Hope.
Science.
Life.

NASDAQ: **NRXP**

NMDA Antagonists for Suicidal Depression

Evidence of Efficacy is in Hand
Risks must be balanced

Jonathan C. Javitt, MD, MPH
January 2024

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Suicidality is a National Crisis

Developing a cure for suicidality has been our mission since 2015

Launching NRX-100 (IV Ketamine)

If approved, this will be the first drug to have a label for treatment of suicidal ideation

The Washington Post

Opinion | Suicide is a national epidemic. We need to treat it like one.

By Jonathan Javitt
July 5, 2018 at 7:03 p.m. EDT

Fashion designer Kate Spade and chef and writer Anthony Bourdain. (Bebeto Matthews, Andy Kropa/AP)

Jonathan Javitt is an adjunct professor at the Johns Hopkins School of Medicine and founder and chief executive of NeuroRx, a start-up biopharma company. He served in health-care advisory roles in the Reagan, George H.W. Bush, Clinton and George W. Bush administrations.

Hope. Science. Life.

https://www.washingtonpost.com/opinions/suicide-is-a-national-epidemic-we-need-to-treat-it-like-one...

Suicidality is a National Crisis

Suicide kills >50,000 Americans every year
Disproportionately affecting people with Bipolar Disorder

Over
48,000
people died by suicide in 2021

1 death every
11 minutes

Many adults think about suicide or attempt suicide

12.3 million
Seriously thought about suicide

3.5 million
Made a plan for suicide

1.7 million
Attempted suicide

Suicide takes our best and brightest

https://www.cdc.gov/suicide/facts/index.html#:~:text=In%202021%2C%20an%20estimated%2012.3,and%201.7%20million%20attempted%20suicide.&text=Suicide%20affects%20people%20of%20all%20ages.

Why IV Ketamine / Why Now

After 20 years of Ketamine research, there are key changes to ecosystem

Compelling evidence of ketamine effectiveness and superiority vs. ECT

- Numerous small trials show effect
- NIH-funded multicenter dose ranging trial confirms the dose
- Two well-controlled randomized efficacy trials (France and USA)
- Large non-inferiority trial vs. ECT actually showed superiority

Failure of Nasal Ketamine to reduce suicidality and depression[1]

- Multiple pharma companies have failed
- Nasal ketamine produces variable and non steady-state blood levels
- Nasal congestion and applicator positioning will cause intra-patient variability
- Once administered, nasal ketamine cannot be stopped for side effects

Rapid Proliferation of Ketamine Clinics and unlicensed compounding

- Fortunately for patients, there are well-staffed clinics providing safe care
- There are also enterprises that are manufacturing a non-approved drug product and marketing across state lines under pharmacy licenses
- Without FDA labeling, only those who can pay cash can get treated
- There is clear risk to patients if treatment is denied and clear risk to patients if unregulated treatment is allowed

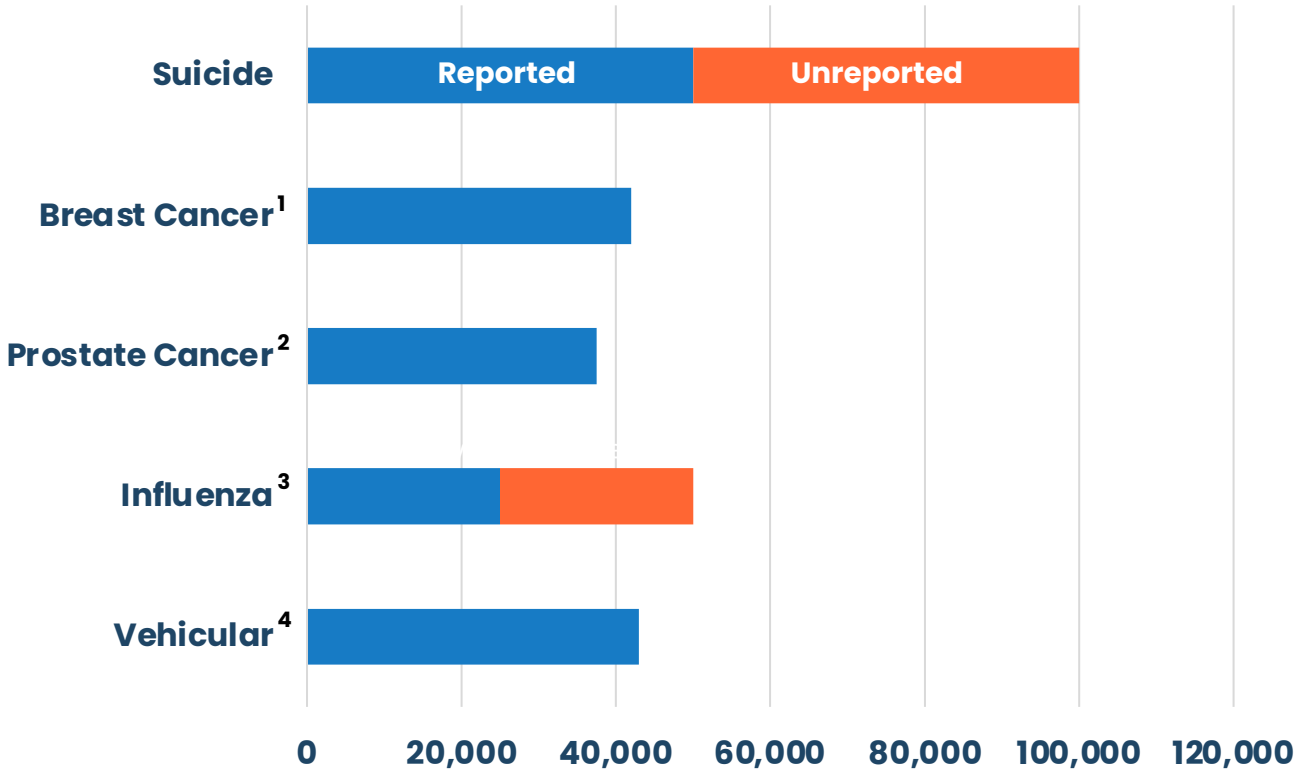
Urgent need for an FDA-approved form of ketamine:

- Need for proper labeling and physician training under a REMS
- Modern formulation with physiologic pH (generic formulation is pH 2.0)
- Need for presentation that can be used in the clinic without a compounding pharmacy
- FDA requested that NRx submit an NDA for ketamine in January 2023 Type B meeting

https://endpts.com/seelos-stock-plunges-by-over-75-after-ketamine-drug-for-suicide-prevention-fails-a-phii-trial/

Suicide is an underreported Cause of Death

US Common Causes of Death



Unlike other common causes of death, suicide

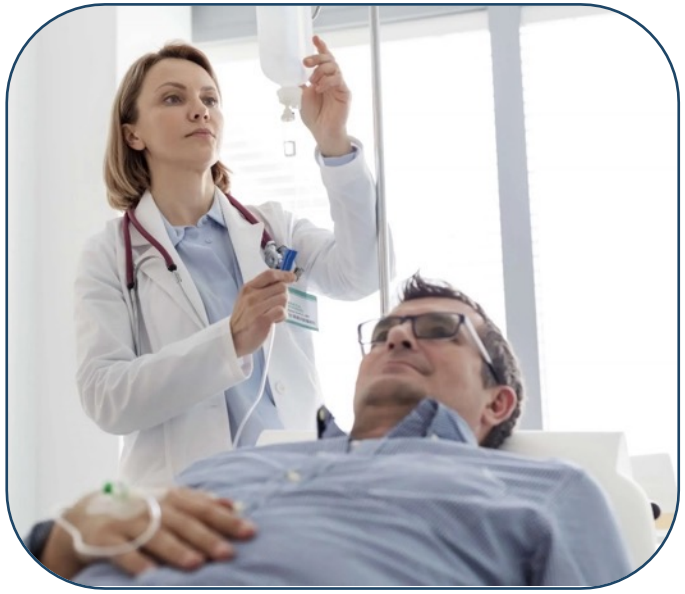
- **Is allocated minimal research funding**
- **Has no approved drugs**
- **Carries enormous social stigma**
- **Can result in incarceration, involuntary treatment with debilitating therapy**
- **Is frequently treated as a psychological, rather than biological disease**

1. https://www.cdc.gov/cancer/breast/basic_info....
2. https://www.cancer.org/cancer/types/prostate-cancer/about/...
3. https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%20estimates,34%2C700%20deaths%20from%20prostate%20cancer
4. https://www.statista.com/statistics/1124915/flu-deaths-number-us/

No FDA-Approved Medication for Suicidal Depression

Only FDA-approved therapy is Electro-Convulsive Therapy (ECT)

IV Ketamine is used off-label
But not FDA-approved
Not reimbursed by Payers



Ketamine Binds to the NMDA Receptor to treat Depression and Suicidality
Developing NRX-100 (IV Racemic Ketamine) as an FDA-approved treatment

125 Drugs for Depression and They All Cause Suicide

For 70 years, we have been looking at the wrong neurochemical pathway (serotonin)

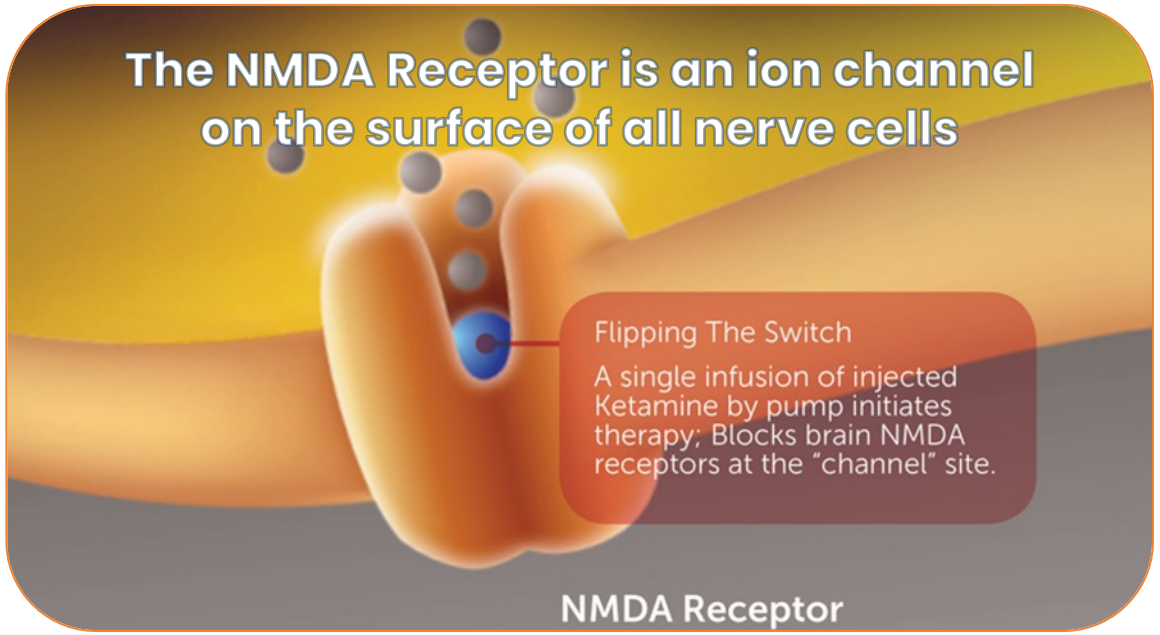
- **No approved drug is shown to decrease suicidal ideation. although esketamine reduces depression in patients with suicidal ideation**
- **Every antidepressant carries a Black Box Warning label against suicide (except esketamine)**
- **All drugs that raise brain serotonin levels cause akathisia which is closely linked to suicide**

There is now overwhelming evidence that NMDA antagonist drugs rapidly reduce suicidal ideation

NMDA Antagonists Decrease Suicidal Ideation:
Uniting Psychiatry & Neurobiology

NMDA is an ION channel that regulates Synaptic Plasticity and Speed of Thought

› Total Blockade› Thoughts race uncontrollably, mania and psychosis
› High NMDA activity› Low ideation, rumination, depression and suicide



NMDA antagonists decrease symptoms of depression and chronic pain in experimental models and clinical studies.

NMDA antagonists "restore synaptic plasticity" the brain by stimulating new connections between brain cells.

NMDA antagonists "modulate cortex gluatamate levels" in the brain as seen on Magenetic Resonance Spectroscopy.

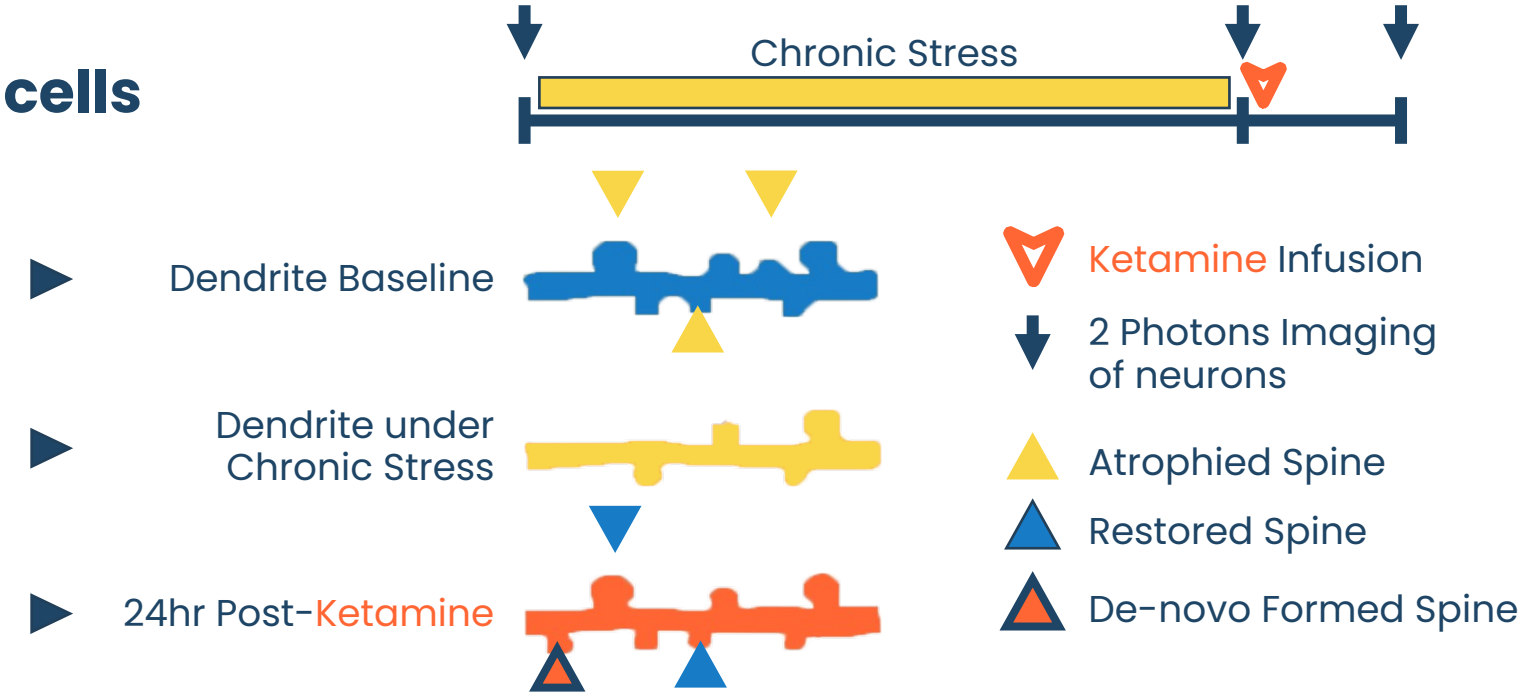
“Re-wiring the Brain,” as shown in the laboratory

Ketamine’s effect on brain cells

High levels of NMDA activity are shown to cause atrophy of the “dendritic spines” that connect brain cells

Loss of dendritic spines is associated with depression-related behavior

NMDA blockade with ketamine is demonstrated to restore lost dendritic spines, while simultaneously reducing depression-related behavior



Chronic Stress

- Clustered Dendridic Spine Loss
- Ensemble Activity
- Depression-related Behavior

Ketamine

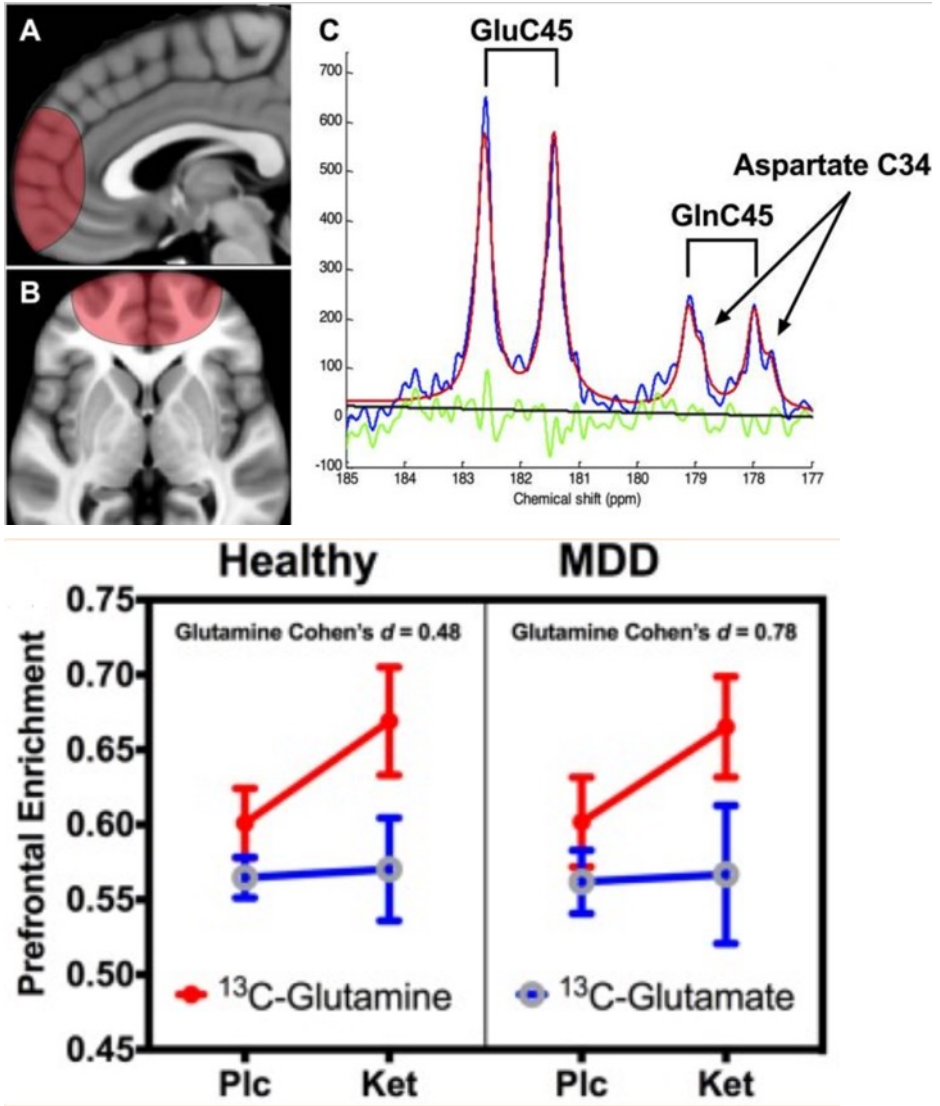
- Clustered Dendridic Spine Formation and Restores Spine Loss
- Ensemble Activity
- Depression-related Behavior

Moda-Sava RN, Murdock MH, Parekh, et.al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 2019 April 12;364

Ketamine increases cortical glutamine levels and reduces depression

- C13 labeling was used to distinguish between glutamine and glutamate
- Glutamine is known to drive synaptic plasticity
- Statistically significant correlation between increased glutamine and CADSS depression score (r2=-.54, P<.05, effect size =1.3

Demonstrated correlation between neurochemical changes in the human brain and corresponding change in depression score

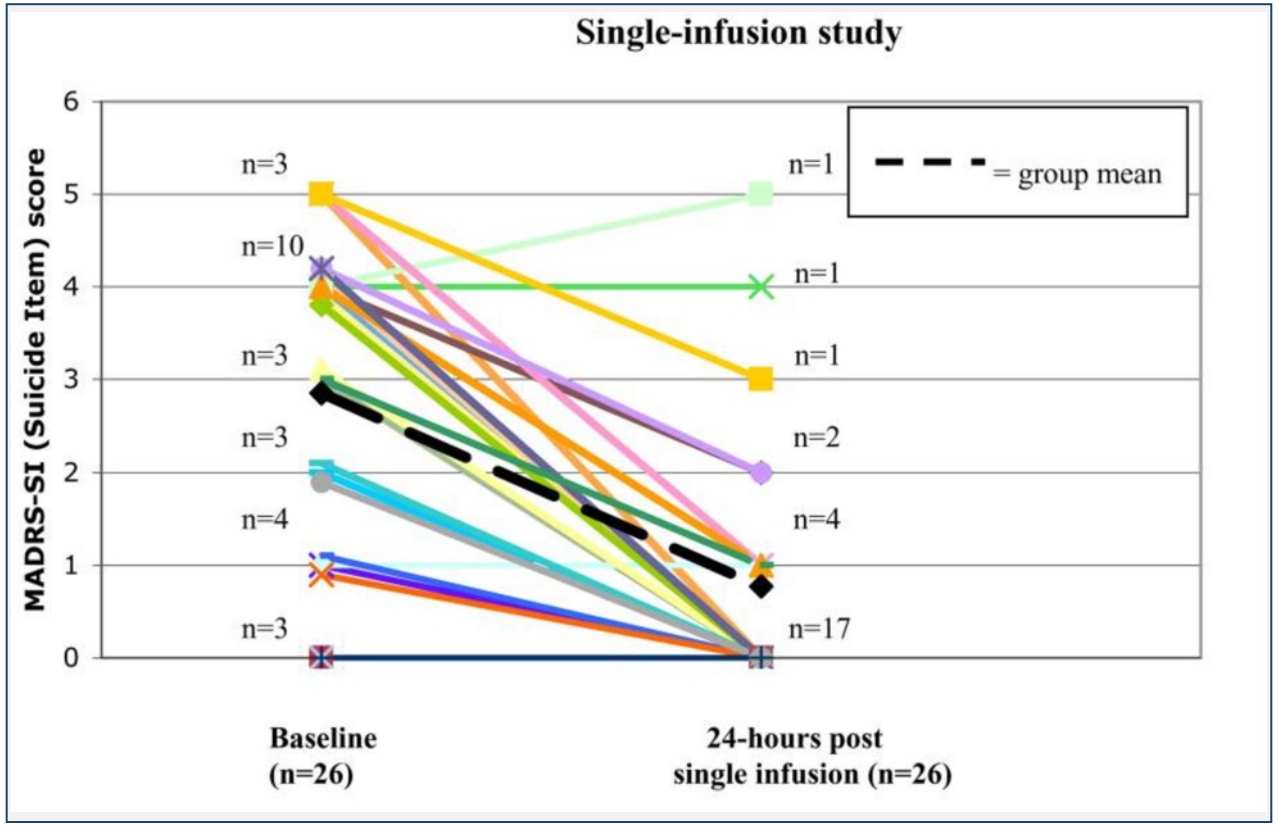


Abdallah, et. al., The effects of ketamine on prefrontal glutamate transmission in healthy and depressed subjects. Neuropsychopharmacology 2018 Sep; 43(10): 2154–2160

1st Reported Observation of Ketamine Effect on Suicidality

Price, et al (Mt. Sinai), single center trial, N=26
Ketamine vs. Midazolam (effect size 0.76, P=.0015)

- Non-randomized observational study
- Mean MADRS suicidality item reduction from 3 at baseline to 0.4 at 24 hours (P<.001)
- Effect size 1.67 (95% CI: 0.7 – 2.6)
- Preliminary findings sparked further study

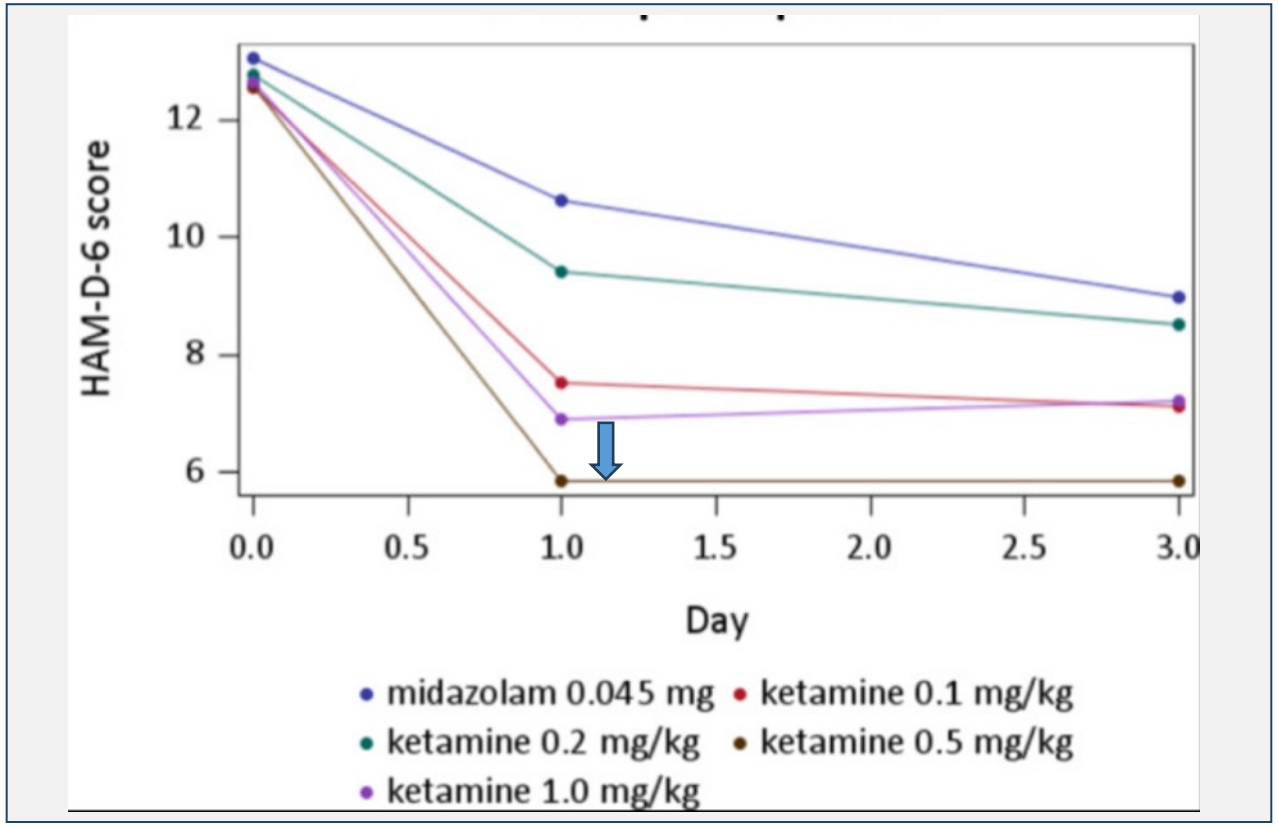


Price, et. al, Effect of Ketamine on implicit and explicit measures of suicidality. Biol Psychiatry 2009, 66(5): 522-526

Multicenter Dose Ranging Trial confirms 0.5 mg/kg dose

Fava (Harvard University), multi-center trial, N=99.
Ketamine 0.5 mg/kg vs. Midazolam (effect size 0.86, adjusted P=.01)

- Depression (not suicidality) endpoint
- Ketamine was most effective at 0.5 mg/kg with reduced effect at both higher and lower doses
- This may explain the failure of nasal ketamine to demonstrate effect because nasal administration yields rapid peak/trough and lack of steady state plasma level

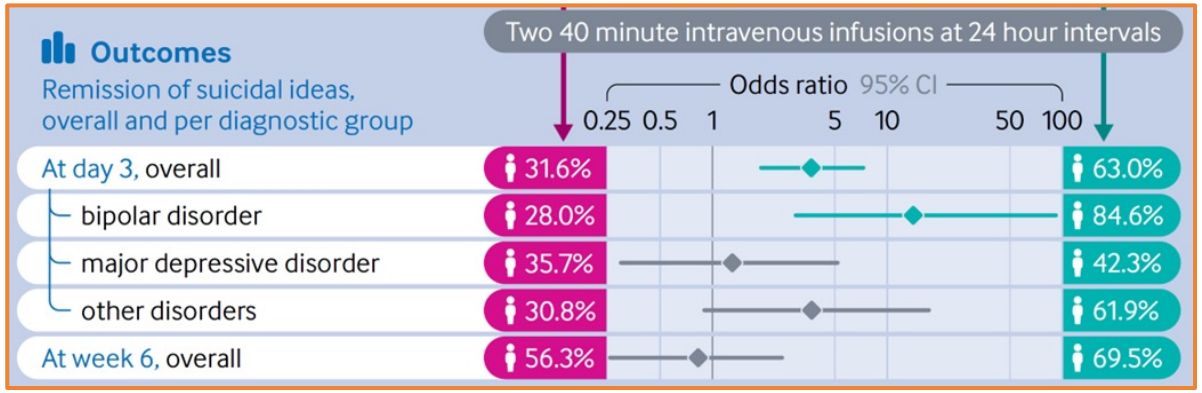


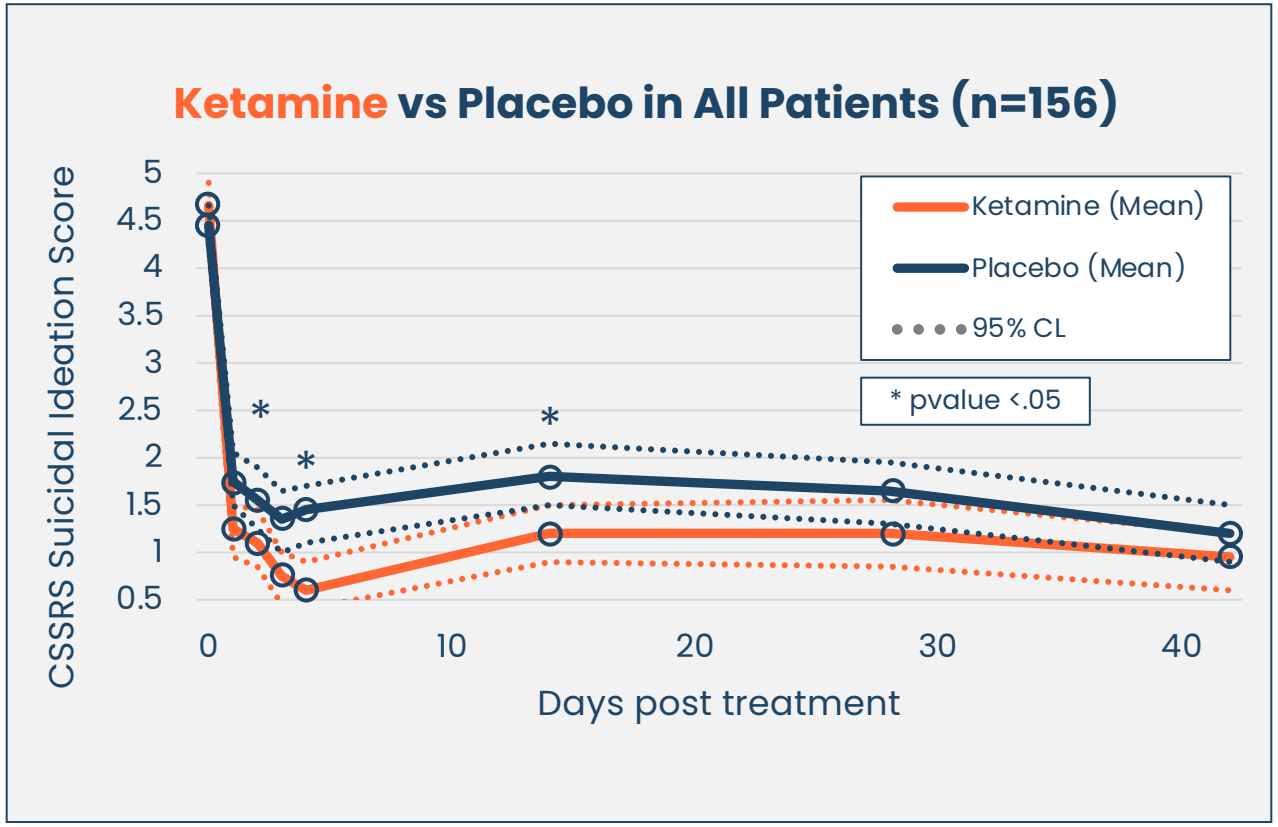
Fava, et. al, Double-blind dose ranging study of intravenous ketamine. Mol Psychiatry 2020, 25(7): 1592-1603

Overwhelming Efficacy in Two Well-Controlled Trials

Abbar, French Psychiatric Hospital Network

- 156 Patients, 7 Hospitals
- Admitted with acute suicidality
- Randomized to Ketamine vs. Placebo
- 84% remission on Ketamine vs. 28% on Placebo in bipolar depression subgroup
- Odds Ratio 14, P<.0001 on Primary Endpoint
- Consistent with earlier (smaller) US studies

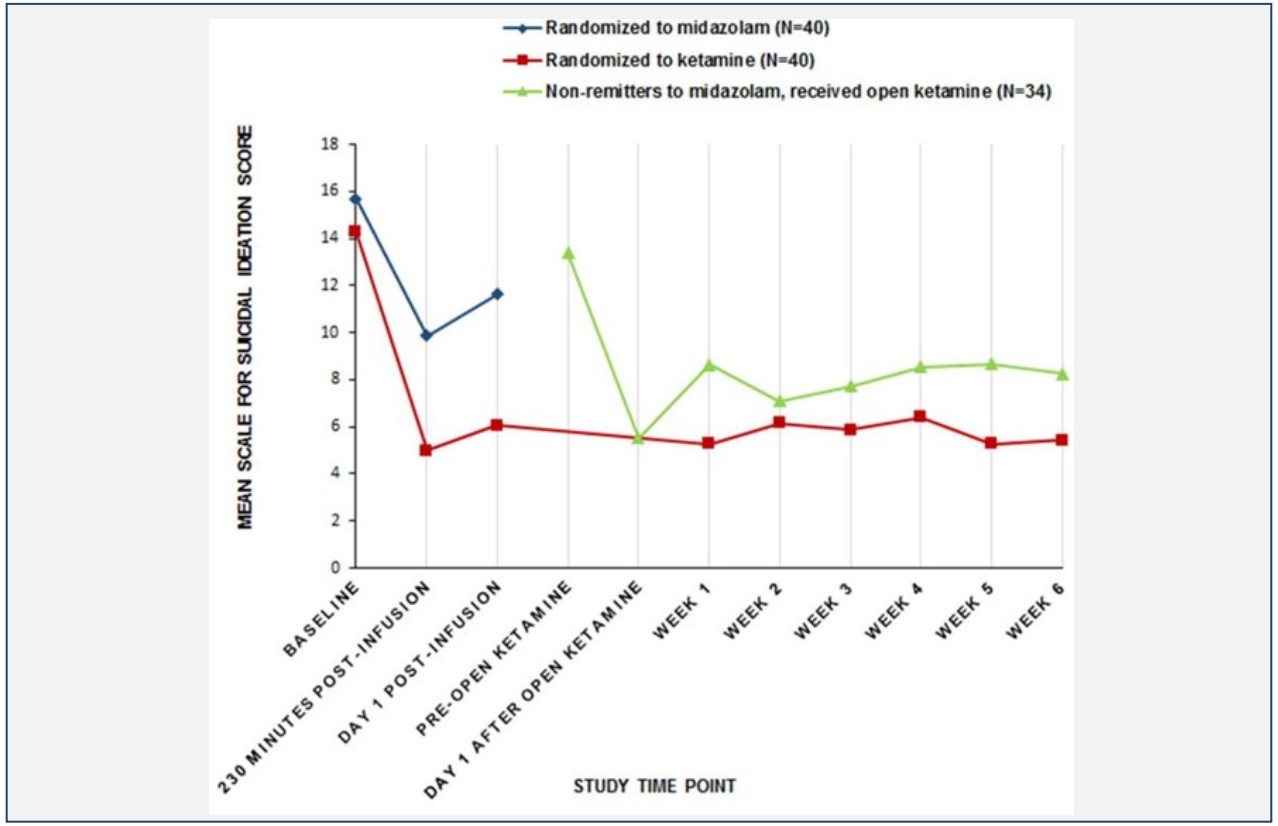




Overwhelming Efficacy in Two Well-Controlled Trials

Grunebaum (Columbia University), single center trial, N=80.
Ketamine vs. Midazolam (effect size 0.76, P=.0015)

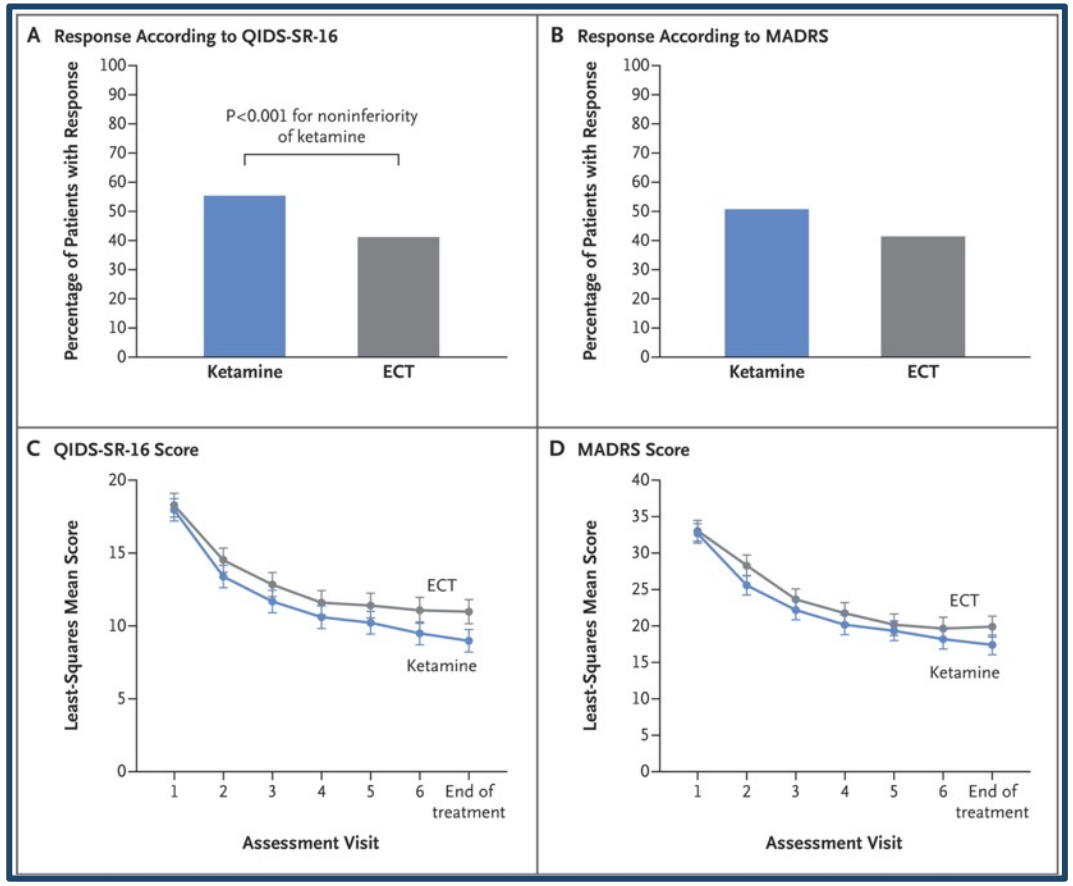
- Initial Randomization to ketamine vs. midazolam
- Midazolam failures treated with open-label ketamine
- Note that open label ketamine effect following midazolam failure matches effect in those initially randomized to ketamine



Grunebaum, et. al, Ketamine for rapid reduction of suicidal thoughts. Am J Psychiatry 2018, 175(4): 327-335

Surprise Finding: Ketamine vs ECT

Anand (Harvard Mass General), multi-center non-inferiority trial, N=420. Ketamine vs. ECT (14% superior, P=.001 for non-inferiority)



3 weeks of treatment: Ketamine 2x/week vs. ECT 3x/week

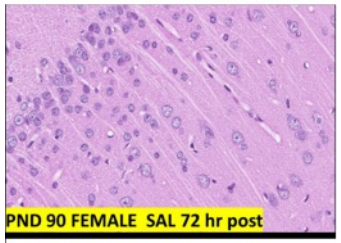
- **Superiority favoring Ketamine P=.007**
  (study designed for non-inferiority, so superiority is post-hoc)
- **Significant memory loss in ECT vs. none with Ketamine**
  (-9.7±1.2 vs. -0.9±1.1; P<.0001)
- **6 month relapse ECT 56.3 vs. Ketamine 34.5 (P<.0001)**
  similar advantage for Ketamine at 1 and 3 months
- **Suicidal ideation 1.4% ECT vs. 3.7% Ketamine (NS)**
- **Severe Hypertension 0% ECT vs. 1.9% Ketamine (NS)**

Anand, et. al, Ketamine is non-inferior to ECT for non-psychotic treatment resistant depression. NEJM 2023 388(25):2315-2325.

Despite clear benefits, Ketamine has clear risks

Ketamine is a DEA Schedule 3 Dangerous Drug

Neurotoxicity
(published by FDA)



Single dose neurotoxicity seen only at 20x the psychiatry dose

Chronic dose neurotoxicity seen at 6 months x 1mg/kg

Addiction

Habituation
Tolerance
Withdrawal

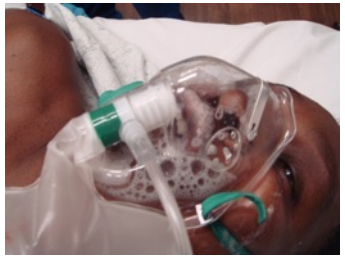
Hallucination

The Washington Post
Democracy Dies in Darkness

Hypertension

Without expert oversight, severe hypertension can be lethal

Vomiting



Vomiting while sedated can be lethal

Uncontrolled Use of Ketamine Represents a Major Public Health Risk

1. https://www.fda.gov/media/168975/download
2. https://www.washingtonpost.com/wellness/2023/02/12/ketamine-depression-treatment-failure/

We expected Ketamine to work from the outset
We never expected it to outperform ECT

JAMA Psychiatry

Viewpoint
October 25, 2023

Choosing Between Ketamine and Electroconvulsive Therapy for Outpatients With Treatment-Resistant Depression—Advantage Ketamine?

Sanjay J. Mathew, MD; Manish K. Jha, MBBS; Amit Anand, MD

JAMA Psychiatry. 2023;80(12):1187-1188.
doi:10.1001/jamapsychiatry.2023.3979

Viewpoint
January 3, 2024

The Rapidly Shifting Ketamine Landscape in the US

Samuel T. Wilkinson, MD[1,2]; Joseph J. Palamar, PhD[3]; Gerard Sanacora, MD, PhD[1,2]

JAMA Psychiatry. Published online January 3, 2024.
doi:10.1001/jamapsychiatry.2023.4945

FDA Warnings Associated with Ketamine Risks

Urgent need for an approved form of IV ketamine for suicidality

Two FDA warning letters regarding off-label and compounded use of ketamine[1]

Urgent need for an FDA-approved form of ketamine:

- Need for proper labeling and physician training under a REMS
- Modern formulation with physiologic pH (generic formulation is pH 2.0)
- Need for presentation that can be used in the clinic without a compounding pharmacy
- FDA requested that NRx submit an NDA for ketamine in January 2023 Type B meeting

https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine

Advantage NRX-100 for Suicidal Depression

Proper use of a potent but potentially dangerous drug

- A new single-dose formulation with reliable potency and shelf stability
  Anesthesiologists and veterinarians will tell you that non-branded generics don't work reliably
  (Clinics cannot use multidose anesthesia packaging (hence the need for compounding)
- A label that guides physicians to proper use for depression (not anesthesia) and that appropriately discloses risks and their mitigation
- A REMS (Risk Evaluation and Mitigation Strategy) program that provides for physician training

Improved Patient Access

- **With an FDA label**, Hope Therapeutics can market and establish trust with physicians and patients
- **With an FDA label,** insurance is likely to reimburse for Ketamine treatment, providing access to people who cannot afford to pay cash

Compliance with the Law

- **In the setting of an FDA label for use, compounding of ketamine is largely illegal**
- **Ketamine** is a Schedule III drug whose use is overseen by both FDA and DEA
- **Diversion/Misuse** carry significant penalties
- **Significant Protection** for practitioners who prescribe ketamine under a REMS

Launching Hope Therapeutics

Hope Therapeutics

Thank You

