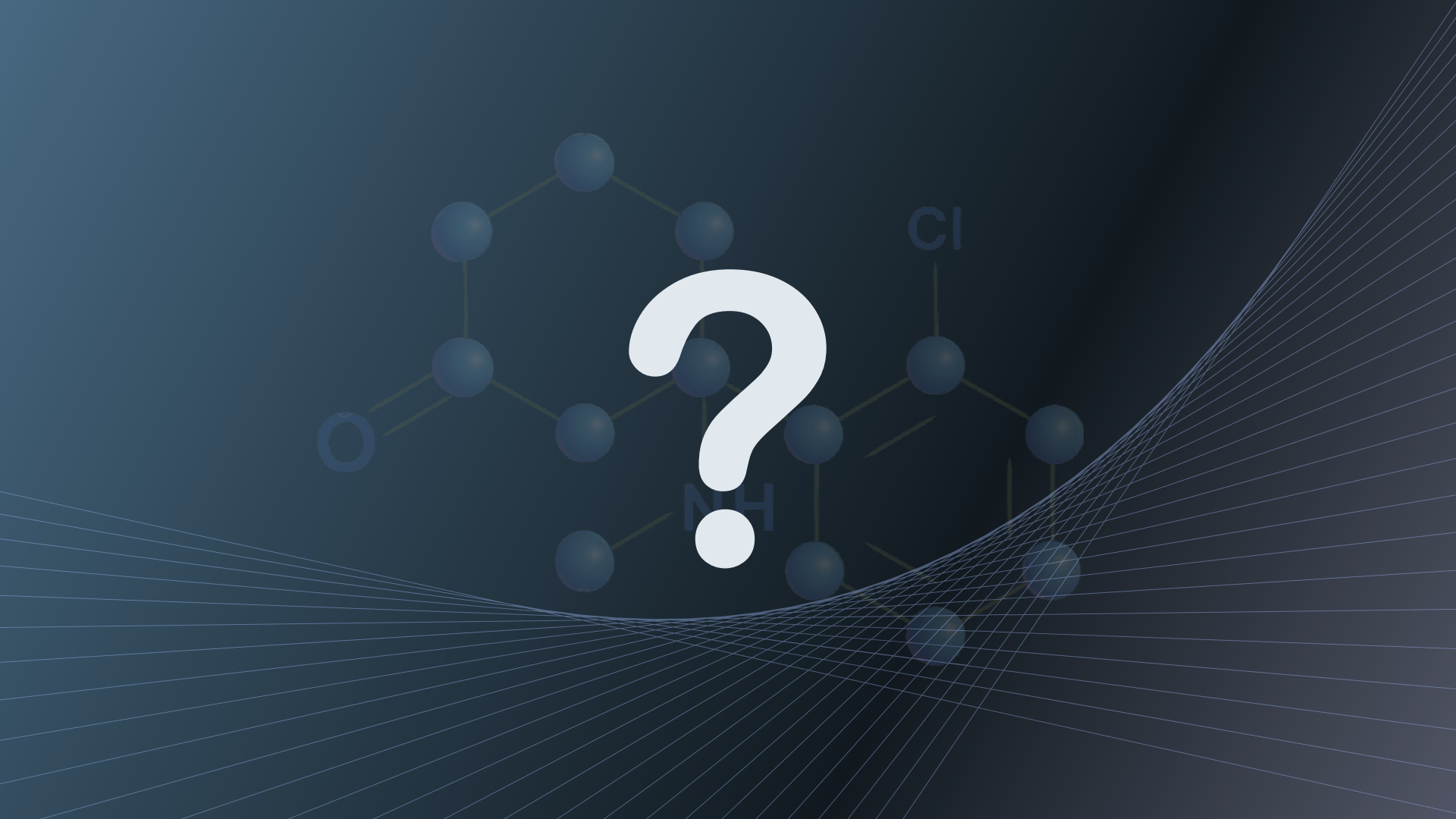
# Ketamine Therapy for Depression

## Real Results

Robert Watson, MD, FACS

# “Emily”

- 20 yo female, TRMDD, Anxiety, PTSD
- QID-SR16: 25 (severe)
- Failed 5-6 yrs failed AD txs
- Home bound with parents, slept most of day, unemployed.
- Parents “exhausted”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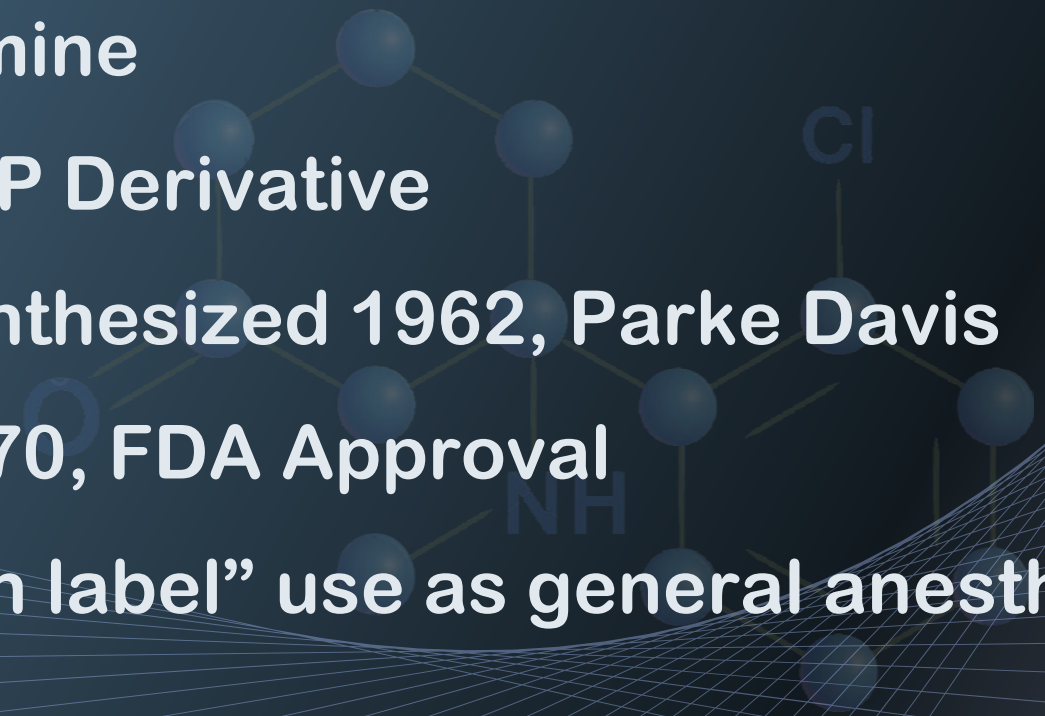
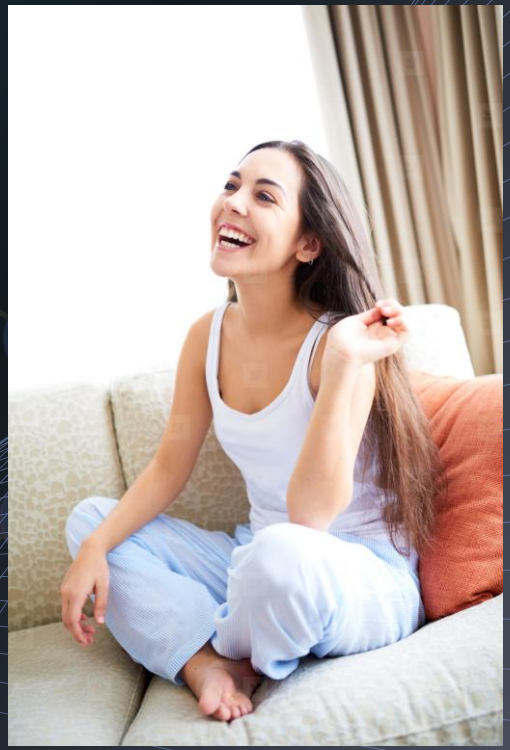
## Ketamine

- PCP Derivative
- Synthesized 1962, Parke Davis
- 1970, FDA Approval
- “On label” use as general anesthetic



# Ask your doctor is ‘our drug’ is right for you.

“Side effects may include headache, nausea, vomiting, diarrhea, constipation, dizziness, excitability, depression, insomnia, cardiac arrhythmia, skin rashes or eruptions, overwhelming infections, certain types of cancer, diabetes, hostility, increased risk of dementia, epistaxis, unwelcomed death, …, …, …,



## Ketamine is Safe

- “Buddy Drug”
- Mild sympathetic response (inc BP)
- No respiratory or CV depression
- WHO list of essential medications

# Dissociative Effects

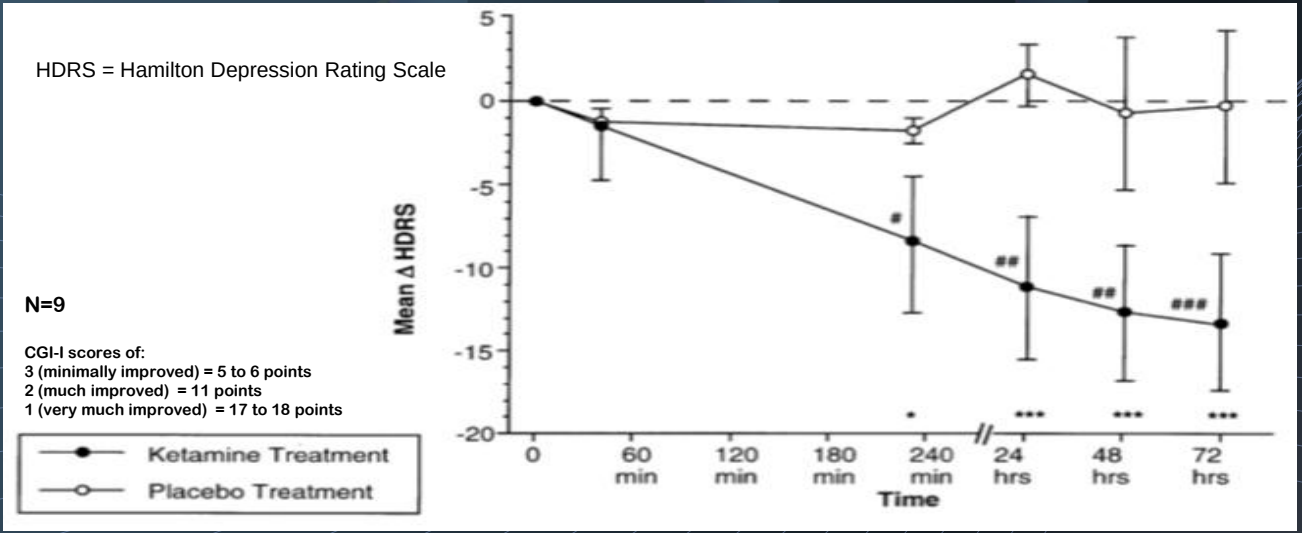
- Preparation of patients is important (set & setting)
- Depersonalization and Derealization
- Side effect vs adverse effect
- Resolved within minutes of infusion completion
- Necessary for antidepressant effects?

## Toxicity

- Seen in abuse situations
- High doses, frequently, prolonged use
- Memory and Cognitive problems
- Liver enzyme elevation
- Lower urinary tract problems
- NOT seen in regimens used for Mood

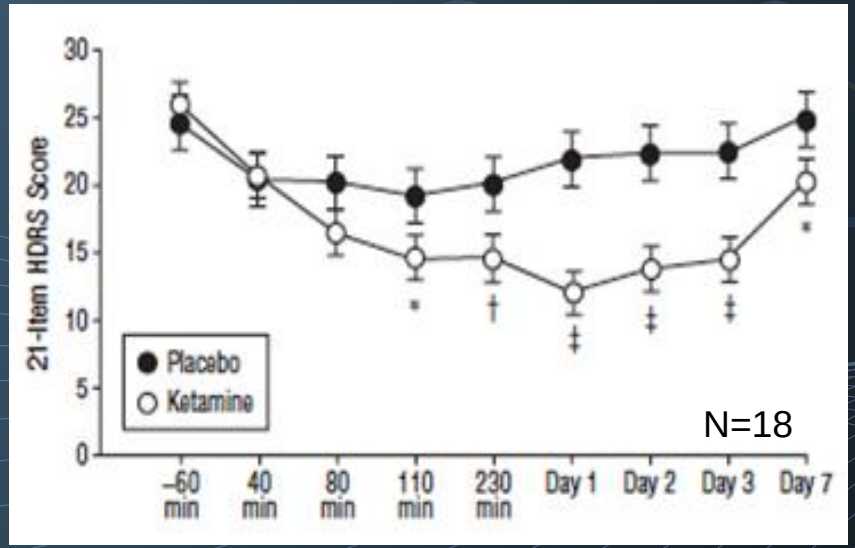
# 2000, R. Berman et al, 1st paper on Ketamine for depression

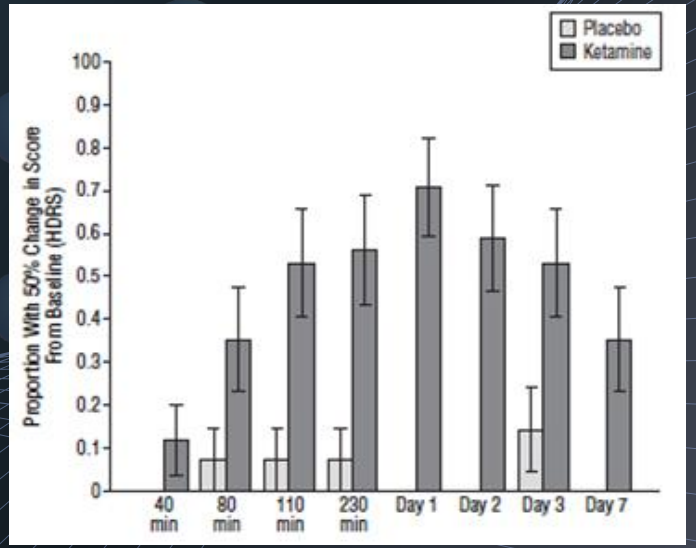
- "Robust" and rapid results.



# 2006, C. Zarate et al, Validation

"…robust, rapid (hours), and relatively sustained (1 week) response to a single dose of the NMDA antagonist ketamine."



# 2006. Correll & Futter

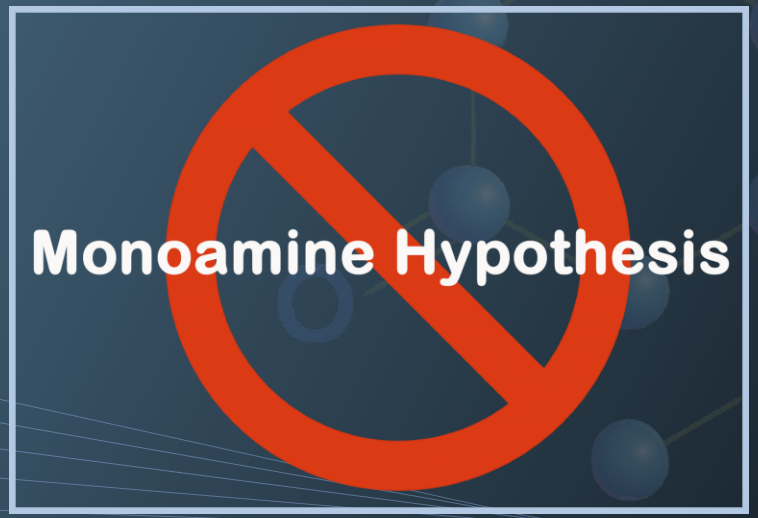
- Case Report, Two patients
- #1. 39 yo F, 18 month hx TRMDD, disabled by her MDD.
- “Nursing staff and family noted a positive improvement in the patient after 24 hours, particularly a decrease in fluctuation of mood. After 48 hours she began to show an interest in her pastimes and after 72 hours began cooking meals and snacks for patients and staff.”
- “…continued to improve for several weeks.”

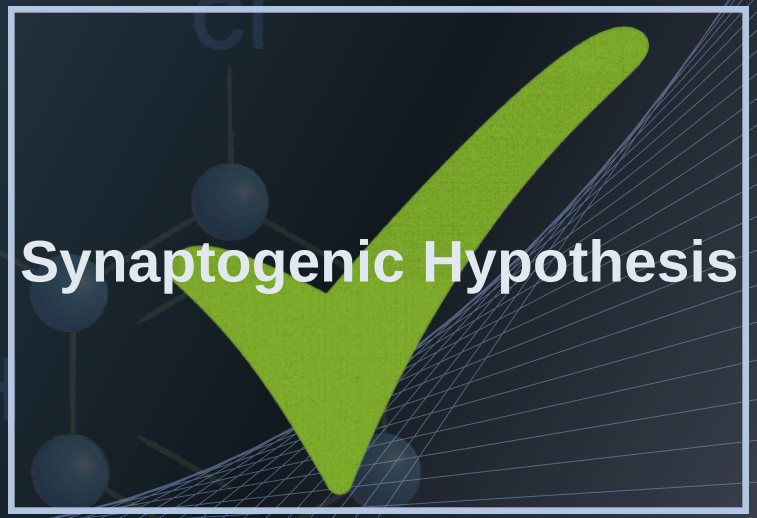
# 2006. Correll & Futter

- Case Report, Two patients
- #2. 33 yo M, 16 year hx TRMDD including ECT.
- After 48° pt “felt better in his mood”

  Staff noted, “he appeared brighter and was more spontaneous in his speech and expressions.”
- After 72°, “he was talking positively about his future plans, interacting with staff, and initiating conversation.”
- Continued to improve and found employment.

# Ketamine's Mechanism of Action

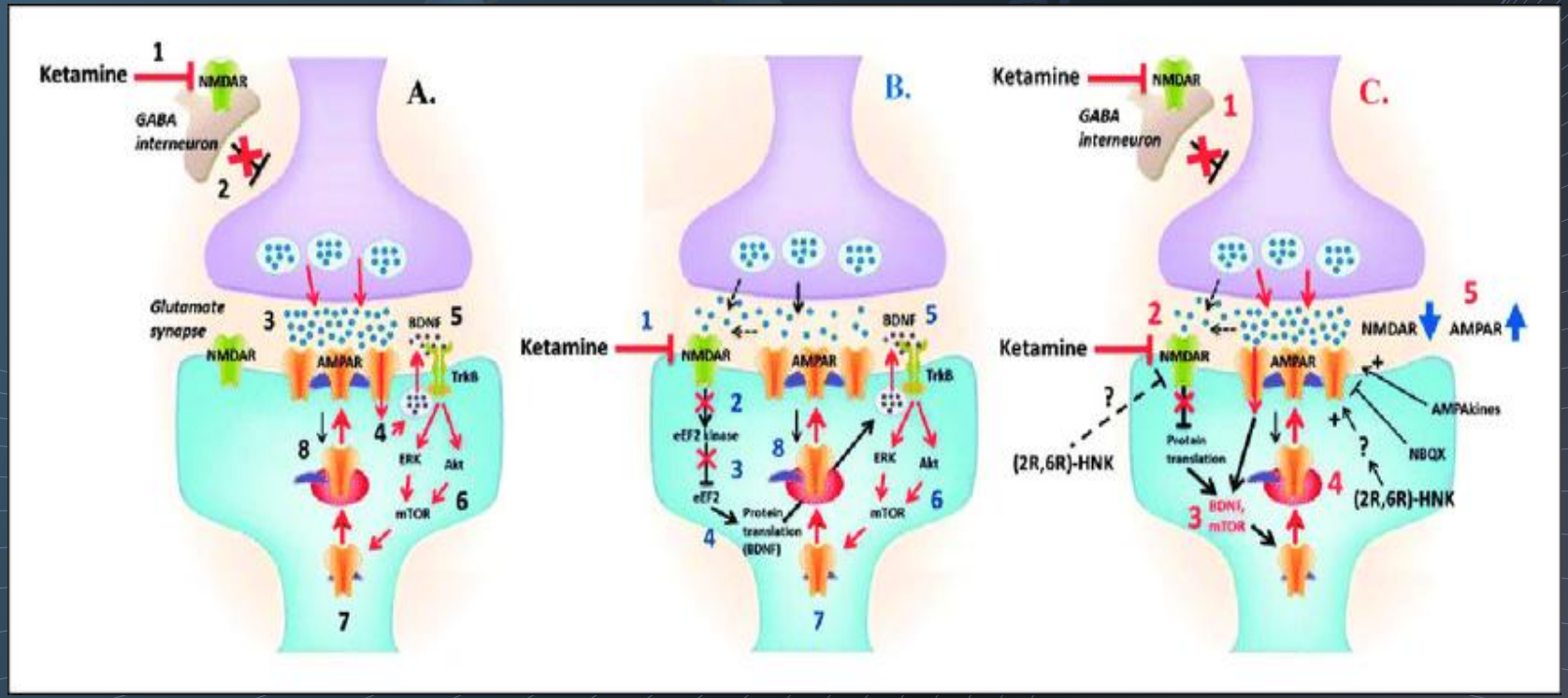


# MOA

- Induces neuroplasticity and synaptogenesis
- Acts on Glutamatergic system (excitatory)
- NMDAR Antagonist, AMPA agonist
- Induces MTOR, BDNF, eEF-2

# Theories on MOA for Ketamine



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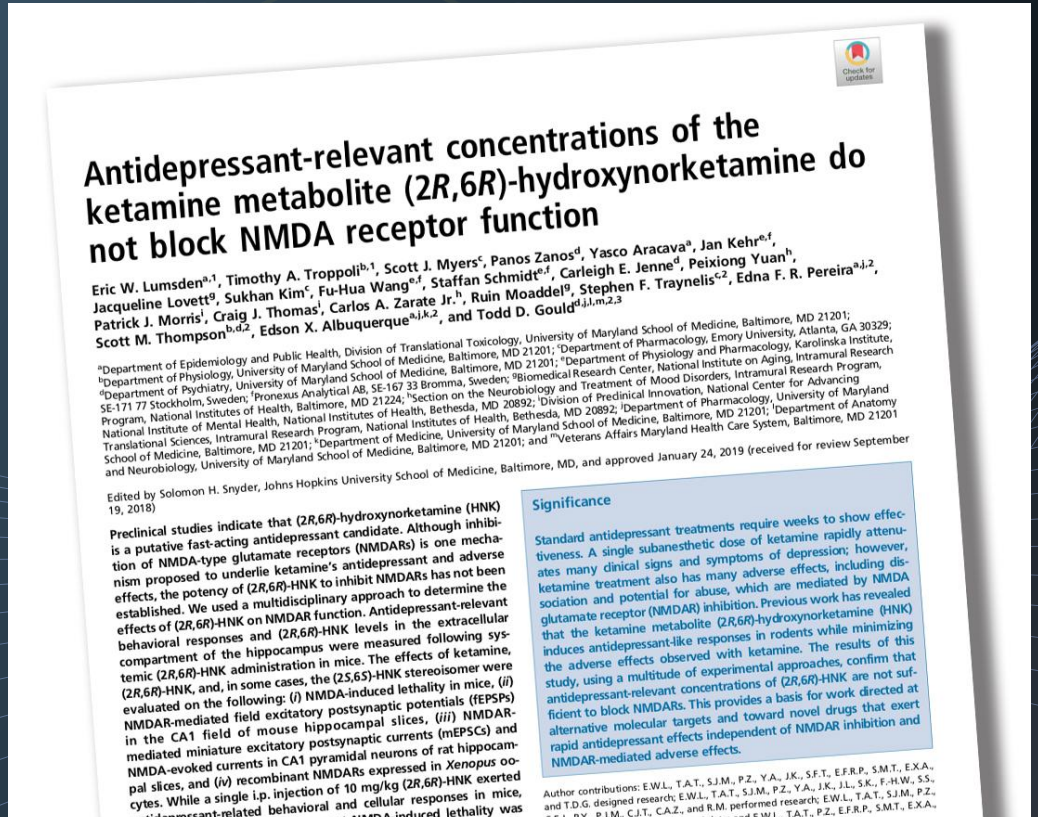

## Antidepressant-relevant concentrations of the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine do not block NMDA receptor function

Eric W. Lumsden[a,1], Timothy A. Troppoli[b,1], Scott J. Myers[c], Panos Zanos[d], Yasco Aracava[a], Jan Kehr[e,f], Jacqueline Lovett[g], Sukhan Kim[c], Fu-Hua Wang[e,f], Staffan Schmidt[e,f], Carleigh E. Jenne[d], Peixiong Yuan[h], Patrick J. Morris[i], Craig J. Thomas[i], Carlos A. Zarate Jr.[h], Ruin Moaddel[g], Stephen F. Traynelis[c,2], Edna F. R. Pereira[a,j,2], Scott M. Thompson[b,d,2], Edson X. Albuquerque[a,j,k,2], and Todd D. Gould[d,j,l,m,2,3]

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Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved January 24, 2019 (received for review September 19, 2018)

**Preclinical studies indicate that (2*R*,6*R*)-hydroxynorketamine (HNK) is a putative fast-acting antidepressant candidate. Although inhibition of NMDA-type glutamate receptors (NMDARs) is one mechanism proposed to underlie ketamine's antidepressant and adverse effects, the potency of (2*R*,6*R*)-HNK to inhibit NMDARs has not been established. We used a multidisciplinary approach to determine the effects of (2*R*,6*R*)-HNK on NMDAR function. Antidepressant-relevant behavioral responses and (2*R*,6*R*)-HNK levels in the extracellular compartment of the hippocampus were measured following systemic (2*R*,6*R*)-HNK administration in mice. The effects of ketamine, (2*R*,6*R*)-HNK, and, in some cases, the (2*S*,6*S*)-HNK stereoisomer were evaluated on the following: (*i*) NMDA-induced lethality in mice, (*ii*) NMDAR-mediated field excitatory postsynaptic potentials (fEPSPs) in the CA1 field of mouse hippocampal slices, (*iii*) NMDAR-mediated miniature excitatory postsynaptic currents (mEPSCs) and NMDA-evoked currents in CA1 pyramidal neurons of rat hippocampal slices, and (*iv*) recombinant NMDARs expressed in *Xenopus* oocytes. While a single i.p. injection of 10 mg/kg (2*R*,6*R*)-HNK exerted**

### Significance

Standard antidepressant treatments require weeks to show effectiveness. A single subanesthetic dose of ketamine rapidly attenuates many clinical signs and symptoms of depression; however, ketamine treatment also has many adverse effects, including dissociation and potential for abuse, which are mediated by NMDA glutamate receptor (NMDAR) inhibition. Previous work has revealed that the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine (HNK) induces antidepressant-like responses in rodents while minimizing the adverse effects observed with ketamine. The results of this study, using a multitude of experimental approaches, confirm that antidepressant-relevant concentrations of (2*R*,6*R*)-HNK are not sufficient to block NMDARs. This provides a basis for work directed at alternative molecular targets and toward novel drugs that exert rapid antidepressant effects independent of NMDAR inhibition and NMDAR-mediated adverse effects.

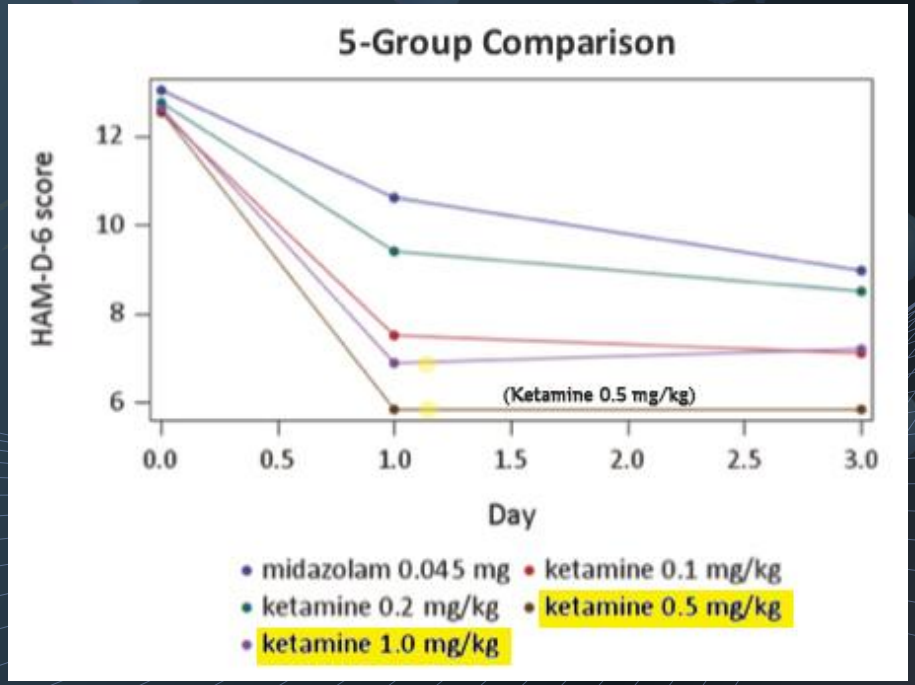
Author contributions: E.W.L., T.A.T., S.J.M., P.Z., Y.A., J.K., S.F.T., E.F.R.P., S.M.T., E.X.A., and T.D.G. designed research; E.W.L., T.A.T., S.J.M., P.Z., Y.A., J.K., J.L., S.K., F.-H.W., S.S., and R.M. performed research; E.W.L., T.A.T., S.J.M., P.Z.,

# Administering Ketamine

- 0.5 mg/kg over 40 minutes
- 2 days/wk
- 5 infusions (additive effect)
- Some require additional induction infusions

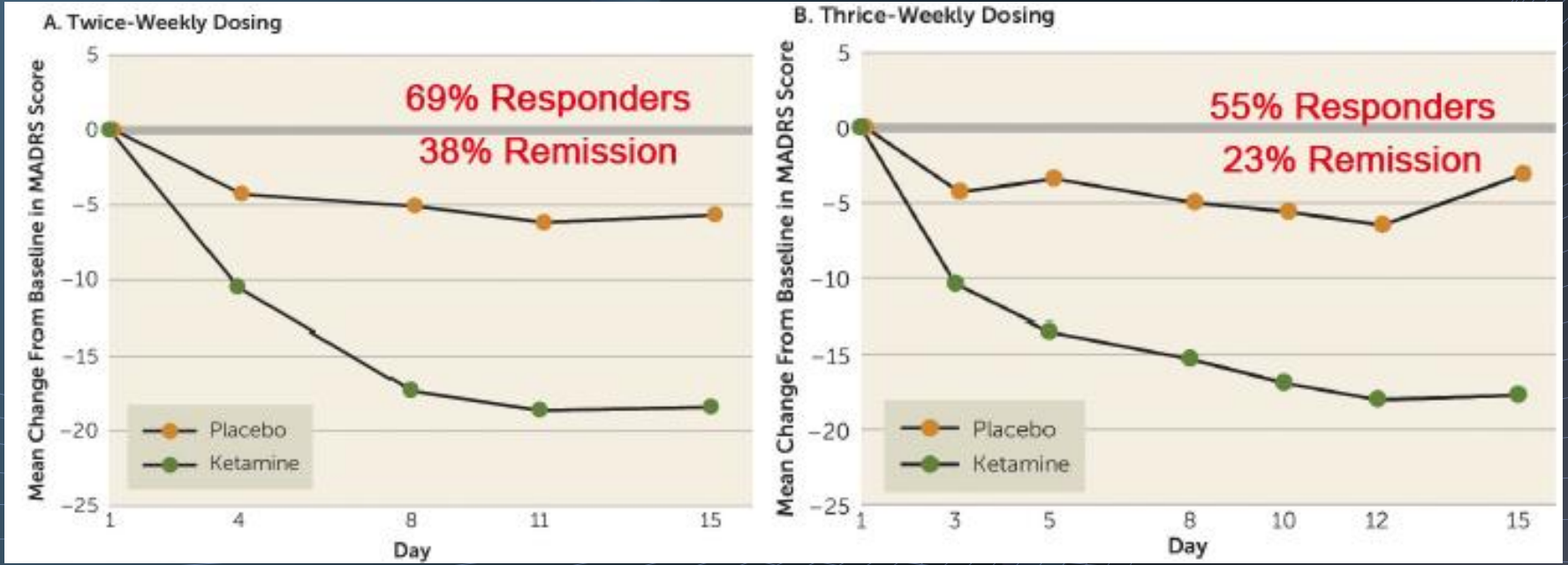
# Ketamine Dose Response

## If a little is good, is more better?




**No**

# Dosing Frequency

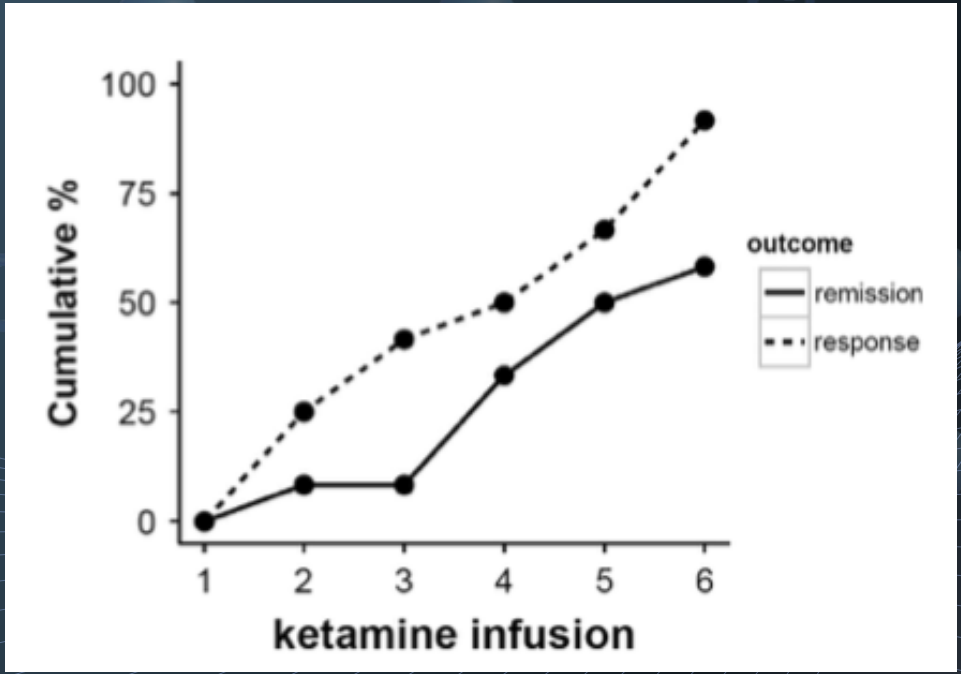



Singh, Jaskaran B., et al. "A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression." *American Journal of Psychiatry* 173.8 (2016): 816-826

Images by G. Sanacora

# Administering Ketamine

## How many doses?



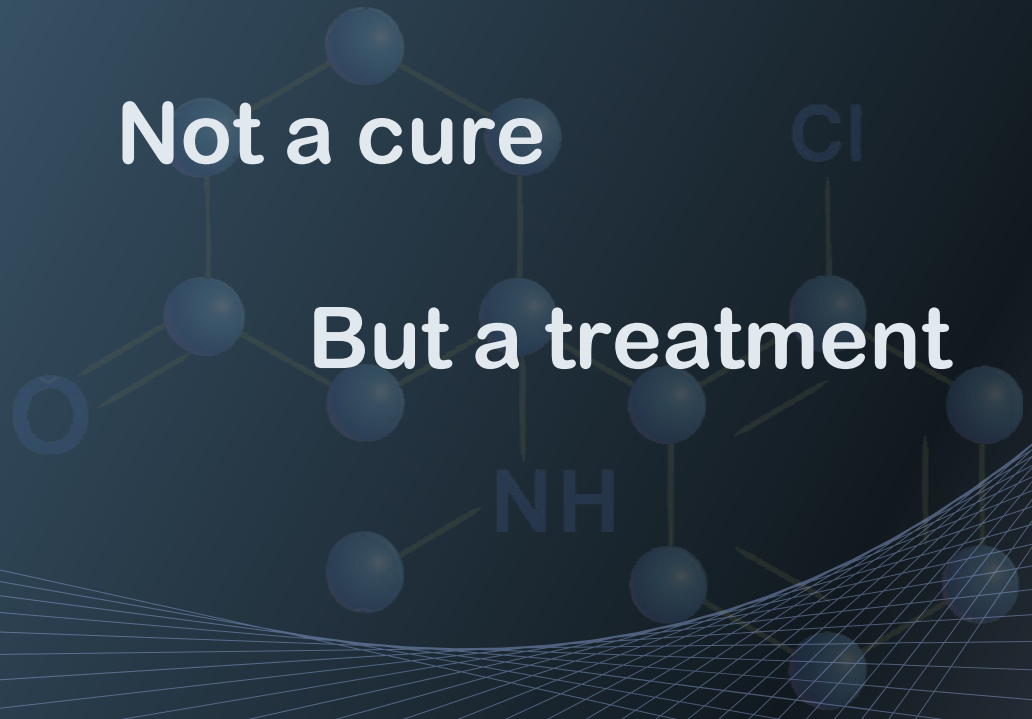

Shiroma, Paulo R., et al. "Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression." *Journal of affective disorders*155 (2014): 123-129

# Post infusion results

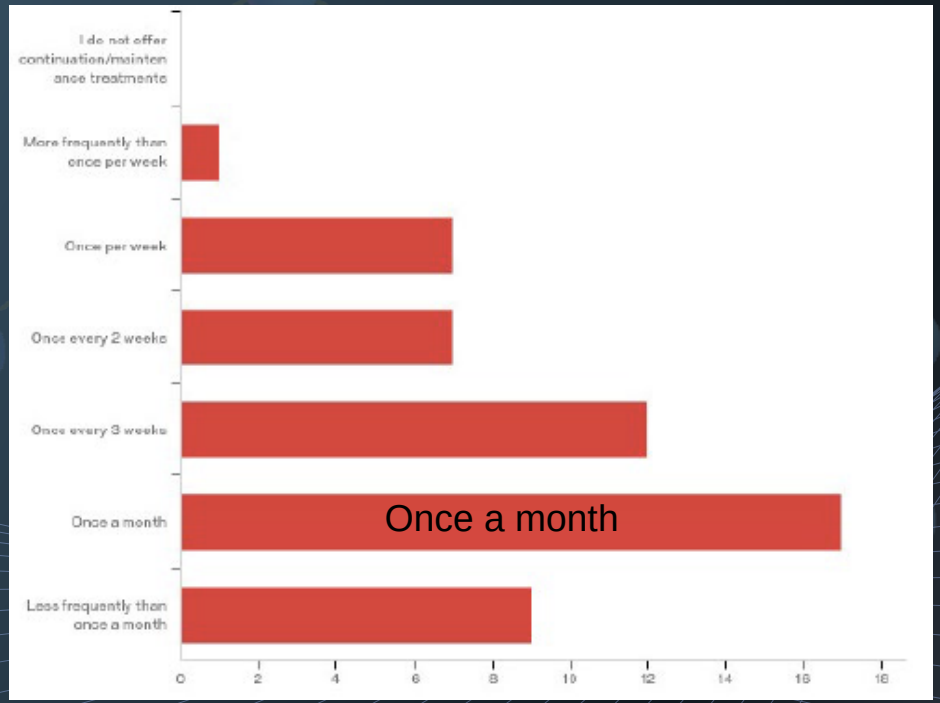
- Day of first infusion, changes usually noted
- Post Infusion Day 1: change variable in degree
- Subsequent infusions- additive effect
- Duration of Effect 3-4 weeks to months

Not a cure

But a treatment



# Frequency of maintance infusions, by survey




Data from a Survey of 54 Ketamine Providers in North, Wilkinson et al. Am. J. Psychiatry 2017

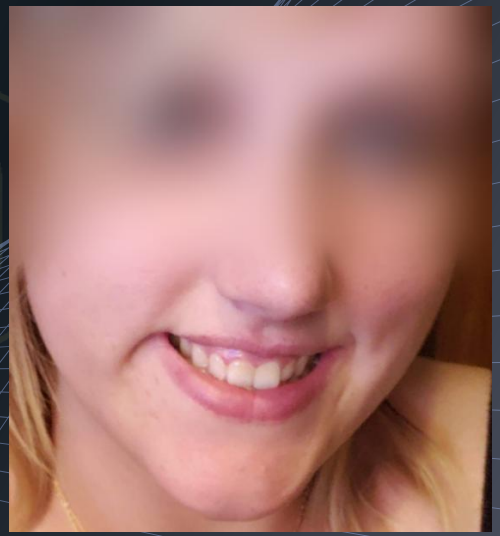
# “Emily”

- Underwent five induction series infusions
- Immediately post:  QIDS-SR = 7 (very mild) (pre: 25)
- Out of bed, out of house, going for walks
- Mom tearfully reports “…new child”

# “Emily”

- 8 wks later:
- Living independently, employed,

& happy



Thank you


# Questions?