Ketamine for suicidal depression:

The benefits are clear,
The risks must be balanced

Prof. Jonathan C. Javitt, MD, MPH
NRx Pharmaceuticals
Johns Hopkins University

Hope Therapeutics

Hope. Science. Life.

NOTE: Investigational Therapy not currently approved by FDA

Ketamine 2024, Oxford, UK

Suicidality is a Global Crisis

Suicidality 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

It often 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.

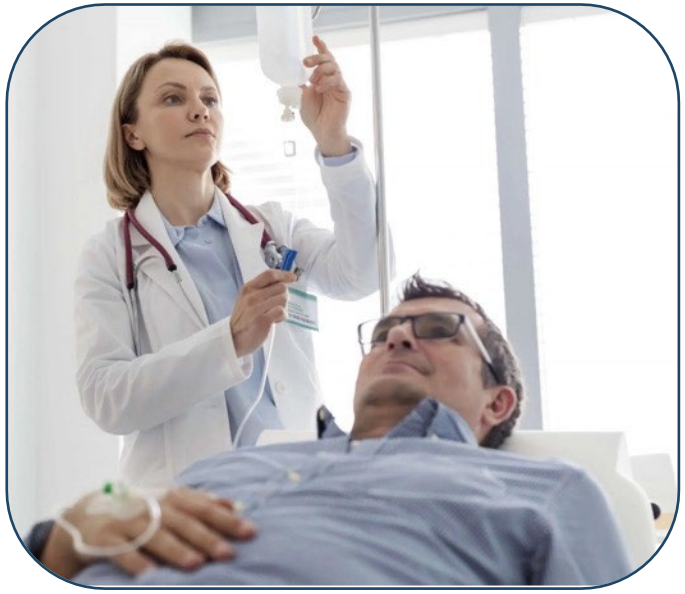
Five Points for Today

1. Ketamine is the **first** drug demonstrated to reverse acute depression and suicidality
2. FDA, EMA, and worldwide approval of ketamine is critical to patient access
   No approval, no coverage. Approval requires both **data** and **chemistry.**
3. The effect of ketamine is too short-lived to succeed as long term monotherapy
4. Ketamine is addictive and neurotoxic within six months but less harmful to the brain than ECT or death by suicide
5. Nontoxic replacement therapies are urgently needed together with adjunctive therapies to extend the ketamine effect

No FDA-Approved Medication today for Acute Suicidality

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

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



Esketamine is currently approved for treatment of depression in patients at risk of self-harm but may not be used in patients with bipolar depression

1 Evidence to support efficacy and safety

i. Berman, Zarate, Murrough, and many other trailblazers -> small studies

ii. Fava: multicenter dose ranging trial to establish 0.5mg/kg dose

iii. Grunebaum: first powered RCT to demonstrate ↓ suicidality and depression

iv. Abbar: only multicenter, randomized controlled trial of acutely suicidal patients

v. Anand/PCORI: Demonstration of efficacy non-inferiority and side-effect superiority of ketamine vs. ECT

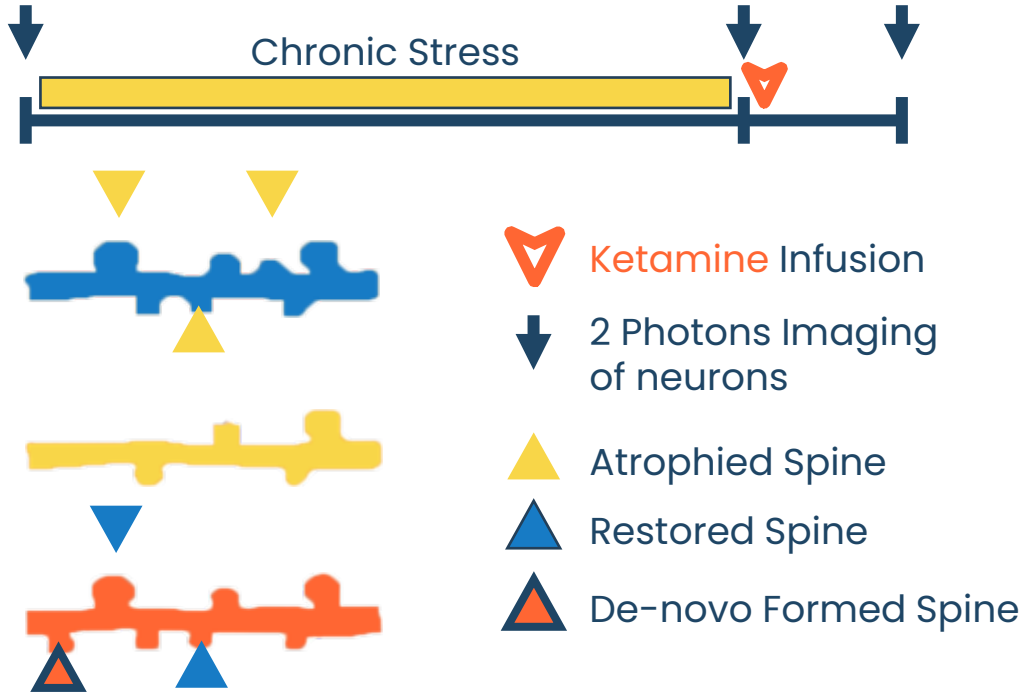
“Re-wiring the Brain,” as shown in the laboratory

Ketamine’s effect on neuronal dendritic spines

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

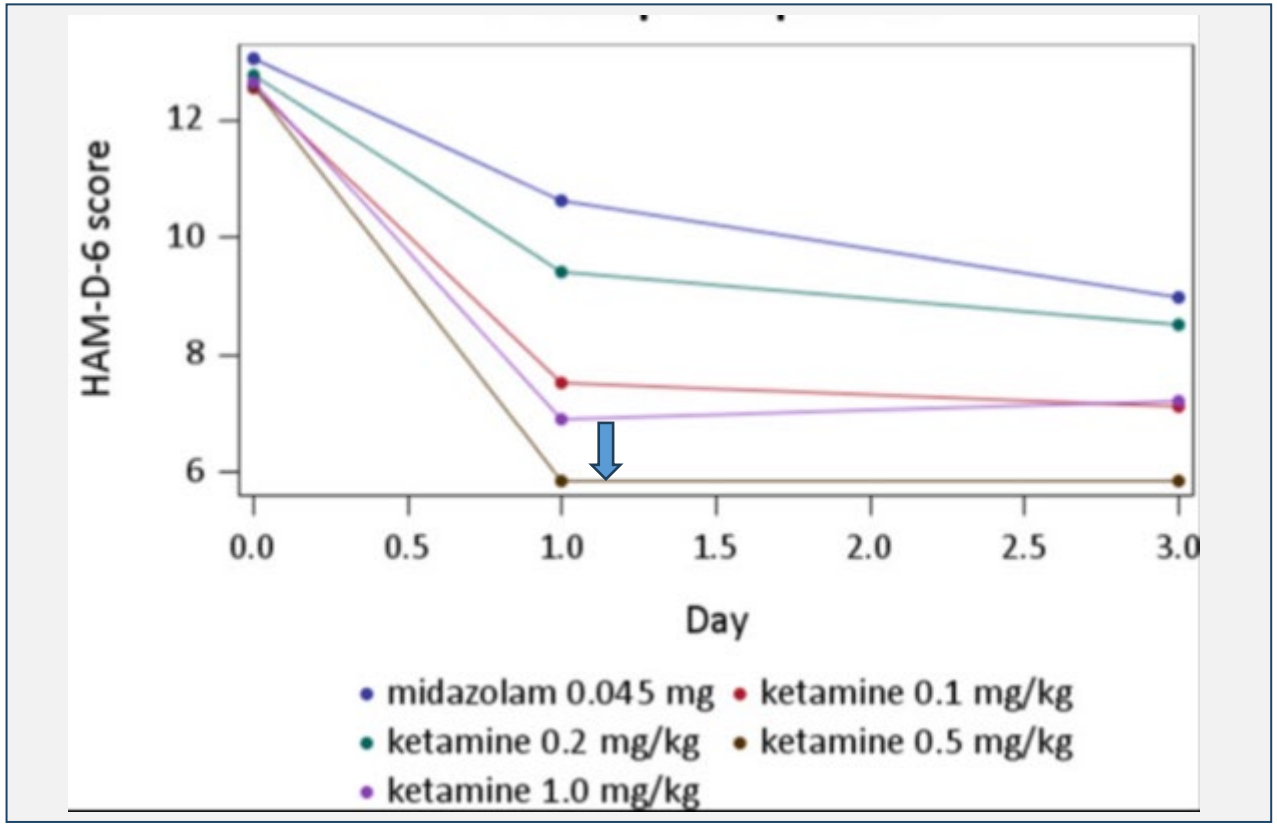
- Clustered Dendridic Spine Formation and Restores Spine Loss
- Ensemble Activity
- Depression-related Behavior

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

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)

- Randomization to ketamine (4 doses) vs. midazolam
- 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

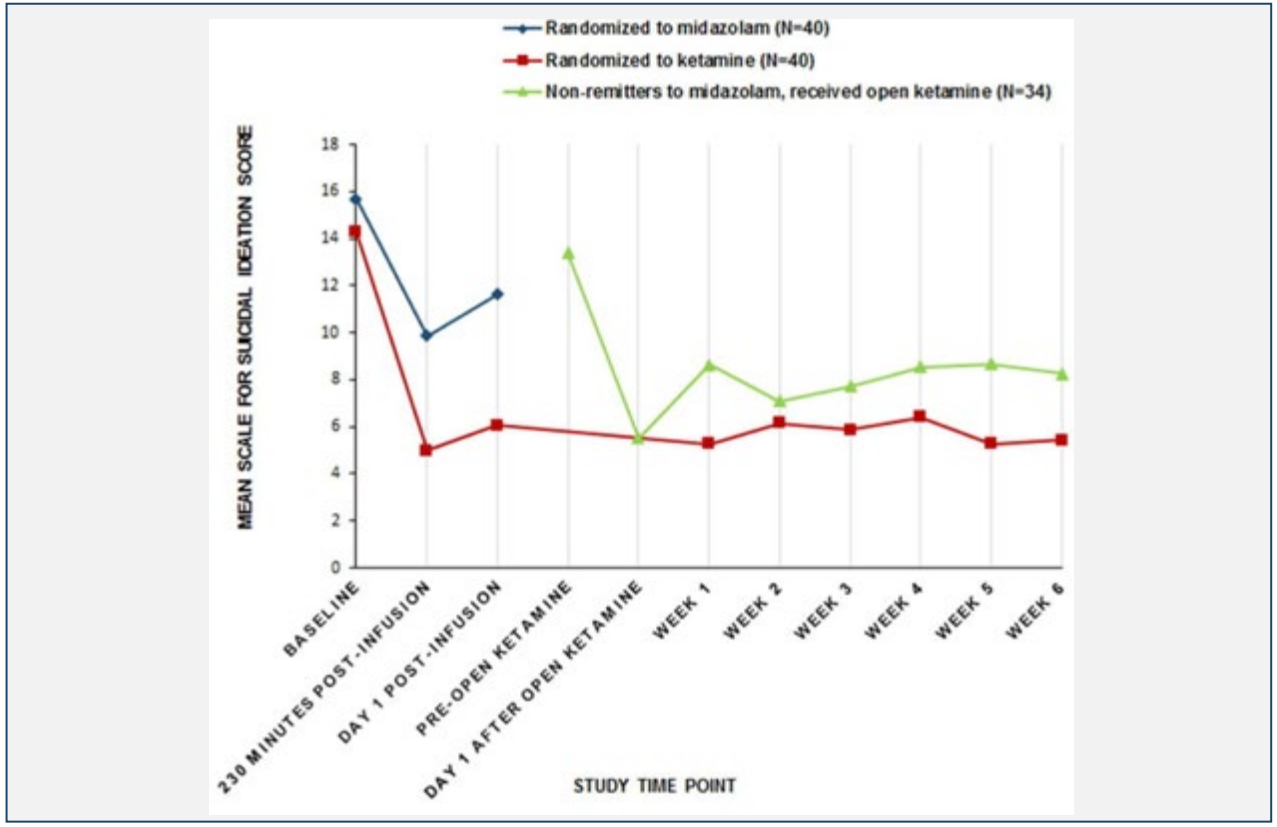


Fava, et. al, Double-blind dose ranging study of intravenous ketamine. Mol Psychiatry 2020, 25(7): 1592-1603

Ketamine vs. Midazolam: Efficacy in MDD and Bipolar Depression

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

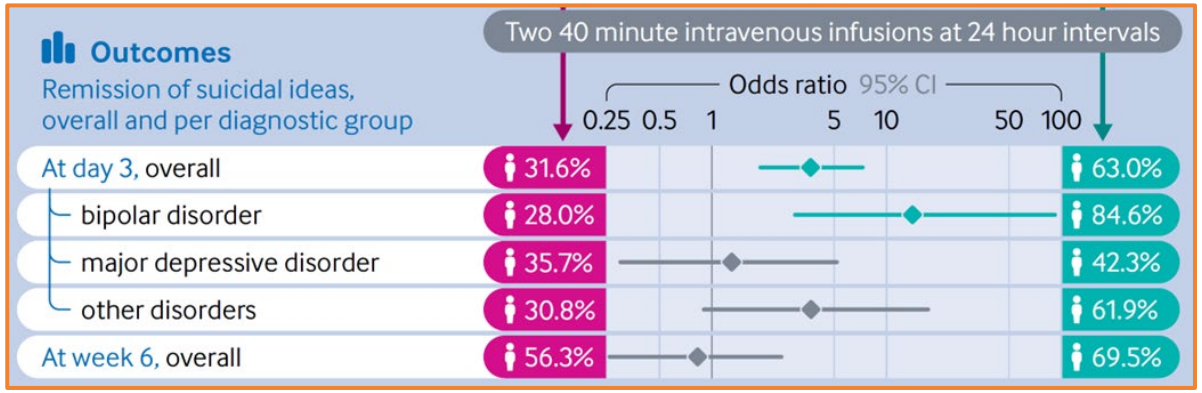


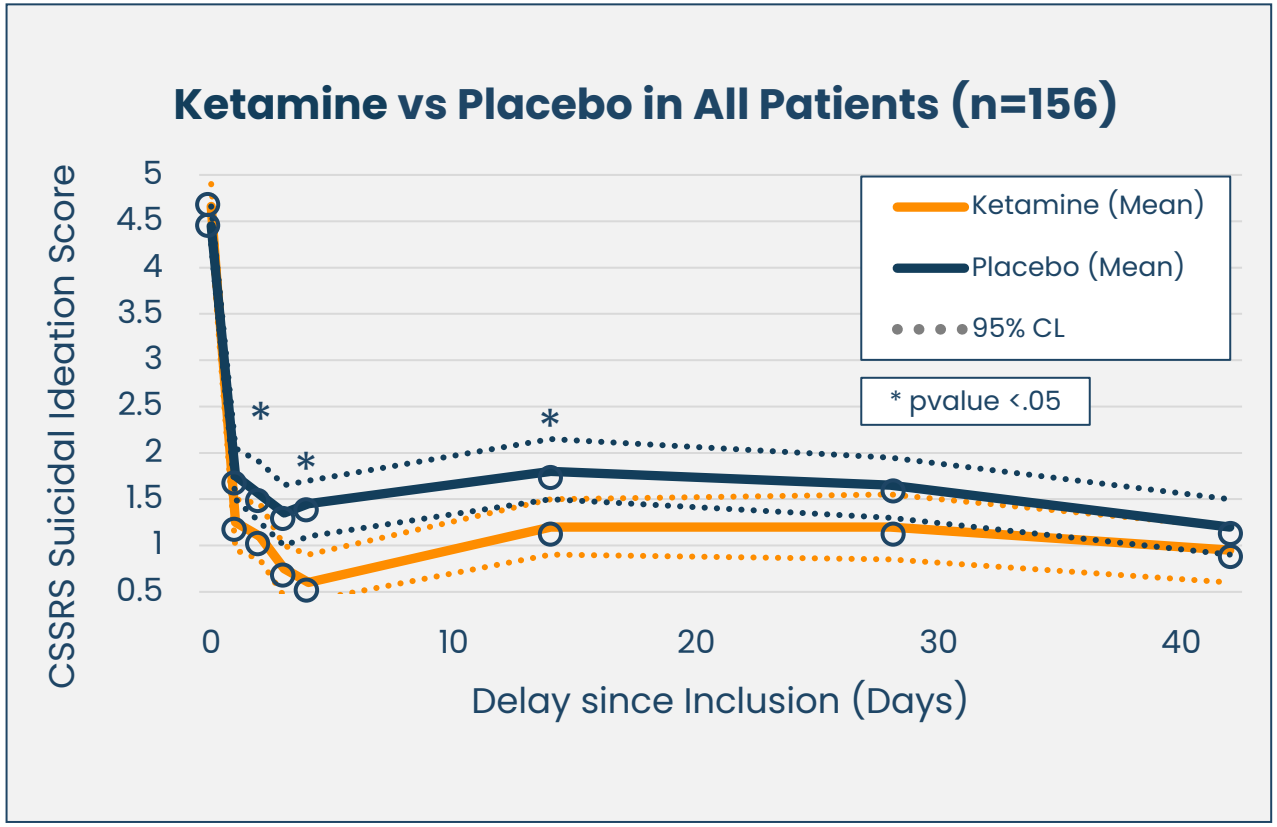
Grunebaum, et. al, Ketamine for rapid reduction of suicidal thoughts. Am J Psychiatry 2018, 175(4): 327-335

Ketamine vs. Placebo: massive advantage in Bipolar Depression

Abbar Study, funded by Gov't of France and the Fondation Fondamental

- 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

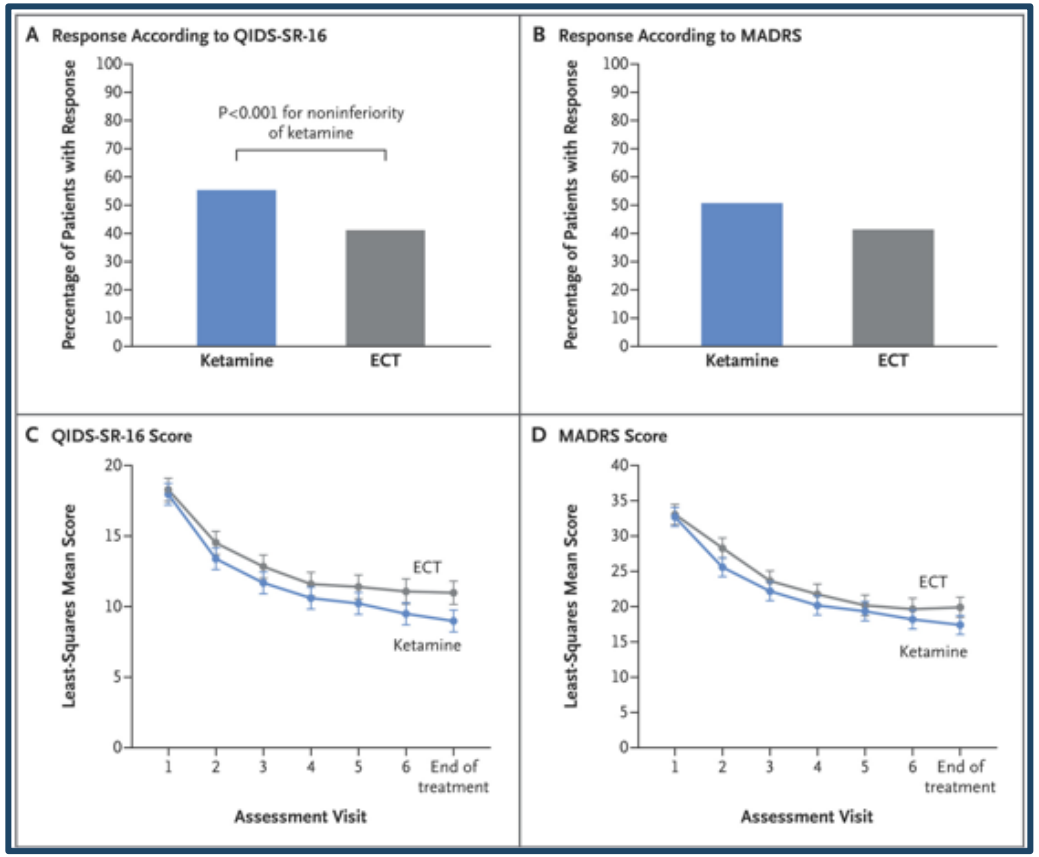




1. Abbar, et al. Ketamine for Acute Treatment of Severe Suicidal Ideation. BMJ 2022;376

Ketamine vs. ECT: noninferior on efficacy, superior on memory loss

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.

Broad Support within the Psychiatry Community

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

2 Without FDA approval, only those who can pay will be treated

Approval needs your help and requires:

i. Safety and Efficacy Data

ii. 9 months of Shelf Stability from 3 manufactured lots in the marketed presentation

iii. Global overview of safety

iv. Labeling

v. REMS: Risk Evaluation and Mitigation Strategy

Why not just use existing medicines?

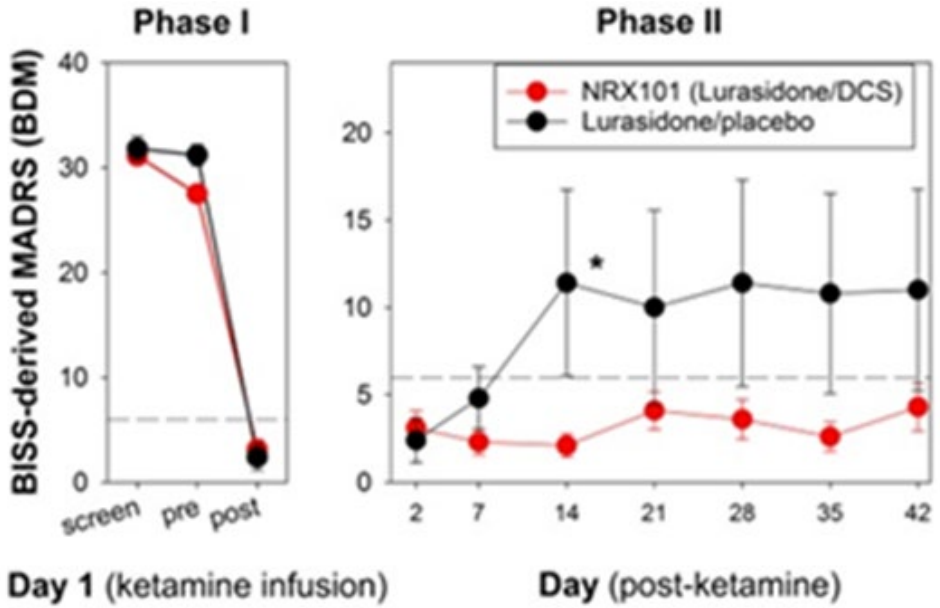
1. The R enantiomer is likely needed as well as the S enantiomer
2. Intranasal administration has variable absorption & less clear effect against suicidality
3. The Seelos failure is highly instructive. The FAVA data shows the narrow threshold
4. Many patients do not prefer intranasal administration
5. Once side effects begin you cannot turn off the drip

3 The effect of ketamine is too short-lived for long term monotherapy

By week two, the effect of ketamine is largely extinguished

NRX-101 (D-cycloserine plus lurasidone) vs. lurasidone for the maintenance of initial stabilization after ketamine in patients with severe bipolar depression with acute suicidal ideation and behavior: a randomized prospective phase 2 trial

Andrew Nierenberg[1], Philip Lavin[2], Daniel C. Javitt[3,4], Richard Shelton[5], Michael T. Sapko[4], Sanjay Mathew[6], Robert E. Besthof[4] and Jonathan C. Javitt[4,7*]



4 Ketamine is a dangerous drug: neurotoxic and addictive

i. Olney's work from 1990 has been overlooked because primate work is **hard**

ii. Numerous studies over 3 decades demonstrate neurotoxicity in cells and small mammals

iii. Critics doubt the correlation between morphologic and functional changes

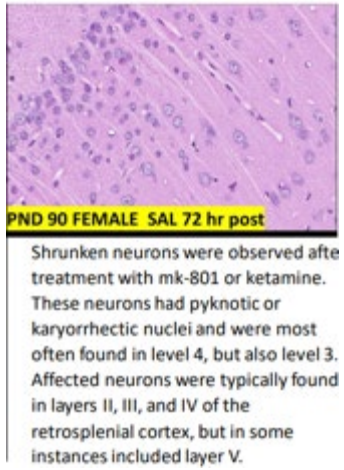
iv. Randomized prospective chronic primate studies are nearly impossible

v. Once you see the data a 1mg/kg, it's hard to "un-see" it

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

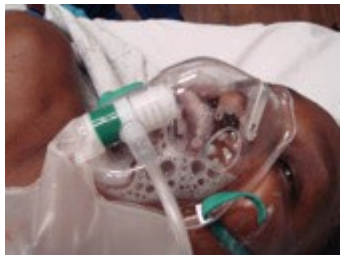
Hallucination

The Washington Post
Democracy Dies in Darkness

Hypertension

Without expert oversight, severe hypertension can be lethal

Vomiting

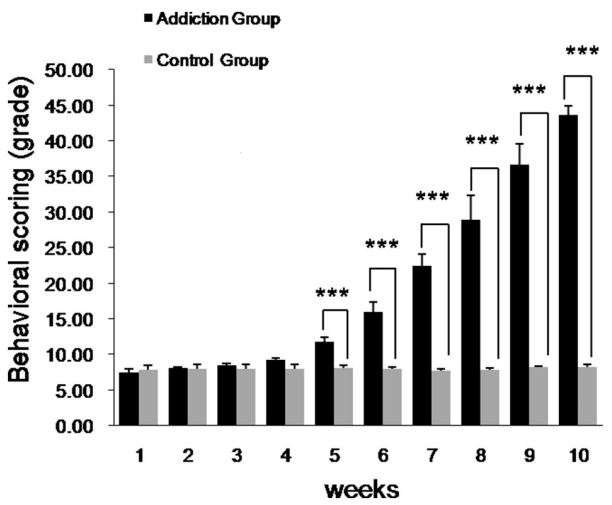


Vomiting while sedated can be lethal

Uncontrolled Use of Ketamine Represents a Major Public Health Risk
Mail-order lozenges may be lunacy

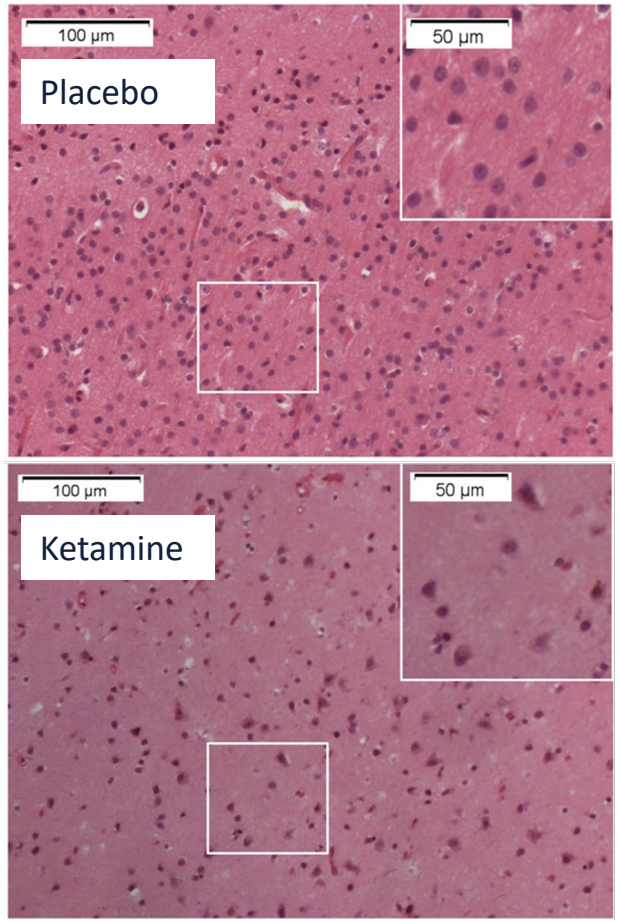
1. https://www.fda.gov/media/168975/download
2. https://www.washingtonpost.com/wellness/2023/02/12/ketamine-depression-treatment-failure/

Behavioral Changes and Neuronal Damage in Rhesus Monkeys after 10 Weeks



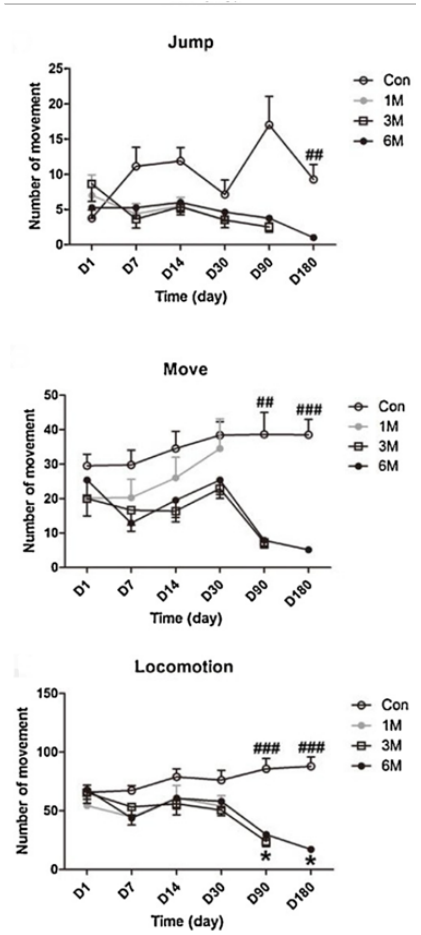
- Toxicity is not seen with less than 10 weeks of chronic administration
- Dose escalation to 1.6 mg/kg vs placebo
- Dramatic increase in psychotic behavior (biting, screeching, kicking, etc.)
- Profound weight loss
- Clear neurotoxicity

(I have sat at the microscope and it's not possible to photograph the dramatic effect on the brain)

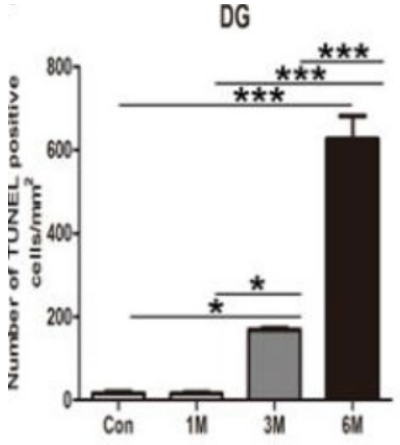


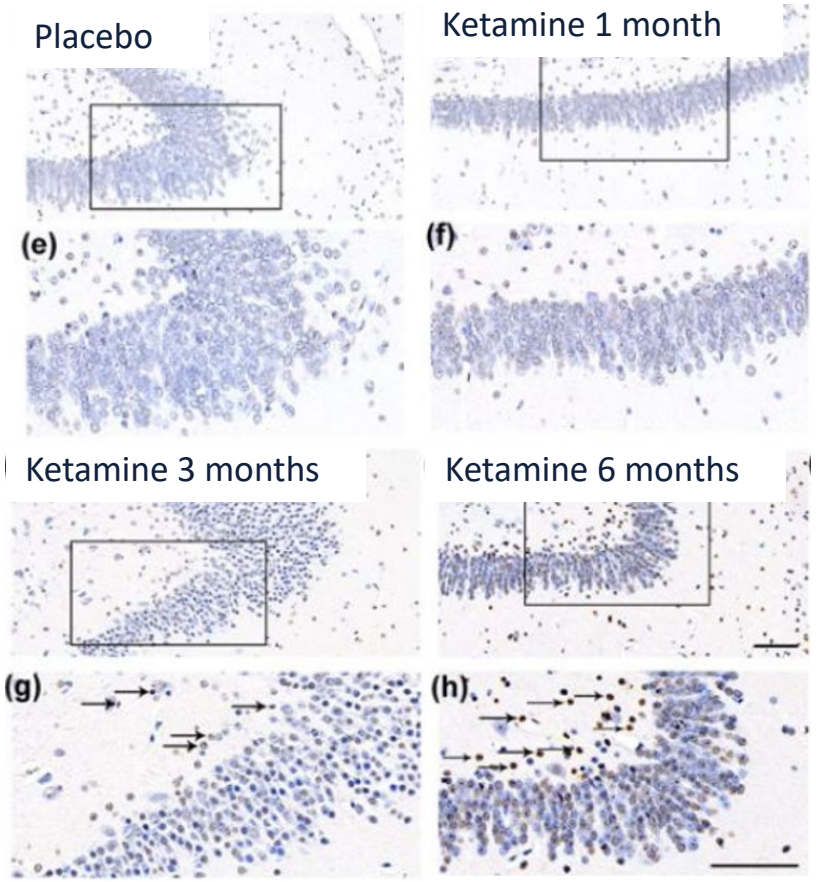
Zongbo Sun, Ye Ma, Lei Xie, et. al. Neuroscience 2019 415: 97-106

Similar effects with S-ketamine
Permanent Hypolocomotion and Hippocampal Impairment in Cynomolgus



- Dramatic effect vs. placebo separates at 3 months at 1.0 mg/kg
- TUNEL Staining demonstrates more recognizeable effect than traditional H&E





Li Qing, Qin Xia-qing, Sun Lin, Neuroscience Letters 2020:134702

The NIH has Human evidence from neuroimaging and behavior change
This is not just a phenomenon in monkeys

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Intelligent Medicine

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

Review

Ketamine use disorder: preclinical, clinical, and neuroimaging evidence to support proposed mechanisms of actions

Leah Vines[#], Diana Sotelo[#], Allison Johnson, Evan Dennis, Peter Manza, Nora D. Volkow, Gene-Jack Wang[*]

Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 10 Center Dr, Rm B2L124, Bethesda, Maryland, United States

5 Nontoxic Therapies are urgently needed to extend the ketamine effect

i. New drugs: oral NMDA antagonists and others

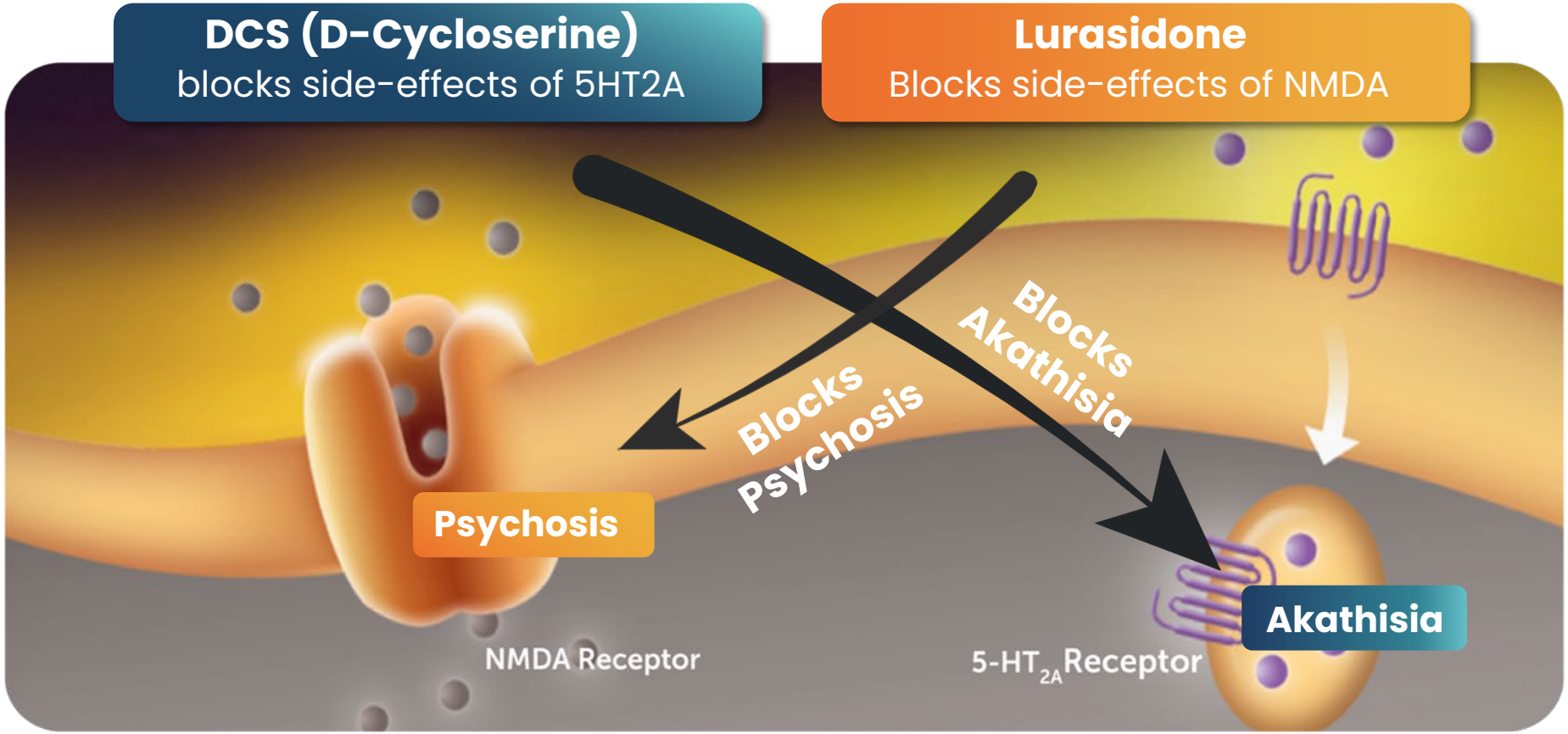
ii. Digital therapeutics that create physiologic change

iii. TMS and other electromagnetic therapies

iv. Future-tech

The Pharmacotherapy Challenge is NMDA-antagonist psychosis

Simultaneous Blockade of NMDA and 5-HT2A Blocks Side Effects



DCS+Lurasidone has preserved the ketamine effect w/o side effects

FDA has required an NDA for ketamine prior to an NDA for this indication

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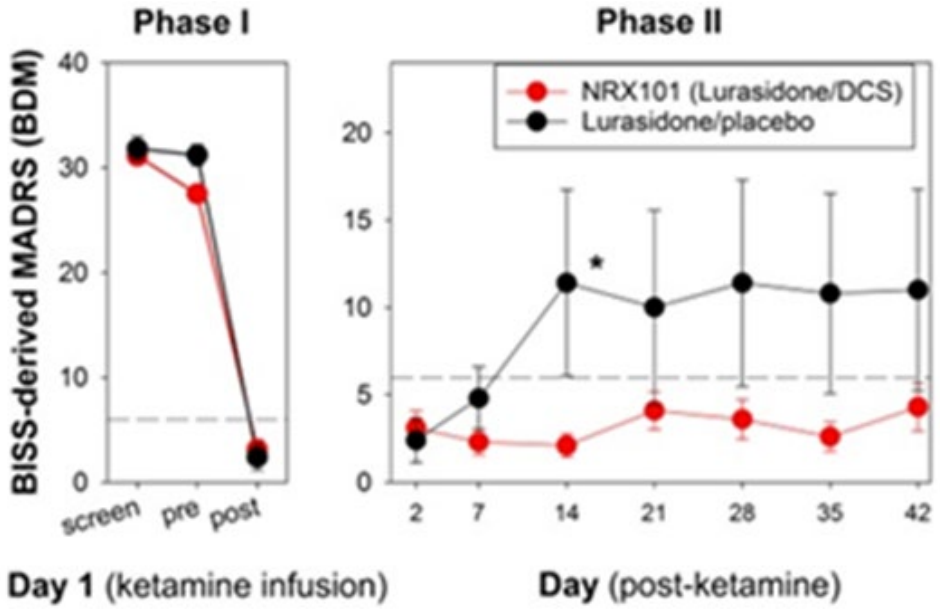


Where is the promise in Digital Therapeutics?

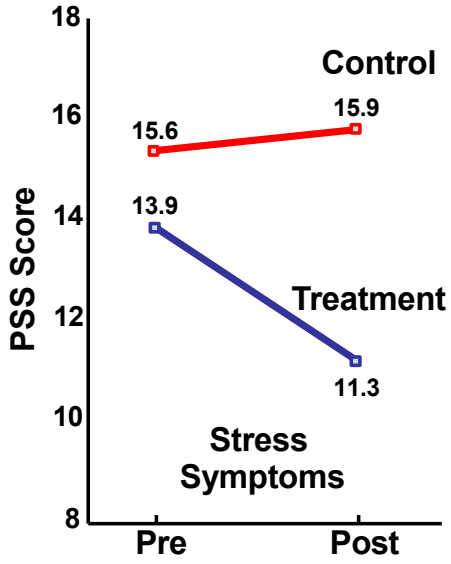
1. The pharmacologic effect of ketamine lasts for < 1 week
2. Patients need ongoing support and Cognitive-based therapy is insufficient
3. Research sponsored by DARPA demonstrates measurable benefit of Digital Therapeutic approach in reducing physiologic measures of depression and stress
4. Recent advances in consumer-targeted sensors (iWatch® and others) together with gaming app advances makes this deployable
5. Addition of a digital therapeutic component to ketamine might provide longer term benefit

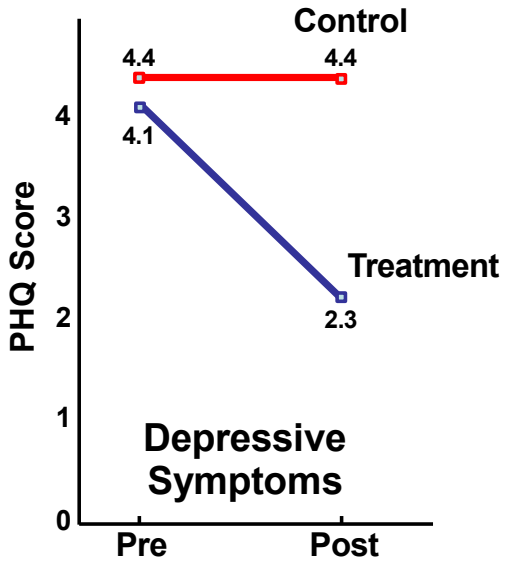
Digital Therapeutics are regulated by the FDA as medical devices and may not make claims of health benefit without FDA clearance or approval

Digital Therapeutics to Create Autonomic Coherence

Methodology:

- 71 personnel from US Navy Coastal and Riverine Expeditionary Group and Squadron
- 8-week Digital Therapeutic Use compared to Control
- Measures are Perceived Stress Scale, Patient Health Questionnaire and Usage Report





Participants demonstrated high acceptance and Digital Therapeutic Use (75%) compared to control

Key Results:

- *Large reductions in Perceived Stress and Depression compared to Control group*
- *Digital therapeutic use before and during stress events is significantly greater than for Control*
- *Quantitative improvements in both performance and mental health*

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Hope Therapeutics

an NRx Daughter Co.

NRX-100 (IV Ketamine)
for **Suicidal Depression**

Hope. Science. Life.

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Ketamine 2024, Oxford, UK