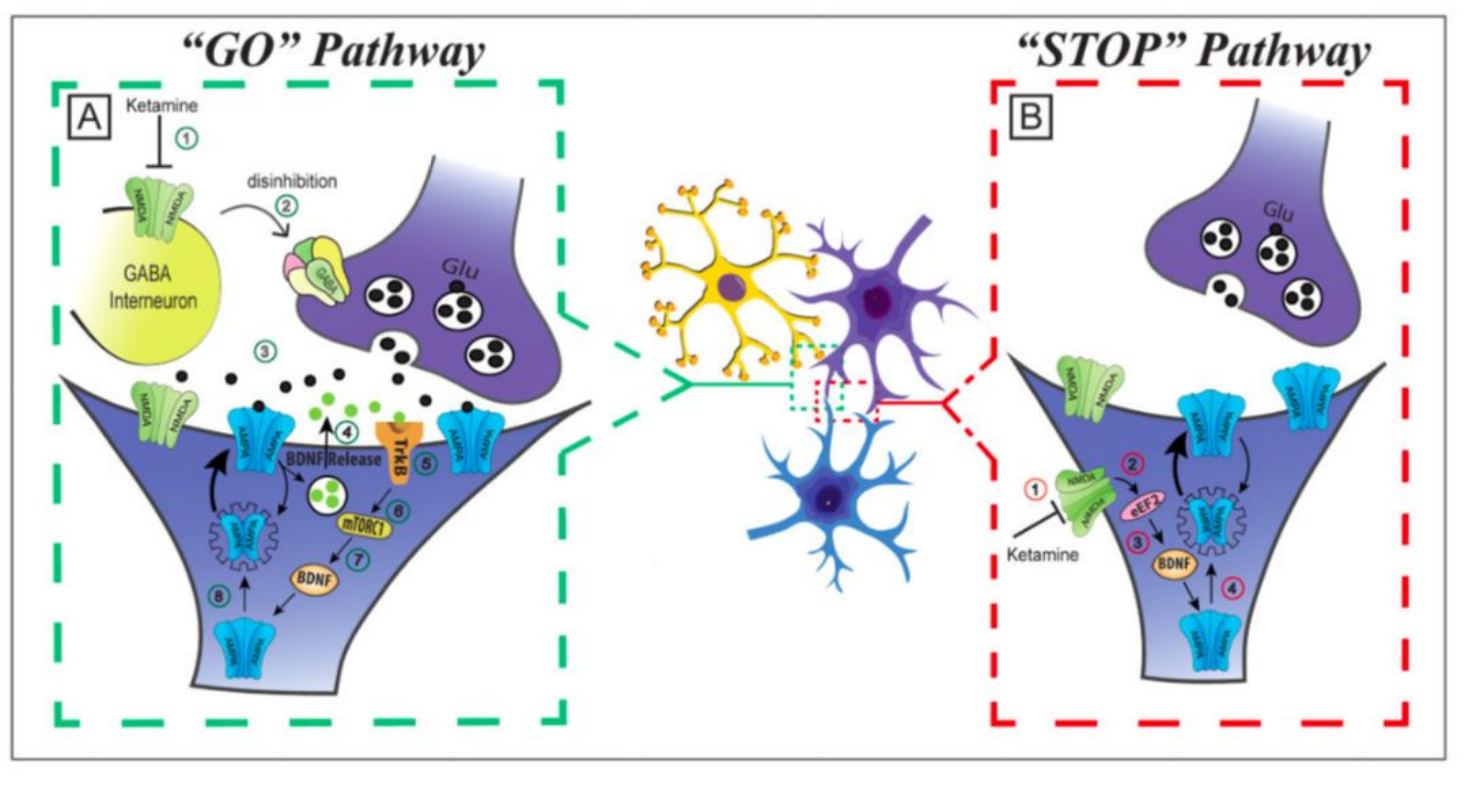
GABA

Cannabinoid

Nitric oxide

Sigma

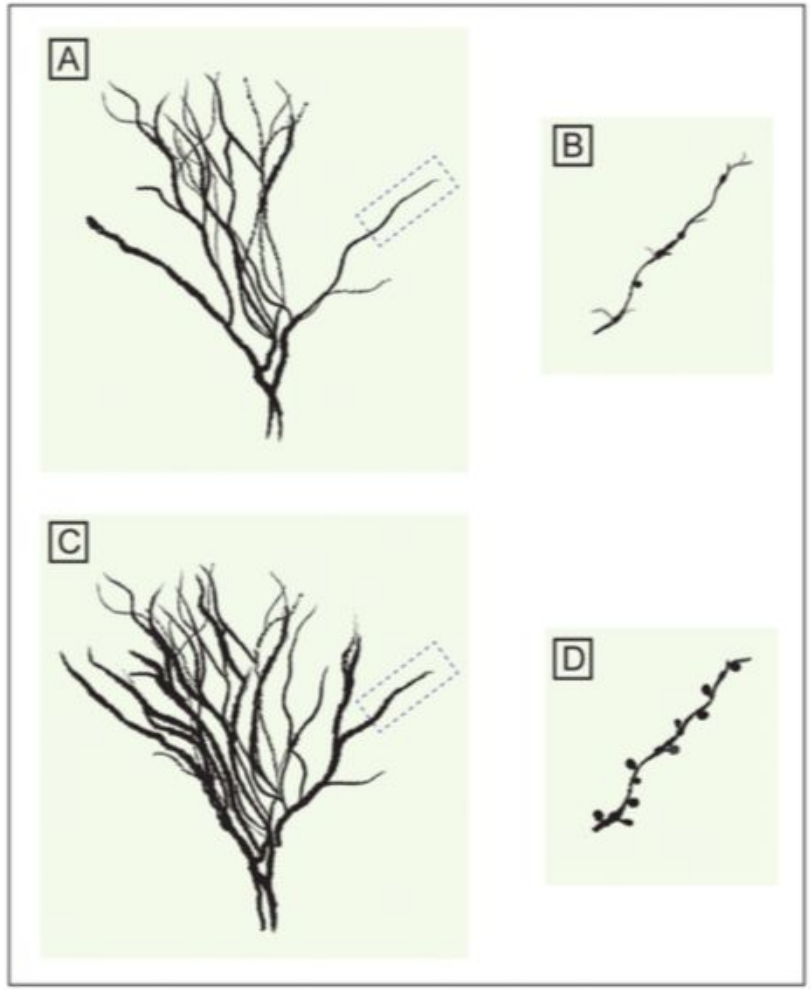
Increases BDNF, Protein Synthesis, Synaptic Strength, and Synaptogenesis



Chronic stress causes excess extracellular glutamate, and subsequent excitoxicity, leading to dendritic retraction, reduced dendritic arborization and spine density

24 hours after ketamine

nty-four hours post-treatment, subanesthetic dose of ketamine reverses the chronic stress-induced structural deficits culminating in rapid increases in spine density



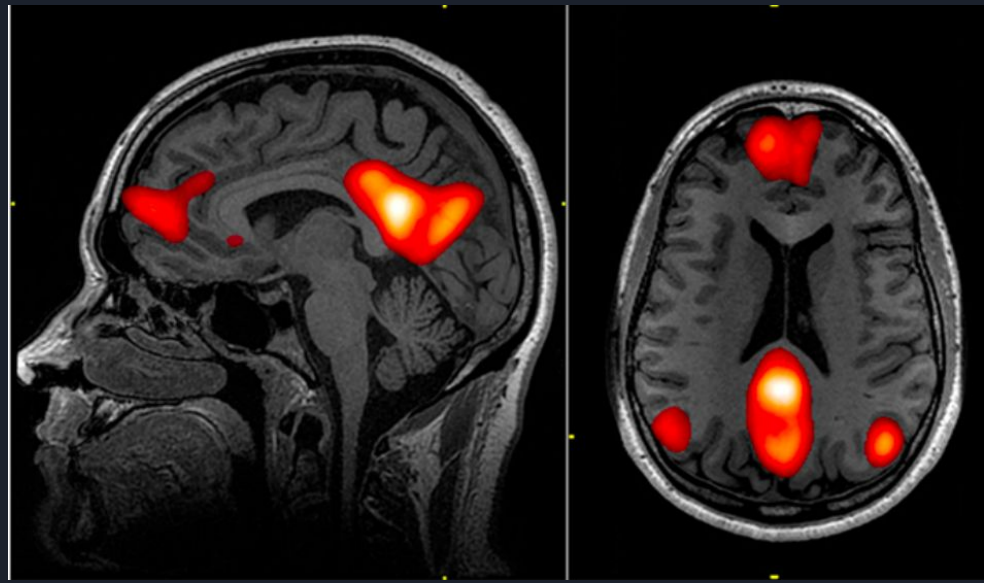
The Default Mode Network (DMN) Hypothesis

Certain portions of the brain that are active when you are resting, daydreaming, not engaged in tasks, & “mind wandering.”

DMN is proposed to play a role in depression, PTSD, schizophrenia, autism, and chronic pain.

Ketamine temporarily disrupts DMN activity and relationship of the DMN to other nodes of the brain.

Allowing the brain to come up with other alternative rest state activities.



Experience for the Patient - Non-ordinary states of consciousness (NOSC)

EMPATHOGENIC EXPERIENCE

Awareness of body; comfort and relaxation; reduced ego defenses; empathy, compassion, and warmth; love and peace; euphoria; mind is dreamy with non-specific colorful visual effects

OUT-OF-BODY EXPERIENCE (OBE)

Complete separation from one's body; significantly diminished ego defenses; visits to mythological realms of consciousness; encounters with non-terrestrial beings; emotionally intense visions (e.g., deceased relatives, spirits); vivid dreams of past and future incarnations; re-experiencing the birth process

Experience for the Patient - Non-ordinary states of consciousness (NOSC)

NEAR-DEATH EXPERIENCE (NDE)

Departure from one's body; complete ego dissolution/loss of identity; experienced physical (body) and psychological (mind) death; experience being a single point of consciousness simply aware of itself; reliving one's life aware of how actions have affected others, with moral judgment of self

EGO-DISSOLVING TRANSCENDENTAL EXPERIENCE (EDT)

Ecstatic state of the dissolution of boundaries between the self and external reality; complete dissolution of one's body and self (soul); transcending normal mass/time/space continuum; collective consciousness; unity with Nature/Universe; sacredness

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Revisiting the Hallucinogenic Potential of Ketamine

A Case Built on Current Research Findings

» David S. Mathai, MD, Sanjay J. Mathew, MD, Eric A. Storch, PhD, and Thomas R. Kosten, MD

Ketamine has caused quite a stir in psychiatric practice. Sub-anesthetic administrations of ketamine have been shown to markedly improve symptoms of depression and anxiety.[1] While the growing off-label use of ketamine speaks to the need for novel approaches to psychiatric care and treatment-resistant illness, it also presents an ethical dilemma, wherein widespread adoption has once again leaped ahead of scientific understanding.

The current literature suggests that therapeutic effects of ketamine involve modulation of glutamate neurotransmission, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor potentiation, downstream influences on neurotrophic signaling cascades and neuroplasticity, and functional changes in assorted neural networks. Additional work is necessary to clarify the importance and reliability of these biological findings.

Another arc to the ketamine story dates back to a decades-old era of psychedelic research and search for medications with transformative power. Indeed, although primarily conceptualized today as a dissociative anesthetic, ketamine has also been classified more broadly as a hallucinogen. Hallucinogens function by various pharmacological mechanisms

(CONTINUED ON PAGE 3)


DEPRESSION

BRIEF REPORTS

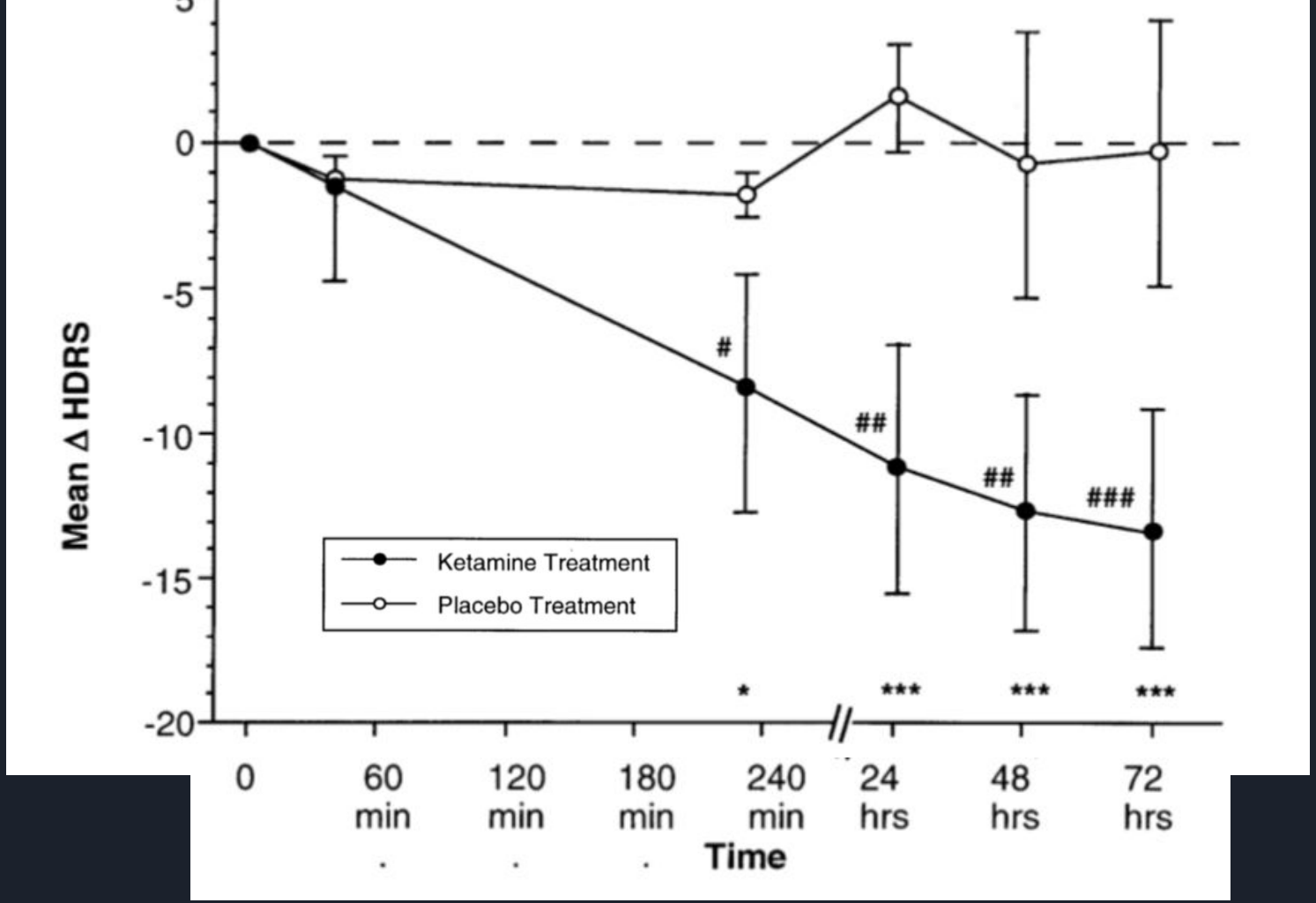
Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

First depression & ketamine study published in 2000, Society of Biological Psychiatry

7 subjects with depression (MDD)

Placebo controlled, double-blinded study.



Berman, et al. Society of Biological Psychiatry. 2000.

Current Neuropharmacology, 2014, *12*, 444-461

The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review

Gianluca Serafini[1,*], Robert H. Howland[2], Fabiana Rovedi[1], Paolo Girardi[1] and Mario Amore[3]

[1]*Department of Neurosciences, Mental Health and Sensory Organs – Sant'Andrea Hospital, Sapienza University of Rome, Italy;* [2]*University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;* [3]*Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genova, Genova, Italy*

Abstract: *Background*: At least 10-20% of the patients suffering from depression meet criteria for treatment-resistant depression (TRD). In the last decades, an important role of glutamate in mood modulation has been hypothesized and ketamine, a non noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptors, has been demonstrated to be effective in both MDD and TRD. However, concerns emerged about the optimal dosage, and frequency of administration of this treatment.

Methods: aiming to systematically review the current literature focusing on the main pharmacological properties and impact of ketamine in TRD, a detailed literature search in PubMed/Medline and ScienceDirect databases was conducted. Twenty-four manuscripts including a total of 416 patients fulfilled inclusion criteria.

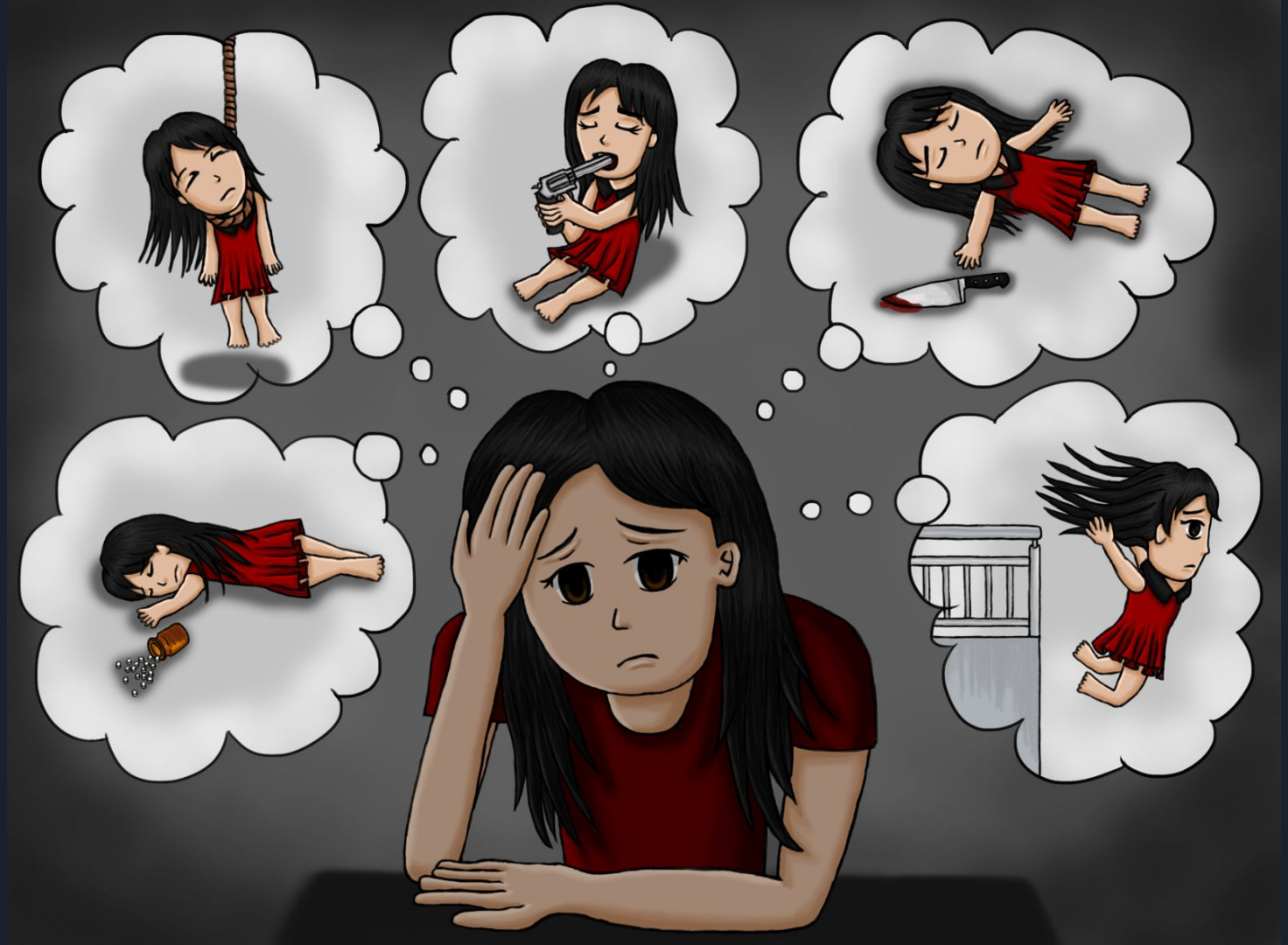
Results: Most studies demonstrated that the NMDA antagonist ketamine has rapid antidepressant effects in TRD patients, confirming the active role of glutamate in the pathophysiology of this complex condition. Ketamine has been demonstrated to be rapidly effective and was associated with a significant clinical improvement in depressive symptoms within hours after administration. Also, ketamine was also found to be effective in reducing suicidality in TRD samples

Systematic Review for Treatment Resistant Depression

Reviewed 24 manuscripts, including 416 patients

Results: Ketamine has rapid antidepressant effects within hours of administration and effective in reducing suicidality.

Limits: Need more studies on sustained effects of ketamine infusions for long-term efficacy.



Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial

Michael F. Grunebaum, M.D., Hanga C. Galfalvy, Ph.D., Tse-Hwei Choo, M.P.H., John G. Keilp, Ph.D., Vivek K. Moitra, M.D., Michelle S. Parris, B.A., Julia E. Marver, B.A., Ainsley K. Burke, Ph.D., Matthew S. Milak, M.D., M. Elizabeth Sublette, M.D., Ph.D., Maria A. Oquendo, M.D., Ph.D., J. John Mann, M.D.

Objective: Pharmacotherapy to rapidly relieve suicidal ideation in depression may reduce suicide risk. Rapid reduction in suicidal thoughts after ketamine treatment has mostly been studied in patients with low levels of suicidal ideation. The authors tested the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder.

Method: In a randomized clinical trial, adults (N=80) with current major depressive disorder and a score ≥4 on the Scale for Suicidal Ideation (SSI), of whom 54% (N=43) were taking antidepressant medication, were randomly assigned to receive ketamine or midazolam infusion. The primary outcome measure was SSI score 24 hours after infusion (at day 1).

Results: The reduction in SSI score at day 1 was 4.96 points greater for the ketamine group compared with the midazolam group (95% CI=2.33, 7.59; Cohen's d=0.75). The proportion of responders (defined as having a reduction ≥50% in SSI score) at day 1 was 55% for the ketamine group and 30% for the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; number needed to treat=4.0). Improvement in the Profile of Mood States depression subscale was greater at day 1 for the ketamine group compared with the midazolam group (estimate=7.65, 95% CI=1.36, 13.94), and this effect mediated 33.6% of ketamine's effect on SSI score. Side effects were short-lived, and clinical improvement was maintained for up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up.

Conclusions: Adjunctive ketamine demonstrated a greater reduction in clinically significant suicidal ideation in depressed patients within 24 hours compared with midazolam, partially independently of antidepressant effect.

AJP in Advance (doi: 10.1176/appi.ajp.2017.17060647)

Grunebaum, et al. American Journal of Psychiatry. 2017.

N = 54, Voluntary inpatients to psychiatric unit.

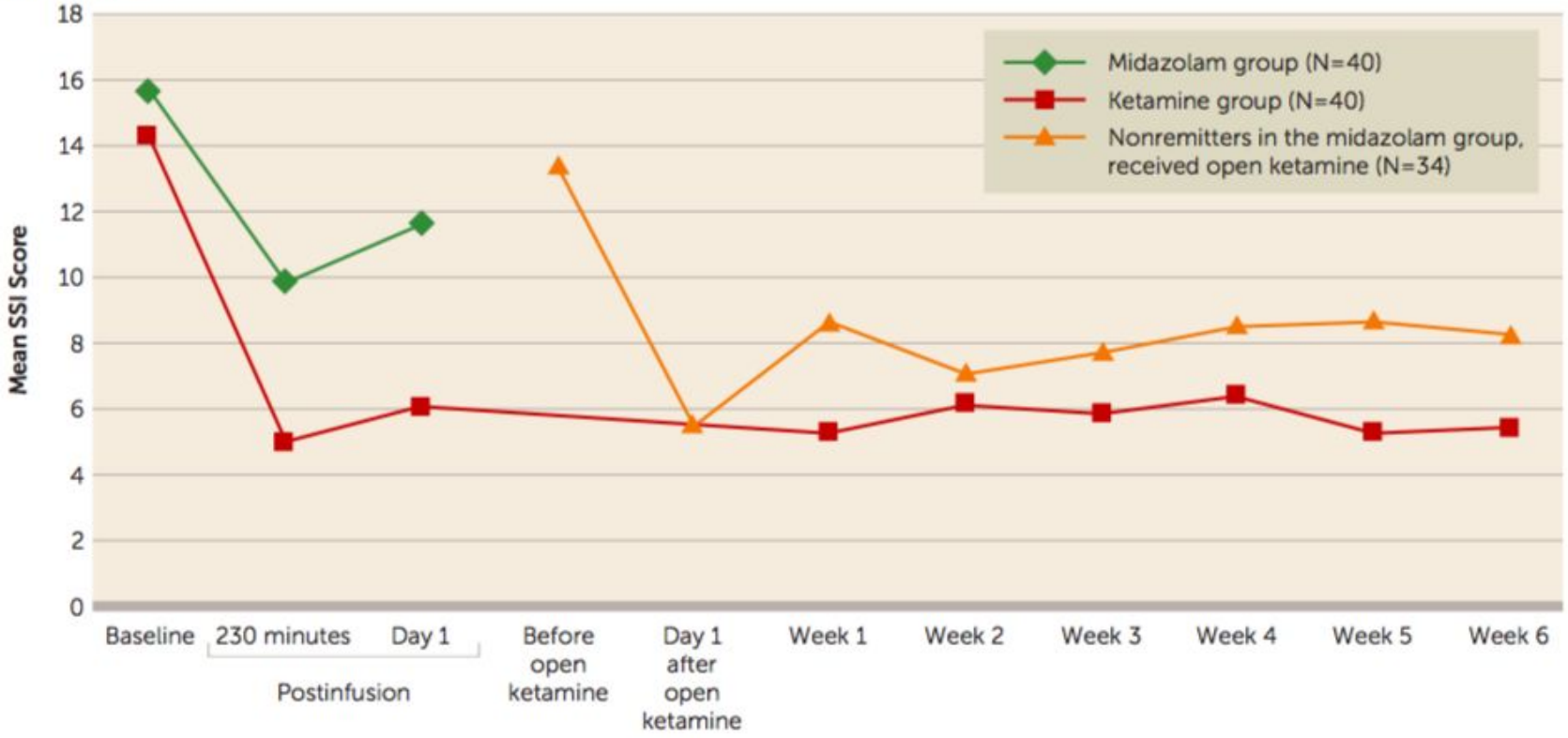
Double blinded study with active placebo (midazolam)

0.5mg/kg of IV ketamine vs 0.02mg/kg midazolam over 40 minutes

Primary outcome: Scale for Suicidal Ideation (SSI) at 24 hour follow-up

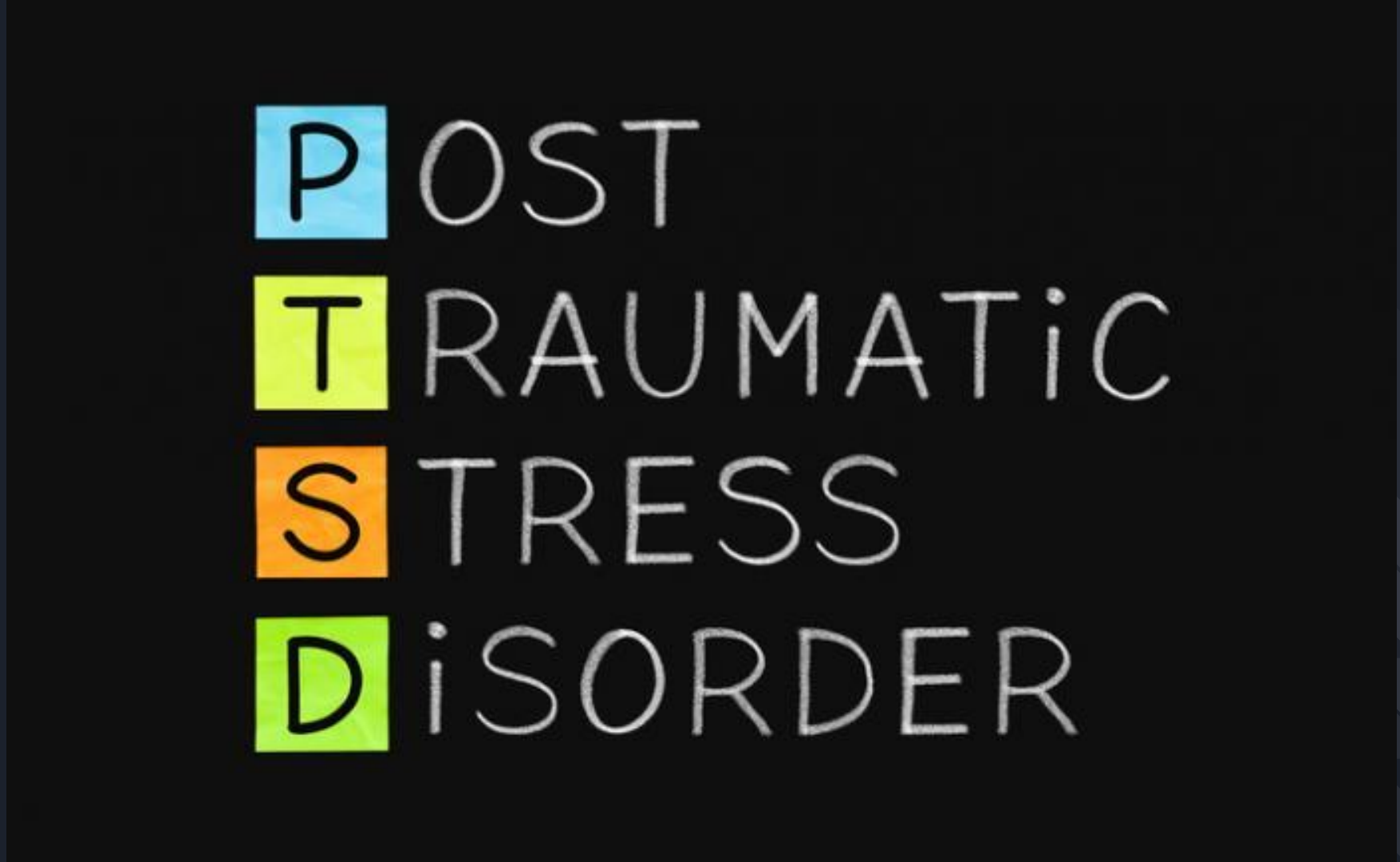
Offered non-remitters in midazolam group to cross-over to ketamine

FIGURE 1. Change in Suicidal Ideation Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]



Is this a *future* option for patients on 5150 or *instead* of 5150*?

(*in conjunction with close psychiatric and social support)


POST
TRAUMATIC
STRESS
DISORDER

Original Investigation

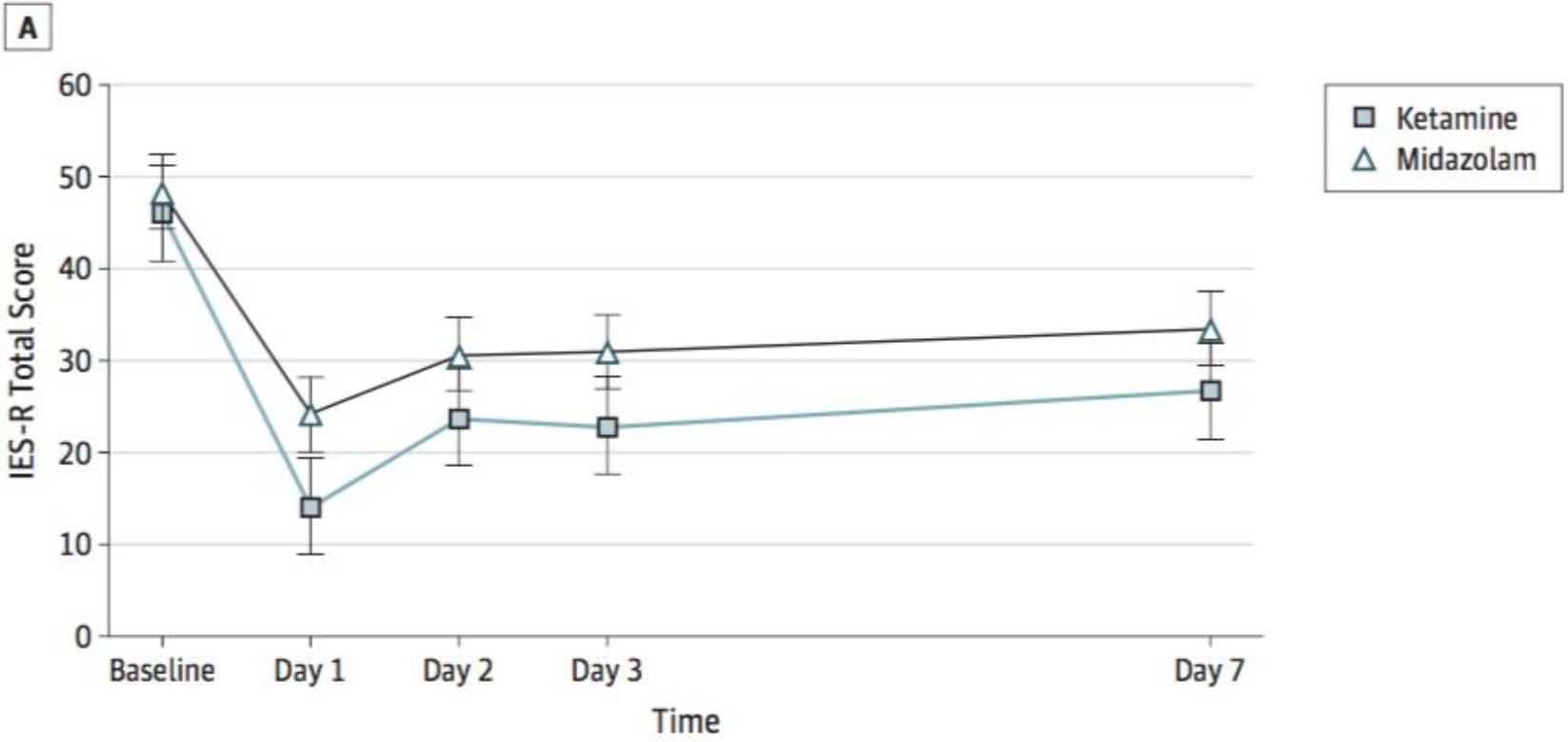
Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder
A Randomized Clinical Trial

Adriana Feder, MD; Michael K. Parides, PhD; James W. Murrough, MD; Andrew M. Perez, MD; Julia E. Morgan, BA; Shireen Saxena, MScPH; Katherine Kirkwood, MS; Marije aan het Rot, PhD; Kyle A. B. Lapidus, MD, PhD; Le-Ben Wan, MD, PhD; Dan Iosifescu, MD; Dennis S. Charney, MD

Feder, et al. JAMA Psychiatry. 2014.

N = 41, Single Infusion. RCT. Midazolam vs. Ketamine

Figure 2. Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period



frontiers in Psychiatry

MINI REVIEW
published: 24 July 2018
doi: 10.3389/fpsyt.2018.00277

Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review

Jennifer L. Jones[1]*, *Camilo F. Mateus*[1], *Robert J. Malcolm*[1], *Kathleen T. Brady*[1,2] and *Sudie E. Back*[1,2]

[1] *Medical University of South Carolina, Charleston, SC, United States,* [2] *Ralph H. Johnson VA Medical Center, Charleston, SC, United States*

Background: Despite advances in behavioral and pharmacotherapy interventions, substance use disorders (SUDs) are frequently refractory to treatment. Glutamatergic dysregulation has received increasing attention as one common neuropathology across multiple substances of abuse. Ketamine is a potent N-methyl-D-aspartate (NMDA) glutamatergic receptor antagonist which has been found to be effective in the treatment of severe depression. Here we review the literature on the efficacy of ketamine in the treatment of SUDs.

Methods: A systematic review of the PubMed, Scopus, and ClinicalTrials.gov databases was undertaken to identify completed and ongoing human studies of the effectiveness of ketamine in the treatment of SUDs between January 1997 and January 2018.

Results and conclusion: Seven completed studies were identified. Two studies focused on alcohol use disorder, two focused on cocaine use disorder, and three

OPEN ACCESS

Edited by:
Wendy J. Lynch,
University of Virginia, United States

Review article. *Frontiers in Psychiatry*. July 24, 2018.

7 studies identified

2 studies on cocaine: Overall, found improvements in craving, motivation, & decreased cocaine usage . One study found that ketamine increased motivation to quit cocaine over lorazepam (median score of 0.15 vs. 3.6, p = 0.012) and reduced cocaine craving on the VAS by a mean of 168 mm (a 60% change, p = 0.012).

2 studies on alcohol: Overall, improvement in abstinence rates. One study found that 1-year abstinence rates were 65.8% in the ketamine-treated group compared to 24% in the follow-up as usual comparison group ($p < 0.01$).

3 studies on opioids: Overall, improvement In abstinence rates. One study found repeated 3 ketamine treatments with psychotherapy had a 50% abstinence rate at 1 year follow up.

BLOG | ALCOHOLISM TREATMENT

Scientists Are Testing Ketamine as a Treatment for Alcoholism

Research has helped us to gain a better understanding of addiction while providing the opportunity to develop new, innovative and more effective ways of treating this deadly disease. Through observation and study, we've amassed a plethora of different treatments and therapeutic techniques that are effective in addressing substance abuse problems.

On This Page:

While we've had small victories, our work is far from over. No matter how much we've learned about addiction and recovery to date, recovery from drug addiction and alcoholism remains a relatively long and arduous process. In fact, we've had to contend with the fact that there's no medication capable of curing a person of addiction. But that hasn't stopped us from testing medications as a means of treating certain aspects of the disease. For example, medications like methadone and buprenorphine are used today in maintenance therapies, allowing individuals to effectively replace chemical intoxicants with pharmaceuticals as part of a supervised treatment program.[1] However, a few notable studies have investigated the use of very different medications as a type of

Ketamine for reduction of Alcoholic Relapse (KARE)

+ Meet the team

KARE is a new and innovative multi-disciplinary project, and stands for "Ketamine for reduction of Alcoholic Relapse".

This clinical trial explores the combined use of psychological therapy and a low dose of ketamine as a possible treatment for alcoholism. KARE is a multi-site project running in both the South West of England as well as London.

Severe alcohol use disorder affects nearly 4 million people in the UK, with devastating consequences to lives. Staying sober is key to reducing the harm that alcohol can do to physical and mental health. Unfortunately, treatments to help people stop drinking alcohol have been shown to be limited in their effectiveness, and people often return to drinking after only a short time of being sober.

If you would like to hear more about this trial or are interested in taking part, please contact us via one of the following methods:

- **Email:** kare@exeter.ac.uk
- **Telephone:** +44 (0)1392 724070

Downsides/Dangers/Costs

Emergence phenomena can occur in 10-20% of adult patients after ketamine PRS.

Set and Setting

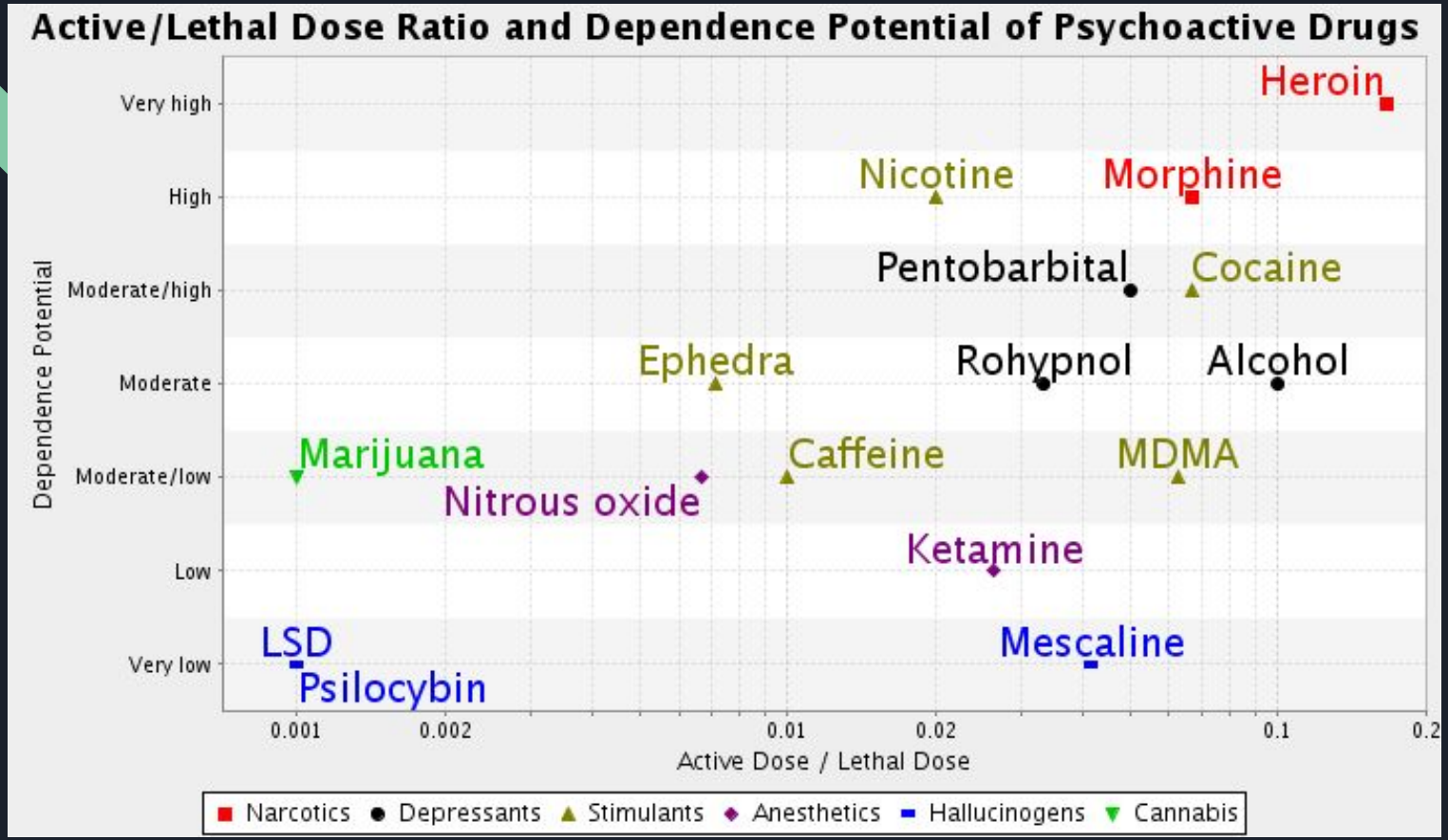
Laryngospasm can also occur (4.2/1,000)

Larson's Point

Agitation (164.1/1,000)

Vomiting (170/1,000)

Elevated BP & Pulse


Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs
Dependence Potential
Very high
High
Moderate/high
Moderate
Moderate/low
Low
Very low
Heroin
Nicotine
Morphine
Pentobarbital
Cocaine
Ephedra
Rohypnol
Alcohol
Marijuana
Caffeine
MDMA
Nitrous oxide
Ketamine
LSD
Mescaline
Psilocybin
0.001
0.002
0.01
0.02
0.1
0.2
Active Dose / Lethal Dose
Narcotics
Depressants
Stimulants
Anesthetics
Hallucinogens
Cannabis

CASE STUDIES

About Reset Ketamine

Biopsychosocialspiritual Medicine and Approach to Health.

Preparation, Intention, and Integration are critical.

We provide 40 minute, 80 minute, and 120 minute ketamine infusions.

Ranging from 0.5 mg/kg to 3 mg/kg, depending upon time frame.

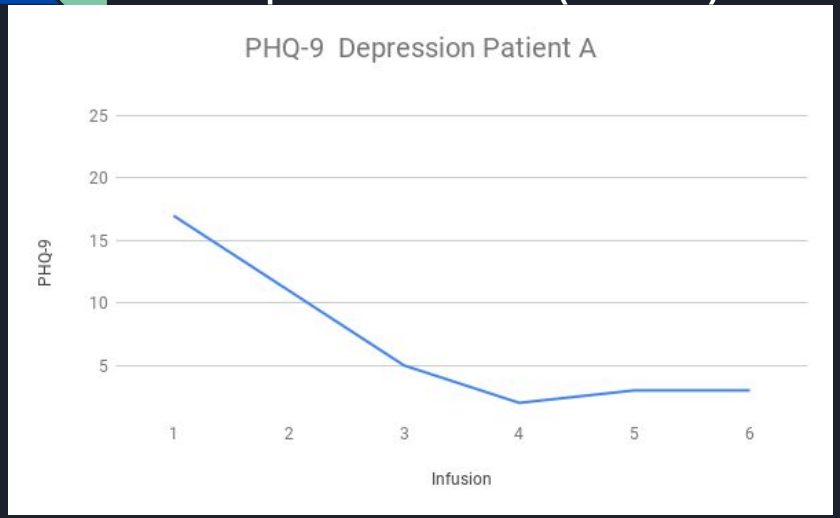
We recommend 6 initial infusions spread over a 2-4 week time frame.

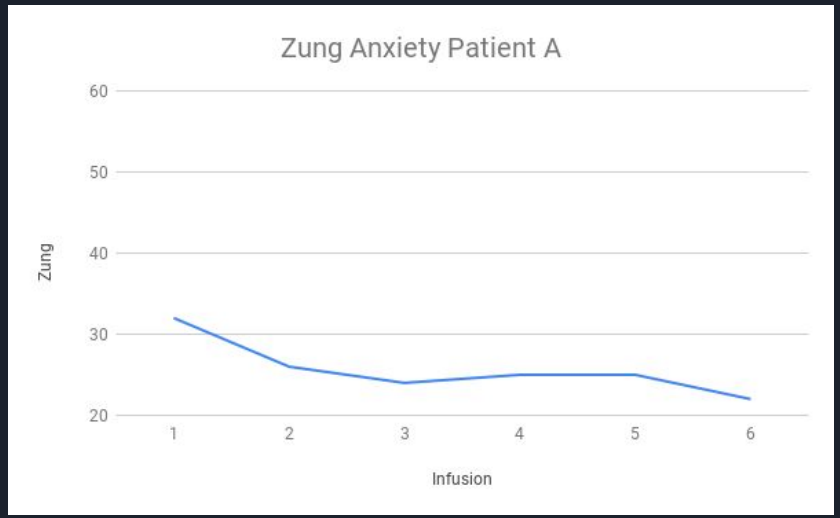
Some patients need booster infusions, ranging from 1 month to 6 months.

10-20% of patients (non-responders) get no relief from ketamine and we usually know after 3-4 infusions.

Not covered by insurance at this time. “Off-Label Use.”

Patient A - 55 YO M with treatment-resistant depression (TRD)





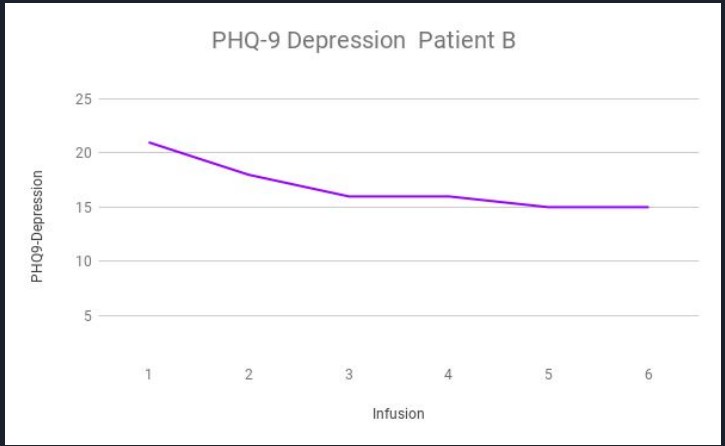
PHQ9
1-4 Minimal depression
5-9 MIld depression
10-14 Moderate depression
15-19 Moderate severe depression
20-27 Severe depression

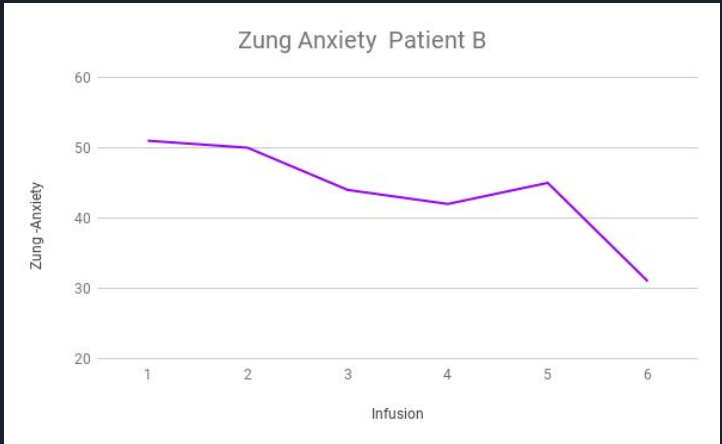
Zung
20-44 Normal Range
45-59 Mild to Moderate Anxiety Levels
60-74 Marked to Severe Anxiety Levels
75-80 Extreme Anxiety Levels

“My depression is simply gone. Now, I can mold my life the way I want it.”

“I can’t remember when I have felt so good. Thank you so much for your help, I feel like I have a future now.”

Patient B: 43 yo F Military Veteran with anxiety, TRD, PTSD, and chronic pain.





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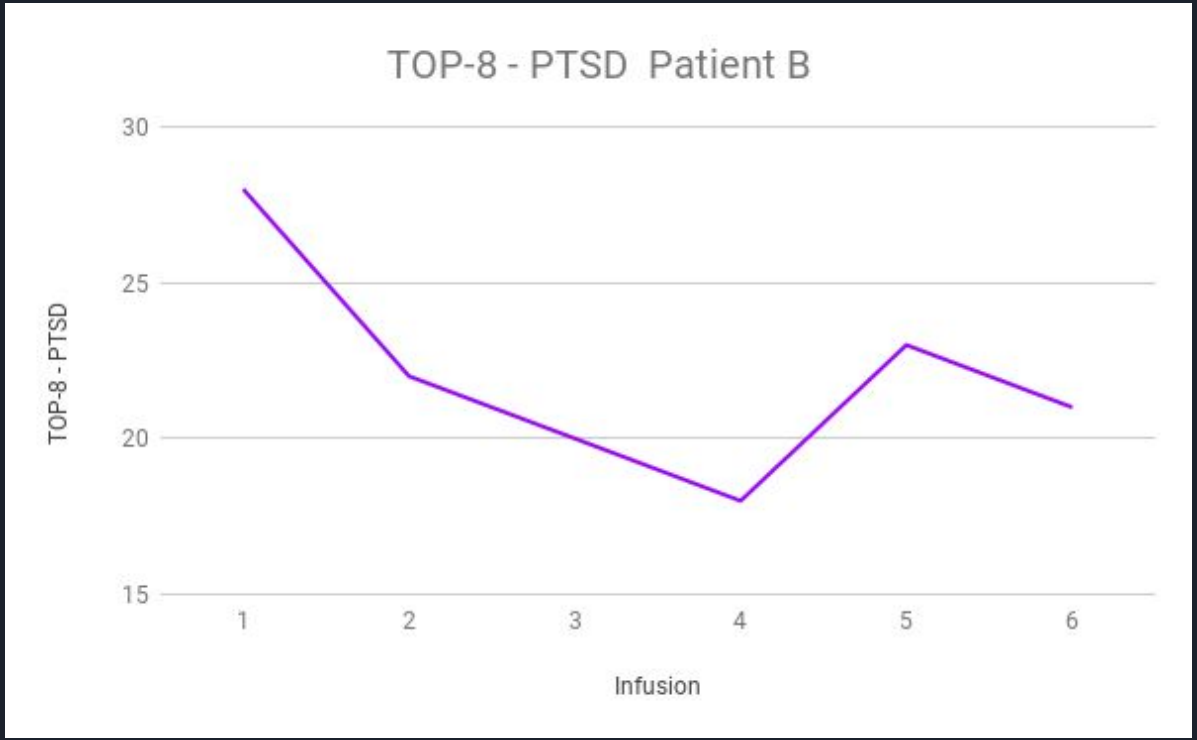
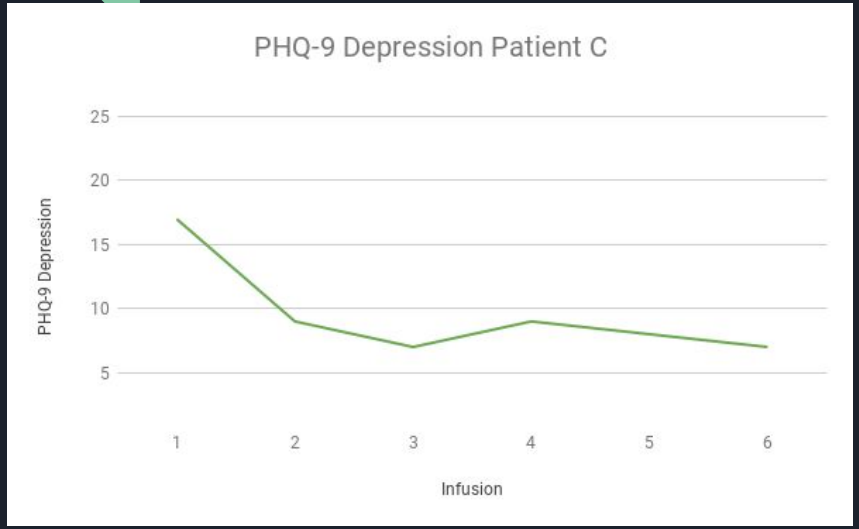
Patient B continued...

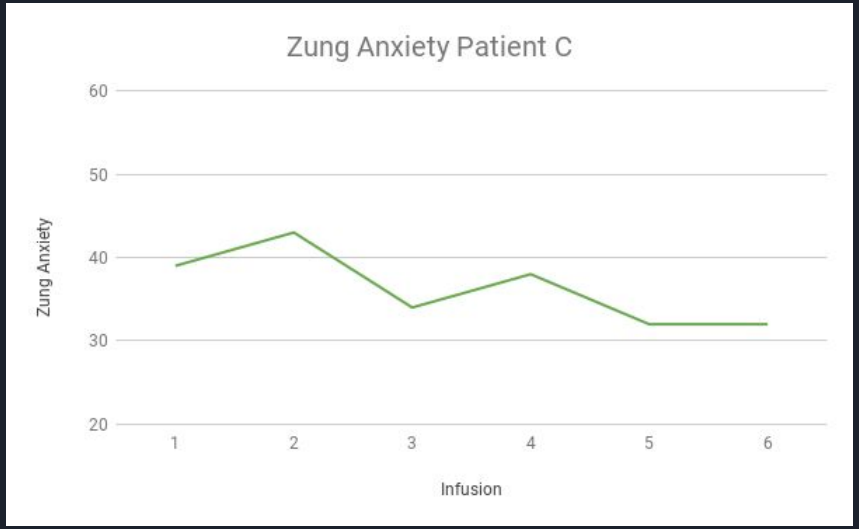


“I am feeling good. I had a good session at my doctor’s office and she said my numbers haven’t looked so good since I started counseling with her. I was pleased, to say the least.”

“I don’t need as much Percocet and Neurontin for my pain. And I’m sleeping better.”

Patient C: 49 YO M with depression and social anxiety





PHQ-9
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5-9 MIld depression
10-14 Moderate depression
15-19 Moderate severe depression
20-27 Severe depression

Zung
20-44 Normal Range
45-59 Mild to Moderate Anxiety Levels
60-74 Marked to Severe Anxiety Levels
75-80 Extreme Anxiety Levels

“This is the first time in my adult life that I feel something is actually changing.”

“I had a great weekend. I have noticed a big improvement in my ability to talk to people and I have a lot more desire to connect with people. So I’m excited and feeling hopeful.”

Conclusions

1. Ketamine is a safe medicine used for over 50 years
2. It is an NMDA receptor antagonist, increases BDNF, disrupts the DMN, and allows for neuroplasticity.
3. Effective in treating Depression, PTSD, Suicidal Ideation, and Addiction.
4. Limitations are no long term studies, abuse potential (low), insurance coverage, and side effects.
5. Ketamine can play a powerful role in transformation but is only one part of the solution

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THANK YOU!

Questions?

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