# Interventional Psychiatry: A practical introduction to modern ECT, rTMS, and ketamine antidepressant therapy for established psychiatric providers

## Washington State Psychiatric Association Fall Conference

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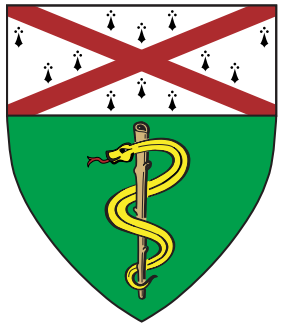

Yale
NewHaven
Health
Yale New Haven
Psychiatric Hospital

# Disclosures

- Dr. Kitay receives funding from Janssen Pharmaceuticals for the conduct of clinical trials involving esketamine administered through Yale University.

- Dr. Kitay has also received honoraria from Janssen Pharmaceuticals.

- This presentation will include discussion of off-label use of ketamine.

# Program Objectives

• Define “Interventional Psychiatry” (IP) and understand its role in current clinical psychiatric practice. Participants will be able to describe the attributes of an "Interventional Psychiatry Service (IPS)" that may be adapted to various settings of clinical psychiatric care.

• Understand the fundamental mechanistic and technical aspects of electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) therapy, and ketamine antidepressant therapy. Participants will become familiar with the current evidence base regarding therapeutic efficacy and the risk/benefit profile for each treatment modality towards understanding appropriate indications for referral.

• Describe practical clinical aspects of IP treatments including: pre-procedure counseling/work-up, elements of safe and effective procedure administration, post-procedure evaluation, and the role of the “outpatient psychiatrist” during various phases of treatment.

• Discuss the role of outpatient psychiatrists in mitigating stigma around- and enhancing access to- IP treatments.

# Program Objectives

Through completion of this course, participants will understand how to incorporate these modalities into their treatment planning and develop skills towards:

1. Formulating appropriate referrals

2. Providing both accurate and effective pre-treatment counseling in anticipation of referral

3. Acknowledging and discussing stigma towards enhancing openness to referral

# Ketamine/Esketamine Antidepressant Therapy

***Outline:***

- Understanding the evidence-base for off-label ketamine treatment and the FDA approval of esketamine
- Understanding the ketamine/esketmaine candidate
  - Diagnoses
  - Demographics
- Understanding the procedure
  - Goals of the procedure itself
  - A typical treatment course
  - Treatment day
  - Anticipatory side-effects
- Role of the outpatient psychiatrist
  - Practical considerations and formulating candidacy
  - Preparing the patient for consultation/referral
  - Remaining the “primary treater” through ketamine/esketamine course

# Ketamine/Esketamine Antidepressant Therapy

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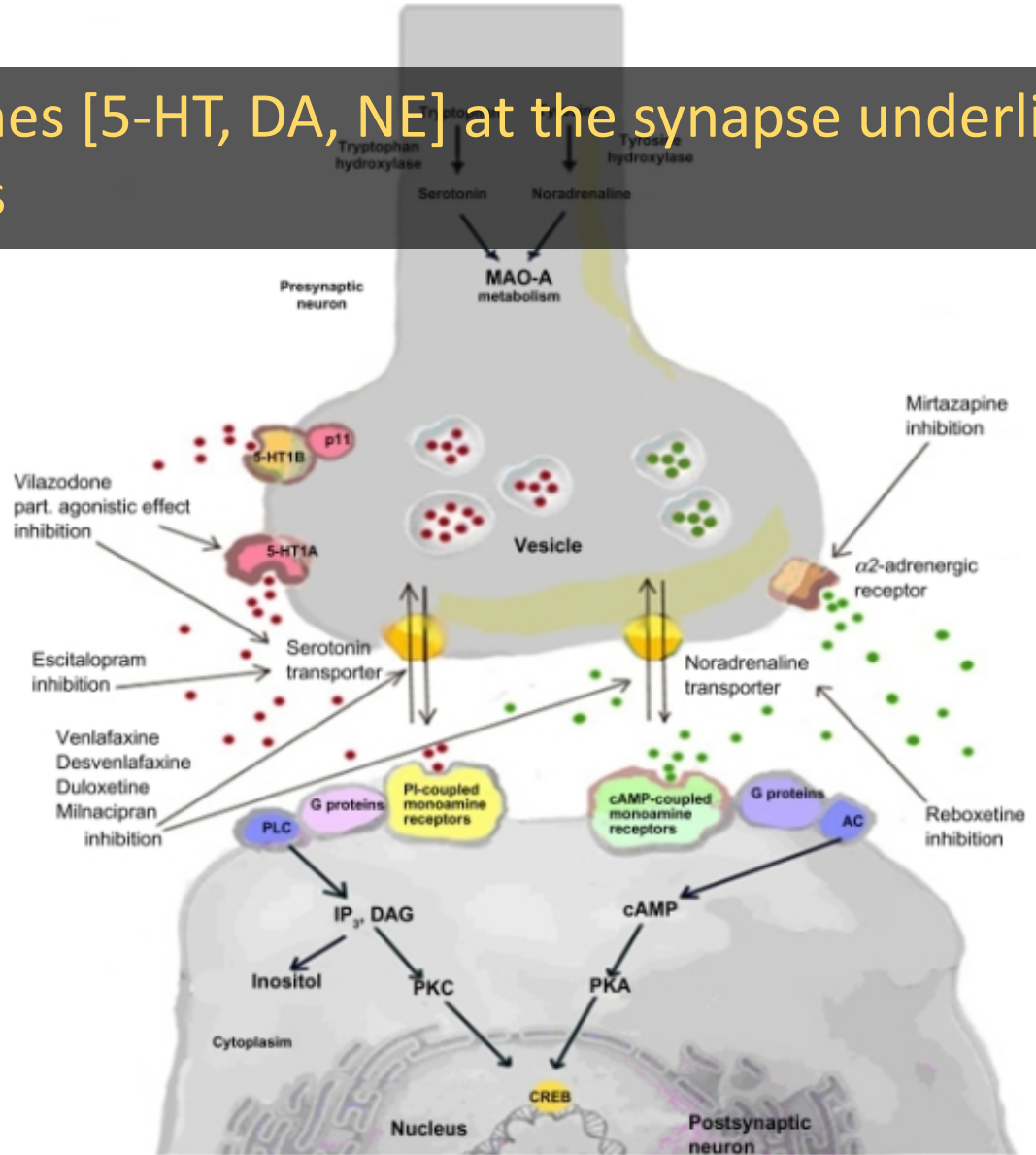
  - Anticipatory side-effects
- Role of the outpatient psychiatrist
  - Practical considerations and formulating candidacy
  - Preparing the patient for consultation/referral
  - Remaining the “primary treater” through an ECT course

# The monoamine hypothesis of depression

Deficiency of monoamines [5-HT, DA, NE] at the synapse underlies the pathophysiology of many mood disorders



# The monoamine hypothesis of depression

- Cannot explain lag time to clinical effect:

  *Current oral antidepressants require 4-6 weeks at an effective dose to evaluate response.*

- Large proportion of patients do *not* improve on standard therapies [STAR*D Trial]:

  ~30% of patients respond to their first antidepressant trial; another ~30% respond to a second trial. Subsequent medication trials have diminishing returns (~10-15% response rate).

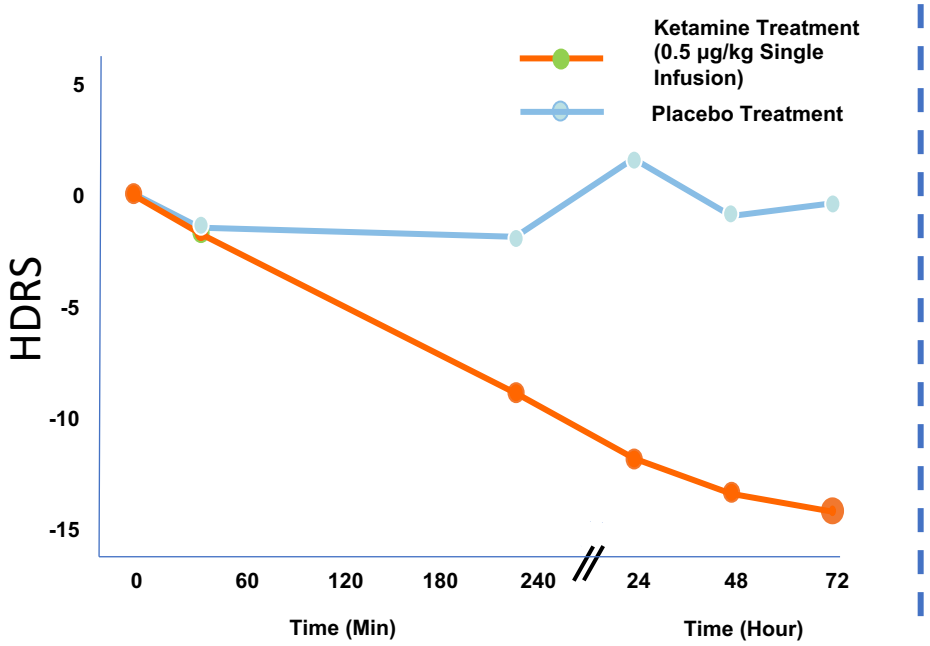
- Monoamine “deficiency” can not fully explain the neurobiology of mood disorders and the heterogeneity of symptoms:

  There are at least 100 known neurotransmitters in the brain and about 100 billion neurons (*not accounting for the number of connections between them*)

# Initial reports of the rapid antidepressant effects of ketamine

*"To the amazement of our patients and ourselves, we found that ketamine produced rapid, profound, and surprisingly durable antidepressant effects that were temporally dissociated from the brief acute behavioral effects of the drug."*

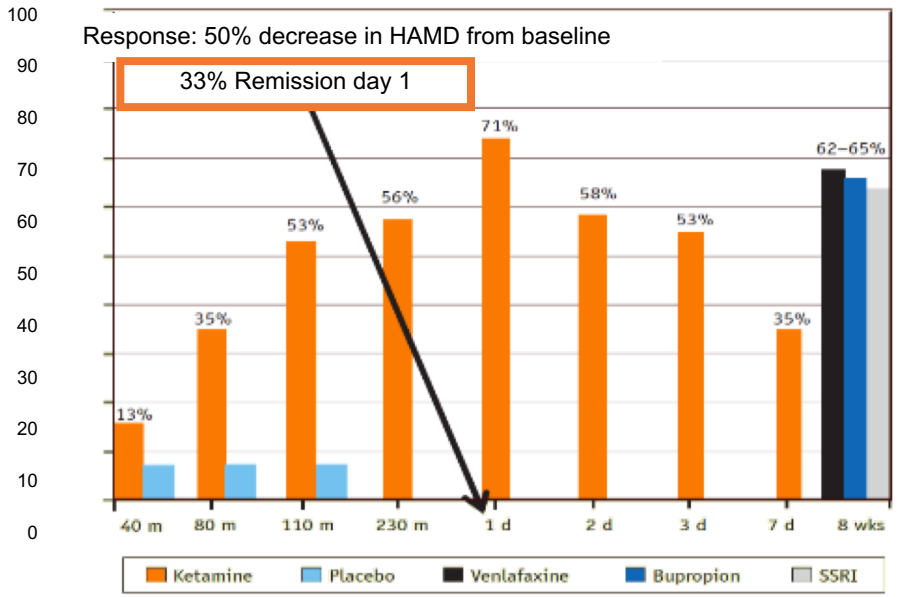
Krystal JH, et al. Neuron. 2019 Mar 6;101(5):774-778




RCT IV Ketamine vs. Saline (N=8)

HDRS = Hamilton Depression Rating Scale for depression.

Berman R, et al. *Biol Psychiatry.* 2000;47:351–354.




RCT IV Ketamine vs. Saline (N=18)

Zarate et al. *Arch Gen Psych*. 2006.

*European Journal of Pharmacology*, 185 (1990) 1–10
Elsevier



EJP 51446

# Functional antagonists at the NMDA receptor complex exhibit antidepressant actions

Ramon Trullas and Phil Skolnick

*Laboratory of Neuroscience, National Institutes of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, U.S.A.*

Received 22 February 1990, revised MS received 22 May 1990, accepted 29 May 1990

Inescapable, but not escapable, stress inhibits the induction of Long Term Potentiation (LTP) in the $CA_1$ region of hippocampus, a process that is dependent upon activation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Since inescapable stress also produces a syndrome of behavioral depression sensitive to clinically effective antidepressants, we examined the actions of functional antagonists at the NMDA receptor complex in animal models commonly used to evaluate potential antidepressants. A competitive NMDA antagonist (2-amino-7-phosphonoheptanoic acid [AP-7]), a non-competitive NMDA antagonist (Dizolcipine [MK-801]), and a partial agonist at strychnine-insensitive glycine receptors (1-aminocylopropanecarboxylic acid [ACPC]) mimicked the effects of clinically effective antidepressants in these models. These findings indicate that the NMDA receptor complex may be involved in the behavioral deficits induced by inescapable stress, and that substances capable of reducing neurotransmission at the NMDA receptor complex may represent a new class of antidepressants. Based on these findings, the hypothesis that pathways subserved by the NMDA subtype of glutamate receptors are involved in the pathophysiology of affective disorders may have heuristic value.

# Emergence of the glutamate hypothesis of depression

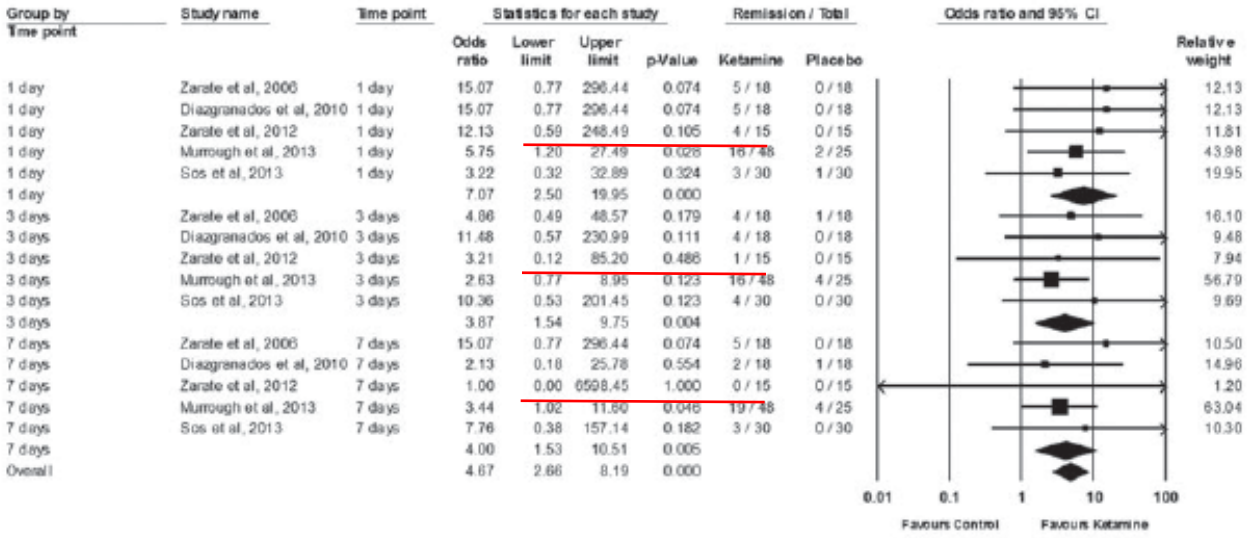
- Several studies report abnormal levels of glutamate/glutamine in plasma, serum, cerebrospinal fluid, and brain tissue of individuals with mood disorders

- Imaging studies have consistently detected abnormalities in the levels and ratios of the amino acid neurotransmitters in several key brain regions

- Conventional antidepressant treatments may converge upon NMDA receptor function and expression as a final common pathway

Sanacora et al 2008 Nat Rev Drug Dis; Ghosal et al., 2017 Curr Opin Behav Sci; Popoli et al., 2011 Nat Rev Neurosci; Altamura et al., 1993 Am J Psychiatry; Abdallah et al., 2014 Am J Psychiatry; Abdallah et al., 2014 Psychother Psychosom

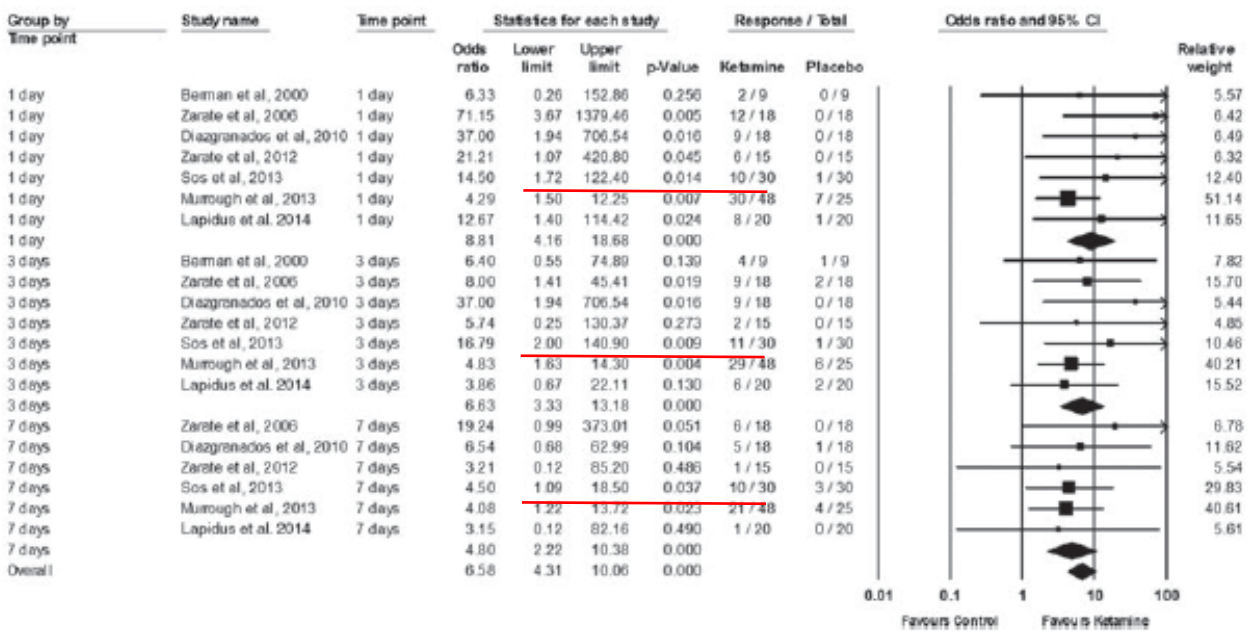
(a) 73 subjects in parallel arms and 110 subjects in cross-over designs



| Group by Time point | Study name | Time point | Odds ratio | Lower limit | Upper limit | p-Value | Remission / Total Ketamine | Remission / Total Placebo | Relative weight |
|---|---|---|---|---|---|---|---|---|---|
| 1 day | Zarate et al, 2006 | 1 day | 15.07 | 0.77 | 296.44 | 0.074 | 5 / 18 | 0 / 18 | 12.13 |
| 1 day | Diazgranados et al, 2010 | 1 day | 15.07 | 0.77 | 296.44 | 0.074 | 5 / 18 | 0 / 18 | 12.13 |
| 1 day | Zarate et al, 2012 | 1 day | 12.13 | 0.59 | 248.49 | 0.105 | 4 / 15 | 0 / 15 | 11.81 |
| 1 day | Murrough et al, 2013 | 1 day | 5.75 | 1.20 | 27.49 | 0.028 | 16 / 48 | 2 / 25 | 43.98 |
| 1 day | Sos et al, 2013 | 1 day | 3.22 | 0.32 | 32.89 | 0.324 | 3 / 30 | 1 / 30 | 19.95 |
| 1 day | | | 7.07 | 2.50 | 19.95 | 0.000 | | | |
| 3 days | Zarate et al, 2006 | 3 days | 4.86 | 0.49 | 48.57 | 0.179 | 4 / 18 | 1 / 18 | 16.10 |
| 3 days | Diazgranados et al, 2010 | 3 days | 11.48 | 0.57 | 230.99 | 0.111 | 4 / 18 | 0 / 18 | 9.48 |
| 3 days | Zarate et al, 2012 | 3 days | 3.21 | 0.12 | 85.20 | 0.486 | 1 / 15 | 0 / 15 | 7.94 |
| 3 days | Murrough et al, 2013 | 3 days | 2.63 | 0.77 | 8.95 | 0.123 | 16 / 48 | 4 / 25 | 56.79 |
| 3 days | Sos et al, 2013 | 3 days | 10.36 | 0.53 | 201.45 | 0.123 | 4 / 30 | 0 / 30 | 9.69 |
| 3 days | | | 3.87 | 1.54 | 9.75 | 0.004 | | | |
| 7 days | Zarate et al, 2006 | 7 days | 15.07 | 0.77 | 296.44 | 0.074 | 5 / 18 | 0 / 18 | 10.50 |
| 7 days | Diazgranados et al, 2010 | 7 days | 2.13 | 0.18 | 25.78 | 0.554 | 2 / 18 | 1 / 18 | 14.96 |
| 7 days | Zarate et al, 2012 | 7 days | 1.00 | 0.00 | 6598.45 | 1.000 | 0 / 15 | 0 / 15 | 1.20 |
| 7 days | Murrough et al, 2013 | 7 days | 3.44 | 1.02 | 11.60 | 0.046 | 19 / 48 | 4 / 25 | 63.04 |
| 7 days | Sos et al, 2013 | 7 days | 7.76 | 0.38 | 157.14 | 0.182 | 3 / 30 | 0 / 30 | 10.30 |
| 7 days | | | 4.00 | 1.53 | 10.51 | 0.005 | | | |
| Overall | | | 4.67 | 2.66 | 8.19 | 0.000 | | | |



(b)



| Group by Time point | Study name | Time point | Odds ratio | Lower limit | Upper limit | p-Value | Response / Total Ketamine | Response / Total Placebo | Relative weight |
|---|---|---|---|---|---|---|---|---|---|
| 1 day | Berman et al, 2000 | 1 day | 6.33 | 0.26 | 152.86 | 0.256 | 2 / 9 | 0 / 9 | 5.57 |
| 1 day | Zarate et al, 2006 | 1 day | 71.15 | 3.67 | 1379.46 | 0.005 | 12 / 18 | 0 / 18 | 6.42 |
| 1 day | Diazgranados et al, 2010 | 1 day | 37.00 | 1.94 | 706.54 | 0.016 | 9 / 18 | 0 / 18 | 6.49 |
| 1 day | Zarate et al, 2012 | 1 day | 21.21 | 1.07 | 420.80 | 0.045 | 6 / 15 | 0 / 15 | 6.32 |
| 1 day | Sos et al, 2013 | 1 day | 14.50 | 1.72 | 122.40 | 0.014 | 10 / 30 | 1 / 30 | 12.40 |
| 1 day | Murrough et al, 2013 | 1 day | 4.29 | 1.50 | 12.25 | 0.007 | 30 / 48 | 7 / 25 | 51.14 |
| 1 day | Lapidus et al, 2014 | 1 day | 12.67 | 1.40 | 114.42 | 0.024 | 8 / 20 | 1 / 20 | 11.65 |
| 1 day | | | 8.81 | 4.16 | 18.68 | 0.000 | | | |
| 3 days | Berman et al, 2000 | 3 days | 6.40 | 0.55 | 74.89 | 0.139 | 4 / 9 | 1 / 9 | 7.82 |
| 3 days | Zarate et al, 2006 | 3 days | 8.00 | 1.41 | 45.41 | 0.019 | 9 / 18 | 2 / 18 | 15.70 |
| 3 days | Diazgranados et al, 2010 | 3 days | 37.00 | 1.94 | 706.54 | 0.016 | 9 / 18 | 0 / 18 | 5.44 |
| 3 days | Zarate et al, 2012 | 3 days | 5.74 | 0.25 | 130.37 | 0.273 | 2 / 15 | 0 / 15 | 4.85 |
| 3 days | Sos et al, 2013 | 3 days | 16.79 | 2.00 | 140.90 | 0.009 | 11 / 30 | 1 / 30 | 10.46 |
| 3 days | Murrough et al, 2013 | 3 days | 4.83 | 1.63 | 14.30 | 0.004 | 29 / 48 | 6 / 25 | 40.21 |
| 3 days | Lapidus et al, 2014 | 3 days | 3.86 | 0.67 | 22.11 | 0.130 | 6 / 20 | 2 / 20 | 15.52 |
| 3 days | | | 6.83 | 3.33 | 13.18 | 0.000 | | | |
| 7 days | Zarate et al, 2006 | 7 days | 19.24 | 0.99 | 373.01 | 0.051 | 6 / 18 | 0 / 18 | 6.78 |
| 7 days | Diazgranados et al, 2010 | 7 days | 6.54 | 0.68 | 62.99 | 0.104 | 5 / 18 | 1 / 18 | 11.62 |
| 7 days | Zarate et al, 2012 | 7 days | 3.21 | 0.12 | 85.20 | 0.486 | 1 / 15 | 0 / 15 | 5.54 |
| 7 days | Sos et al, 2013 | 7 days | 4.50 | 1.09 | 18.50 | 0.037 | 10 / 30 | 3 / 30 | 29.83 |
| 7 days | Murrough et al, 2013 | 7 days | 4.08 | 1.22 | 13.72 | 0.023 | 21 / 48 | 4 / 25 | 40.61 |
| 7 days | Lapidus et al, 2014 | 7 days | 3.15 | 0.12 | 82.16 | 0.490 | 1 / 20 | 0 / 20 | 5.61 |
| 7 days | | | 4.80 | 2.22 | 10.38 | 0.000 | | | |
| Overall | | | 6.58 | 4.31 | 10.06 | 0.000 | | | |



# Rates of Clinical Remission

Number Needed to Treat
24hr NNT = 5
3 days NNT = 6
7 days NNT = 6

# Rates of Clinical Response

24 h NNT = 3
3 days NNT = 3
7 Days NNT = 4

McGirr et al. Psychol Med. 2014 Jul 10:1-12.

# Media Reports of Ketamine's Rapid Antidepressant Effects Dramatically Increase Public Interests

CBSNEWS Video | US | World | Politics | Entertainment | Health | Mone

By RYAN JASLOW / CBS NEWS / April 3, 2014, 12:26 PM

## Ketamine, or "Special K," effectively treats severe depression in study

Glass capsules containing ketamine are seen in Bang Pa In Thailand on June 26, 2008. / NICOLAS ASFOURI/AFP/GETTY IMAGES

TIME

HEALTH MENTAL HEALTH/PSYCHOLOGY

## 'Club Drug' Ketamine Provides Hope in Fight Against Depression

Alice Park @aliceparkny | May 11, 2016

**Ketamine is remarkably good at erasing away the worst symptoms of depression—but there's a catch**

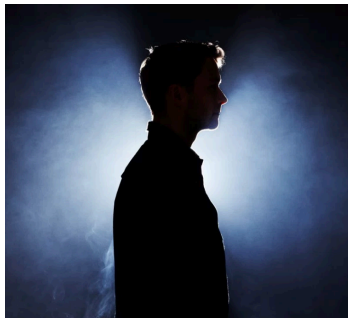
Scientists are increasingly convinced that ketamine, a popular "club drug," may be a viable treatment option for people who suffer from depression. The drug could hold particular promise for people who are suicidal, according to the results of one small study.

David Gonzalez / EyeEm—Getty Images/EyeEm

MENTAL HEALTH/PSYCHOLOGY

## The Dangers of Using the Club Drug Ketamine for Depression

Mandy Oaklander
Mar 02, 2017



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NEWS HEALTH

npr

## Ketamine For Severe Depression: 'How Do You Not Offer This Drug To People?'

March 20, 2017 · 3:19 PM ET
Heard on All Things Considered

JON HAMILTON

chuwy/Getty Images

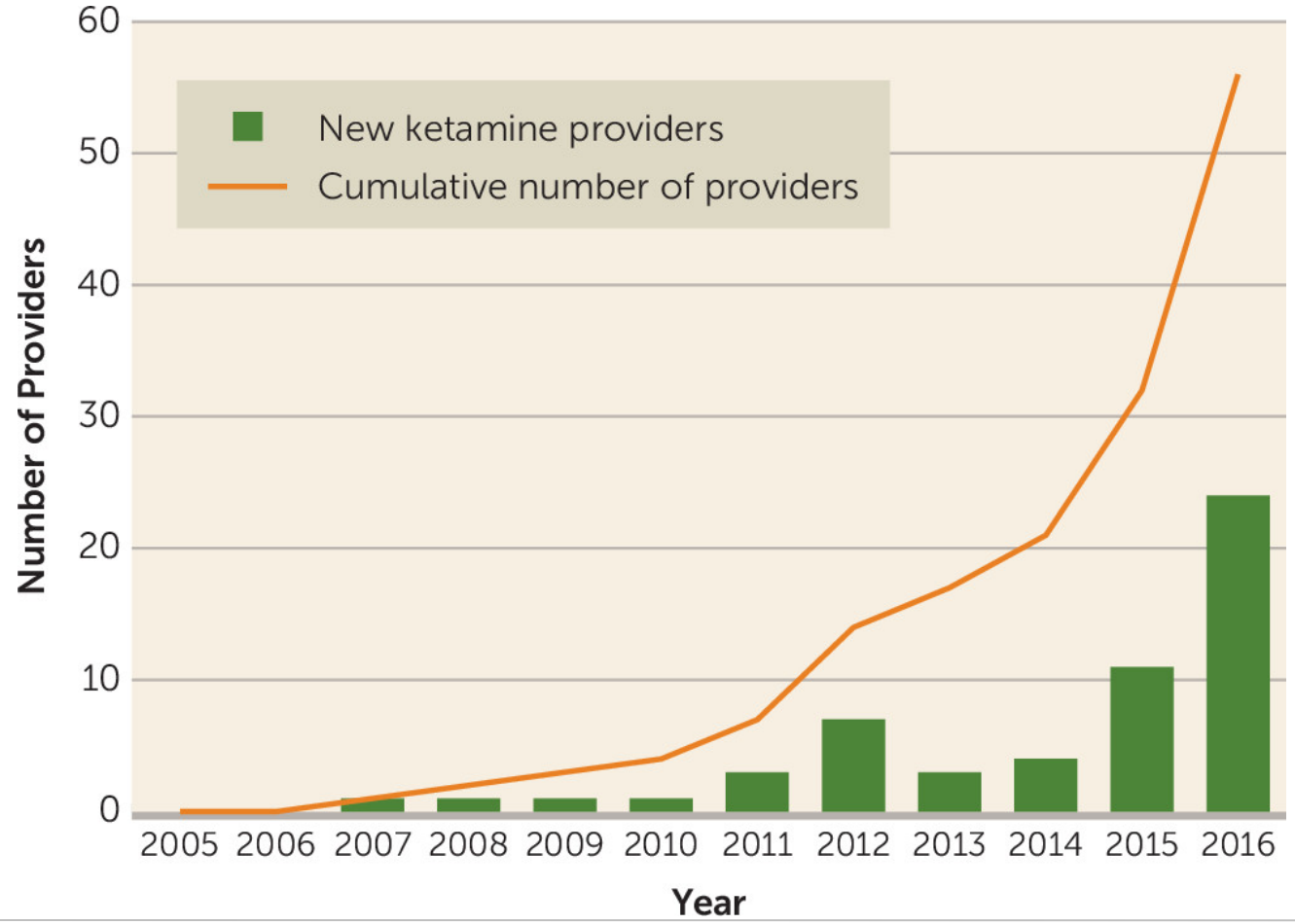
## Ketamine 'exciting' depression therapy

By James Gallagher
Health and science reporter, BBC News

Ketamine offers an avenue of research into a field that has struggled to find new treatments for depression

# Rapid increase in clinicians providing ”off-label” ketamine

**A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders**




Total Number of Physicians Initiating the Practice of Providing Ketamine Off Label for the Treatment of Psychiatric Disorders per Calendar Year (Bars), and Cumulative Number of Ketamine Providers Over Time (Line)

Wilkinson et al. *Am J Psychiatry,* 2017 Jul 1;174(7):695-696

# A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression

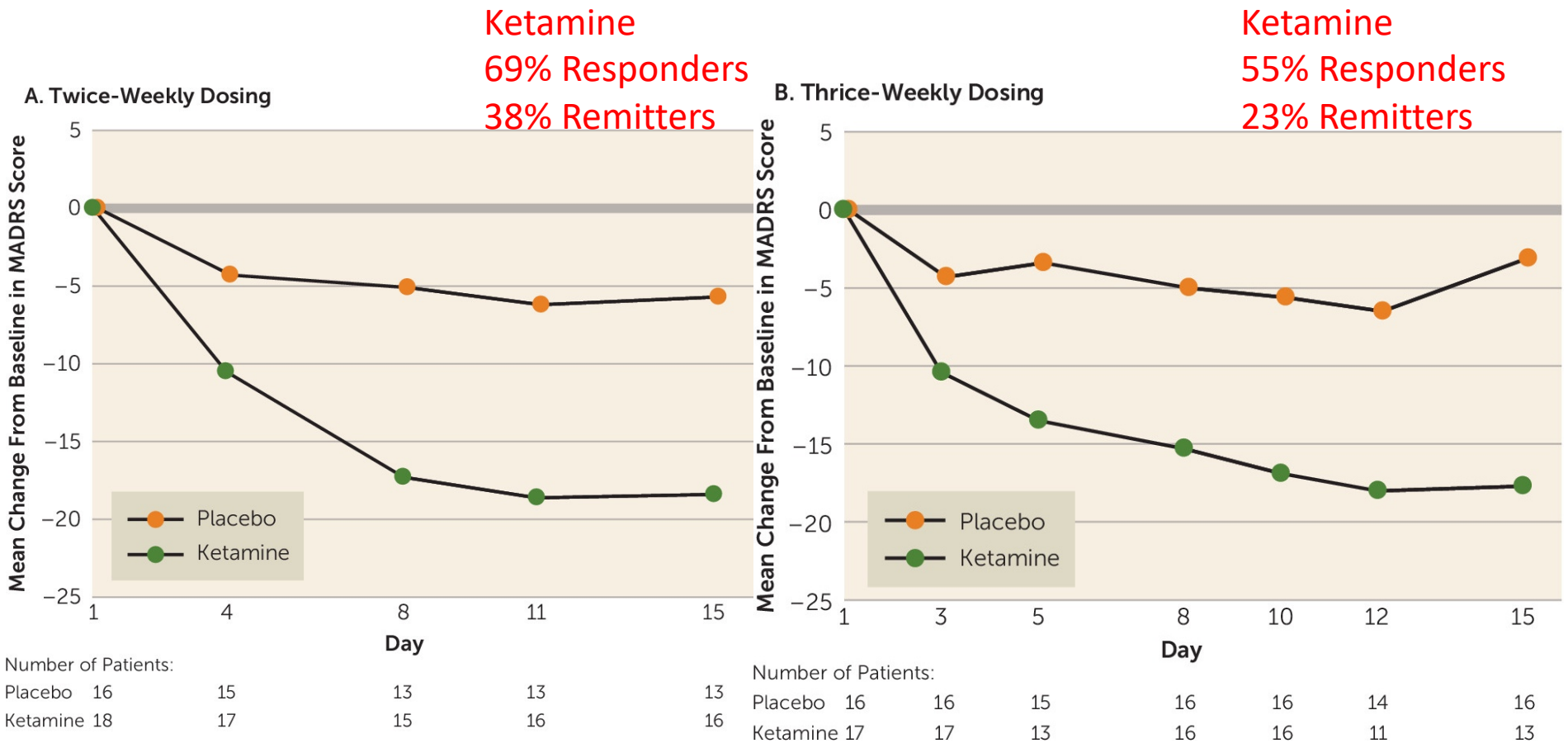
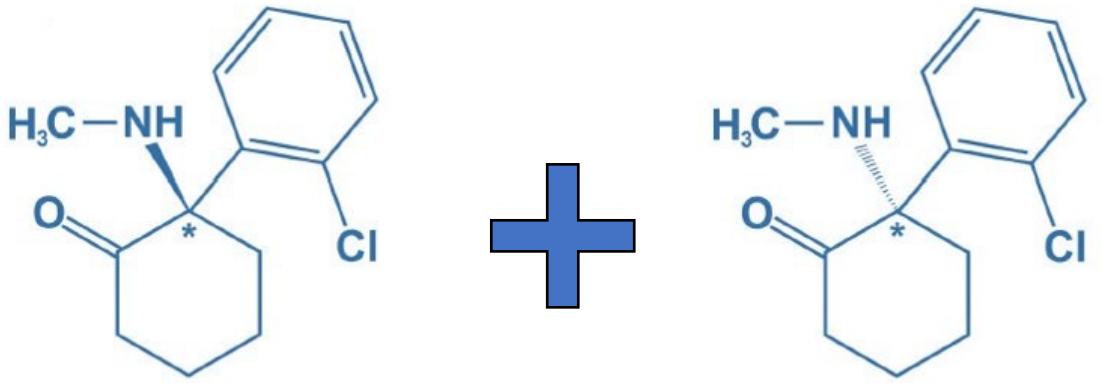



FIGURE 2. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Score, by Dose Frequency, From Baseline Through Day 15 of the Double-Blind Phase in a Study of Intravenous Ketamine in Treatment-Resistant Depression

Singh et al., *Am J Psychiatry,* 2016 Aug 1;173(8):816-26.

# What is ketamine?




*(S)*-ketamine HCL

*(R)*-ketamine HCL

- *General anesthetic and analgesic,* commonly used in pediatric as well as veterinary medicine

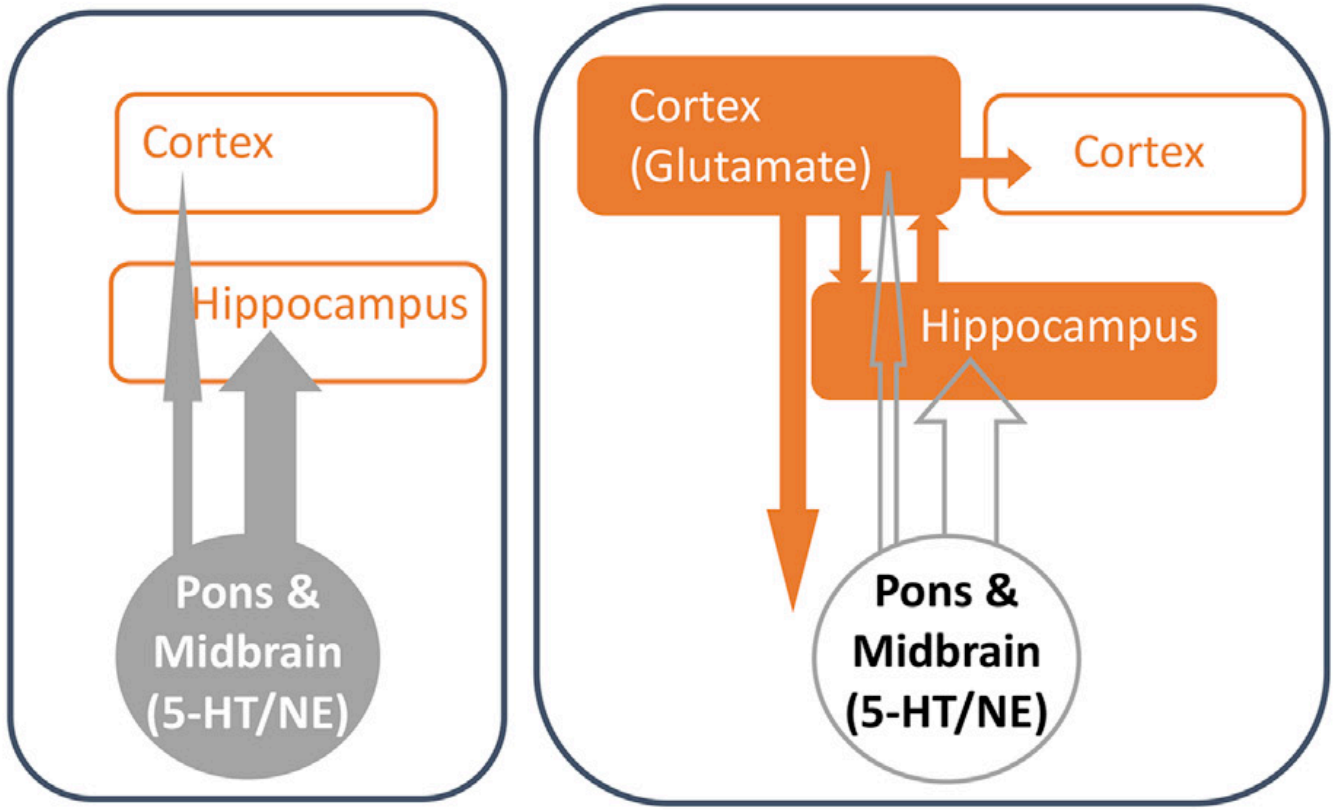
  (Misconception: not *just* a horse tranquilizer)

- A *dissociative* and *psychotomimetic* agent

  (Used as recreational drug by some, AKA “Special K,” “Kitty,” “Vitamin K,” etc.)

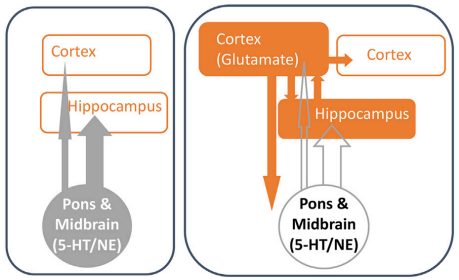
- A *selective, uncompetitive antagonist (e.g. ”activity dependent,” requires activation by glutamate before binding to an allosteric site)* of the **NMDA receptor**

# How does ketamine work? *Hypothetical MoA's*



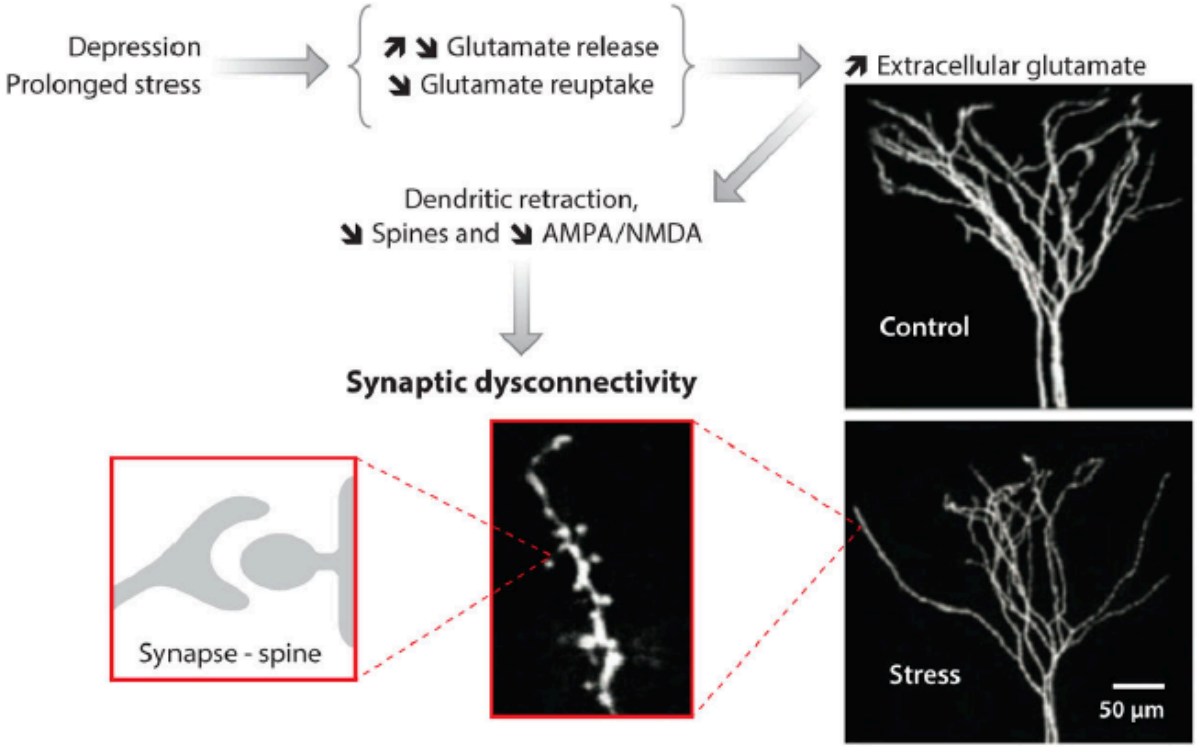

Krystal JH et al. *Neuron,* 2019

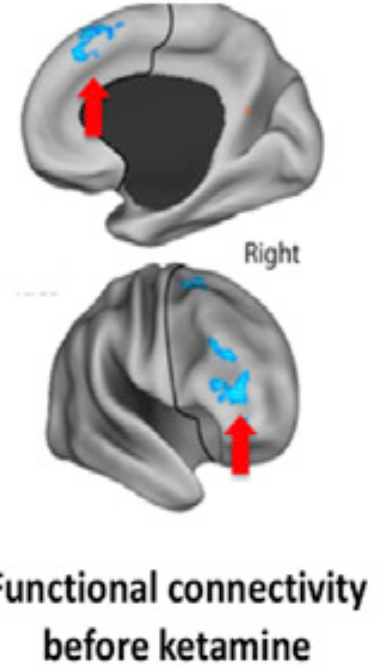
# How does ketamine work? *Hypothetical MoA's*







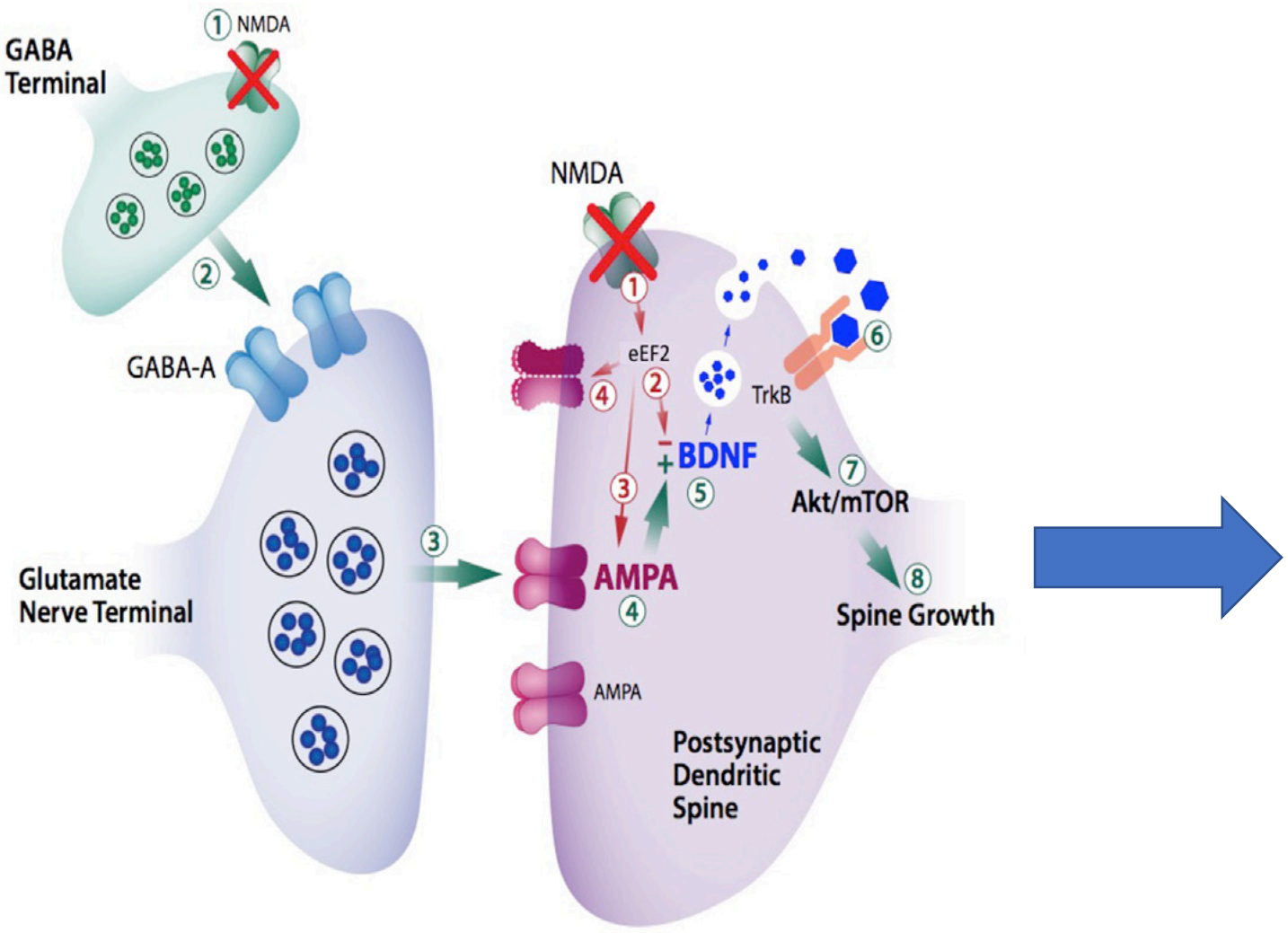


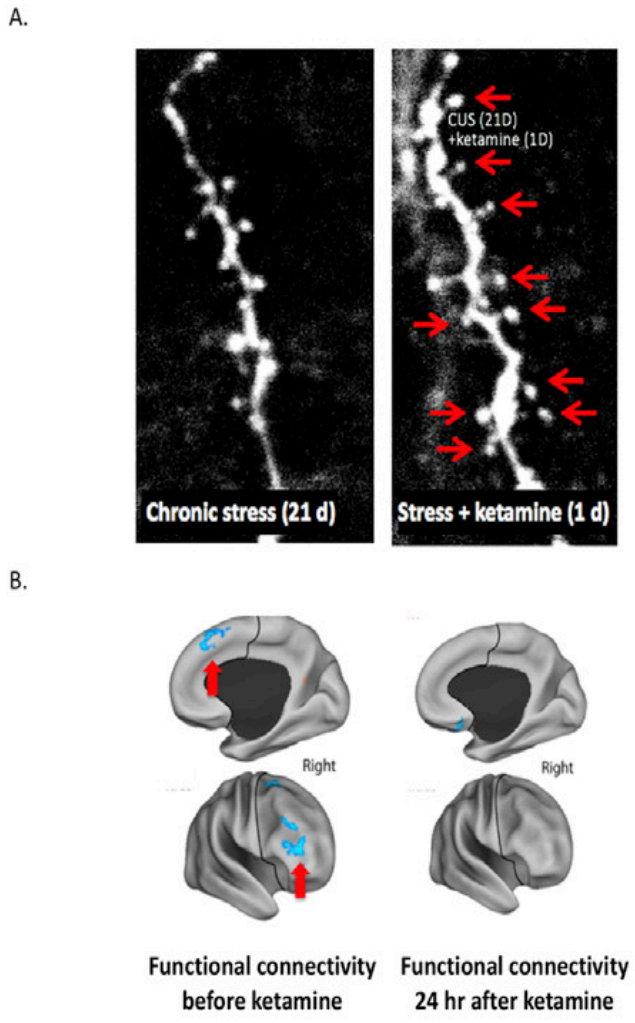




Krystal JH et al. *Neuron,* 2019

Abdallah CG et al., *Ann Rev Medicine*, 2015

# How does ketamine work? *Hypothetical MoA's*



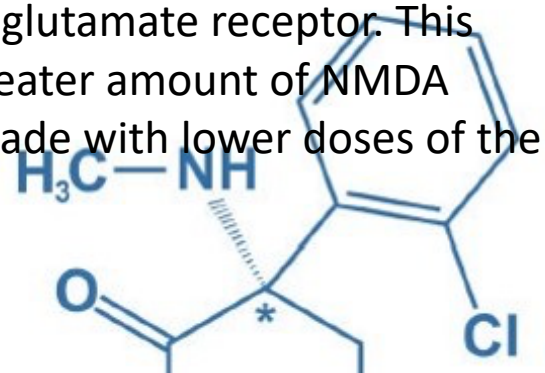



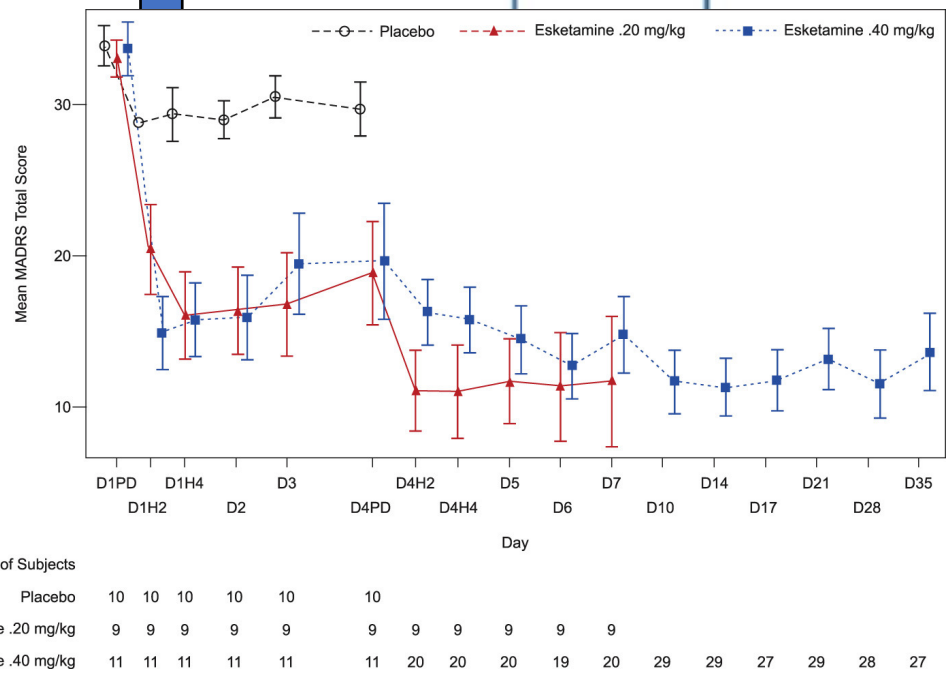

Abdallah CG et al., *Ann Rev Medicine*, 2015

# EsKetamine


(S)-ketamine HCL

The (S) enantiomer has a greater affinity for the NMDA glutamate receptor. This allows for a greater amount of NMDA receptor blockade with lower doses of the drug.

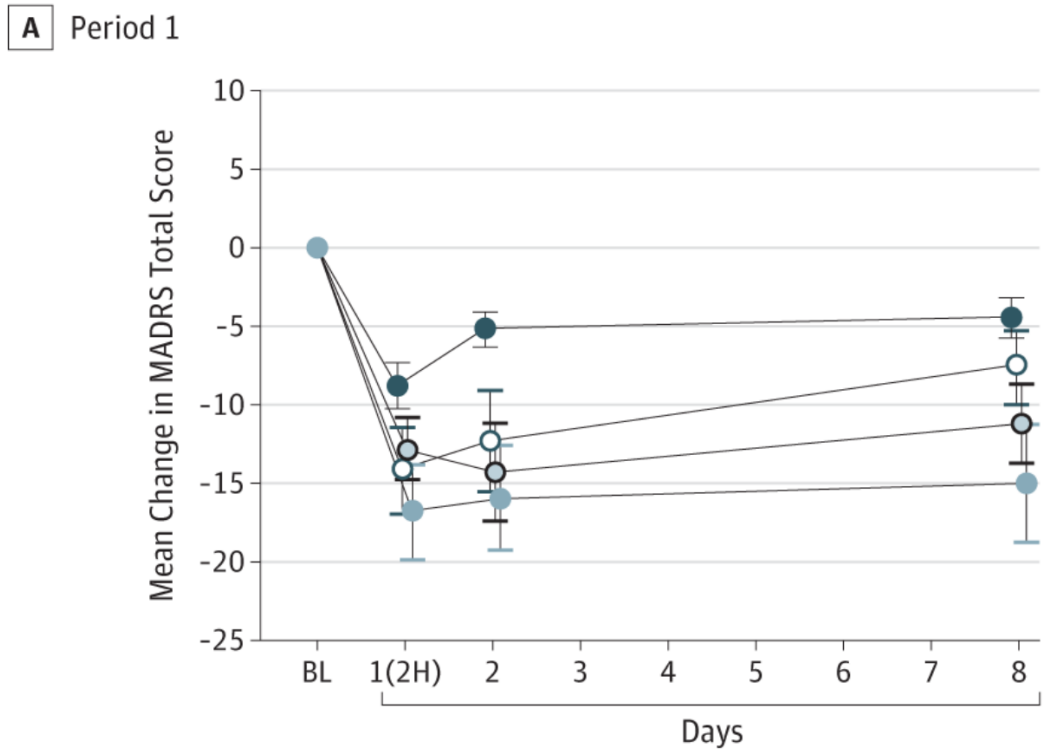


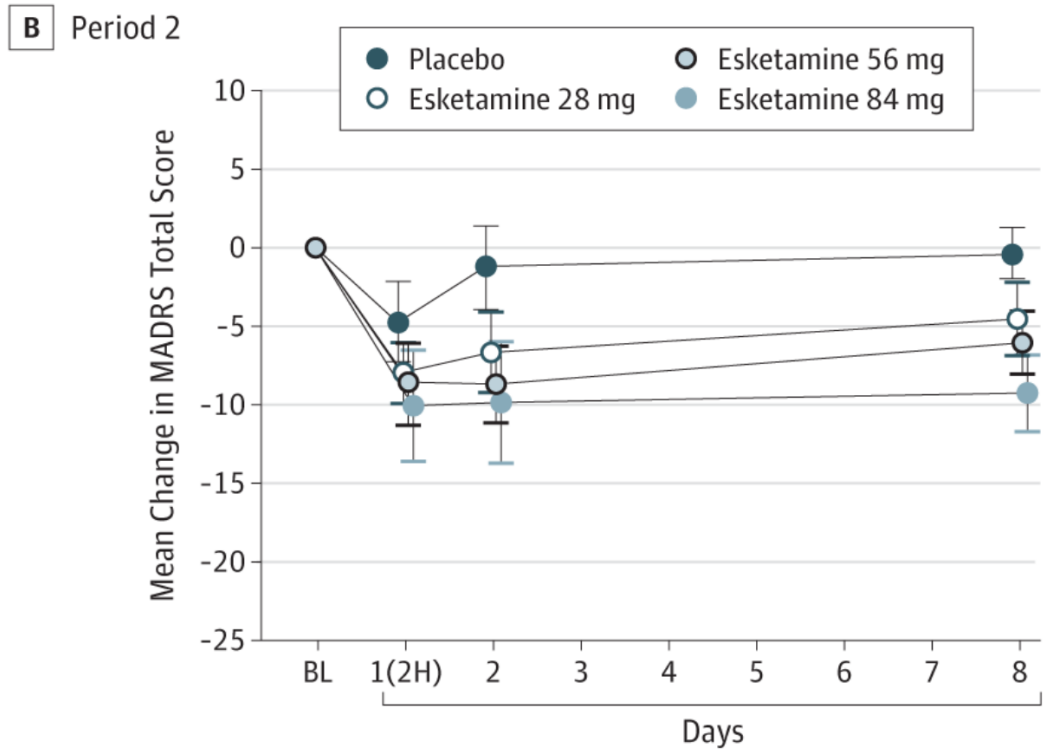

Antidepressant effects of esketamine delivered intravenously

Singh et al. Biol Psychiatry. 2016 Sep 15;80(6):424-431

# Efficacy of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression (Phase 2)




| No. of participants | | | | |
|---|---|---|---|---|
| Placebo | 33 | 33 | | 33 |
| Esketamine 28 mg | 11 | 11 | | 11 |
| Esketamine 56 mg | 11 | 11 | | 11 |
| Esketamine 84 mg | 12 | 12 | | 12 |

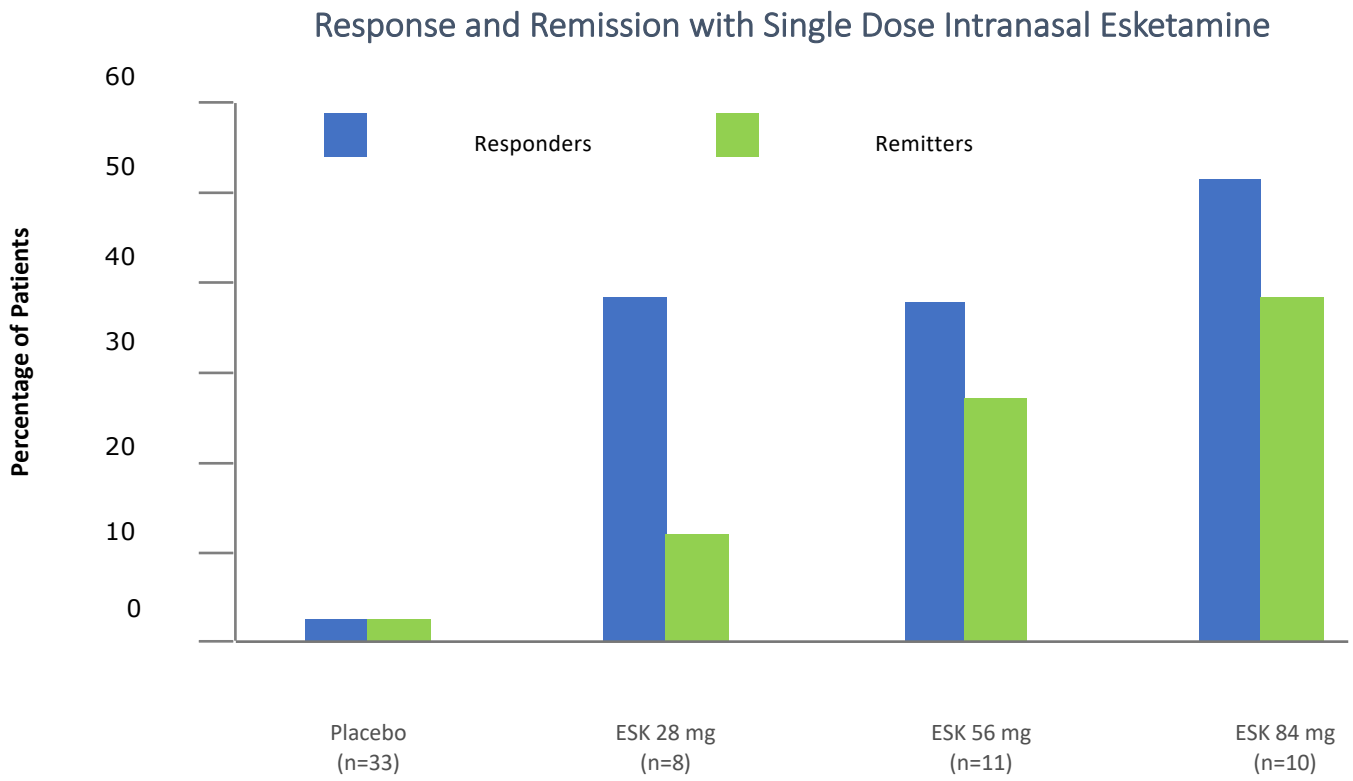



| No. of participants | | | | |
|---|---|---|---|---|
| Placebo | 6 | 6 | | 6 |
| Esketamine 28 mg | 8 | 8 | | 8 |
| Esketamine 56 mg | 9 | 9 | | 9 |
| Esketamine 84 mg | 5 | 5 | | 5 |

Daly et al. ACNP 2015

Daly et al. JAMA Psychiatry. 2018;75(2):139-148

# Efficacy of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression (Phase 2)




Daly et al. JAMA Psychiatry. 2018;75(2):139-148.

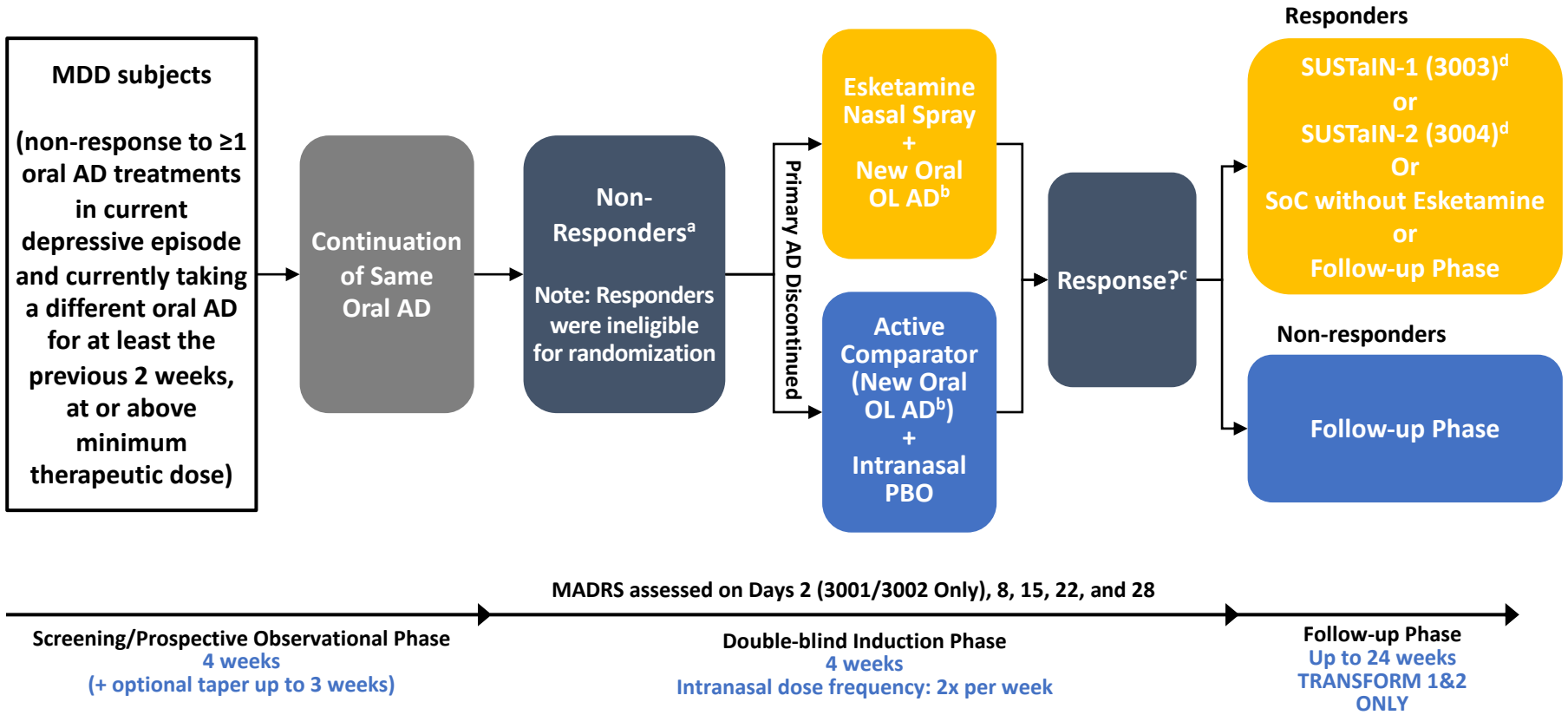
Daly et al. ACNP 2015

# Esketamine Phase 3 Clinical Development Program in Treatment-Resistant Depression (TRD)

| Study | Design | n | Duration (wk) | Main endpoints |
|---|---|---|---|---|
| **Acute, fixed dose study (3001, TRANFORM-1)[1]** | Double-blind, active controlled | 346 | 4-week induction | MADRS change at 4 weeks |
| **Acute, flexible dose study (3002, TRANSFORM-2)[2]** | Double-blind, active controlled | 223 | 4-week induction | MADRS change at 4 weeks |
| **Elderly, acute, flexible dose study (3005, TRANSFORM-3)[5]** | Double-blind, active controlled | 138 | 4-week induction | MADRS change at 4 weeks |
| **Maintenance, relapse prevention study (3003, SUSTaIN 1)[3]** | Open-label or double-blind induction (4-wks) and optimization (12-wks), followed by double-blind, active-controlled maintenance | 705 | Variable duration, longer term | Time to relapse; relapse in stable remitters; relapse in stable responders |
| **Maintenance, safety study (3004, SUSTaIN 2)[4]** | Open-label | 802 | 52-weeks | Safety and tolerability |

**1.** Fedgchin M, et al. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX.* **2.** Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. **3.** Daly EJ, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. **4.** Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. **5.** Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL.

# TRANSFORM (3001[1], 3002[2], and 3005[3]) Short-Term Study Design Overview



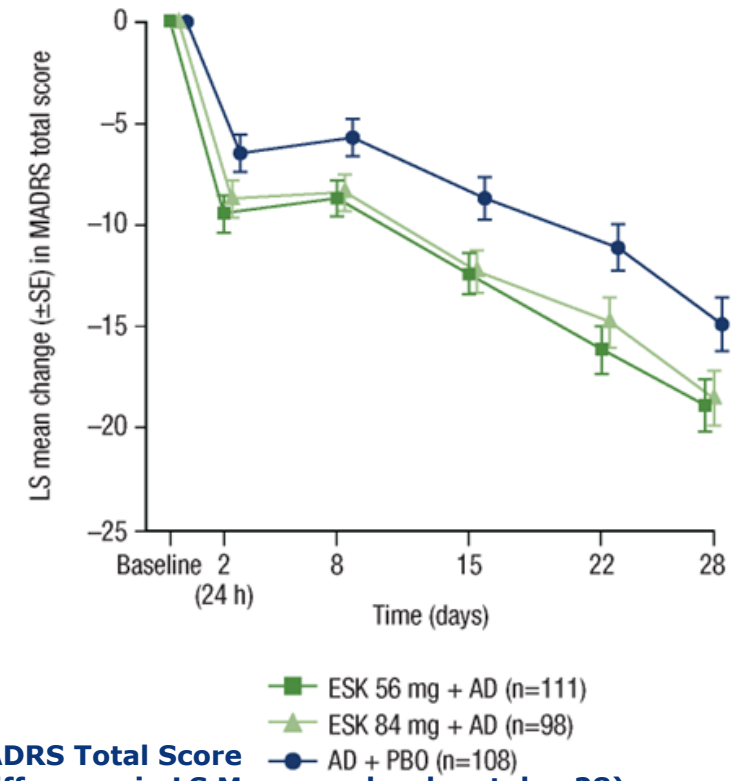

AD, antidepressant; MADRS, Montgomery-Asberg depression Rating Scale; MDD, major depressive disorder; OL, open label; PBO, placebo.
a. Non-response at end of screening (3001 and 3002) = ≤ 25% improvement in MADRS total score from week 1 to week 4 and a MADRS total score ≥ 28 at weeks 2 and 4; Non-response at end of screening (3005) = ≤25% improvement in MADRS total score from week 1 to week 4 and a MADRS total score of ≥24 at weeks 2 and 4.
b. Oral antidepressants included: duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]
c. Responder = ≥ 50% reduction in the MADRS total score from baseline (day 1 pre-randomization) to the end of the double-blind phase.
d. Responders in TRANSFORM-1 (3001)/TRANSFORM-2 (3002) could enter SUSTAIN-1 (3003) or follow-up phase; Regardless of response in TRANSFORM-3 (3005) patients could enter SUSTAIN-2 (3004) or follow-up phase.



1.Fedgchin M, et al. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX.* **2.** Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. **3**. Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL.

# Acute, fixed dose study of Esketamine I.N. (3001, TRANFORM-1)

## LS Mean Change in MADRS Total Score Over Time in Double-blind Phase; Primary Endpoint




**MADRS Total Score (Difference in LS Mean vs placebo at day 28):**

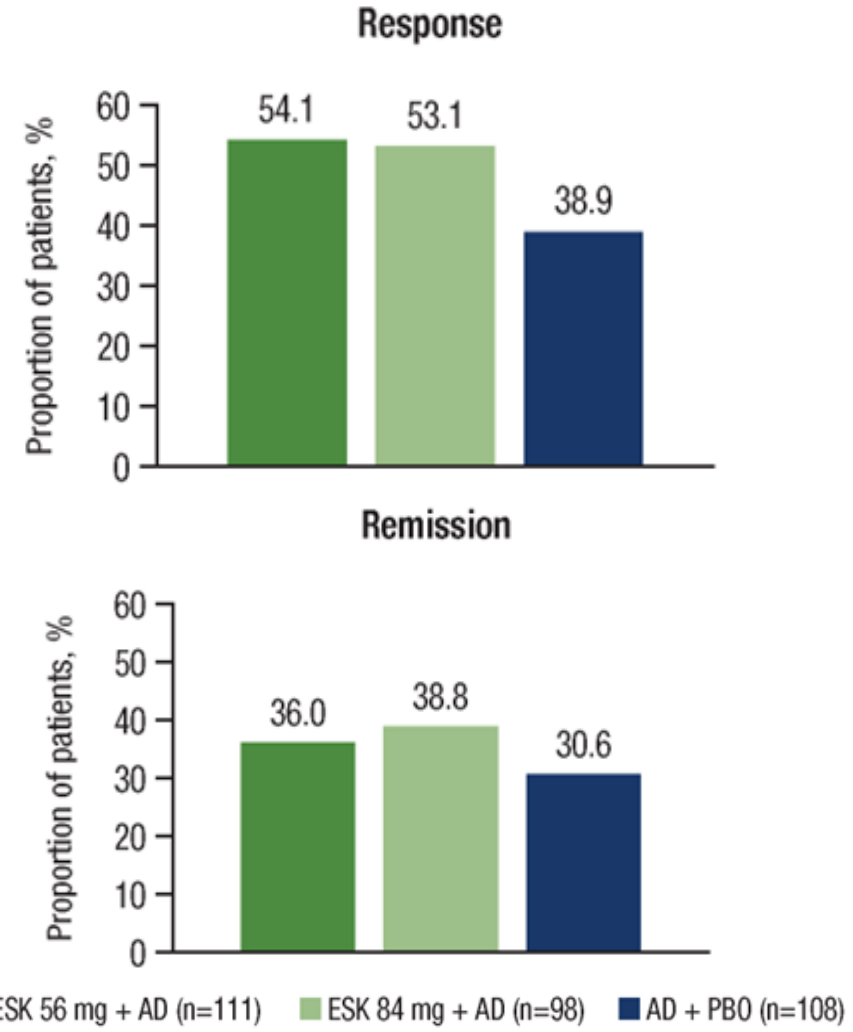
Esketamine 56 mg + oral AD: -4.1
Esketamine 84 mg + oral AD: -3.2

ESK: esketamine; LS: least squares; MADRS: Montgomery-Asberg Depression Rating Scale; SE: standard error

Both ESK + oral AD groups (ESK 56 mg and 84 mg) showed numerically greater change from baseline at every timepoint to day 28 in mean MADRS total score compared to AD + PBO (–19.0 vs. –18.8 vs. –14.8, respectively). However, statistical significance was not demonstrated with the 84 mg ESK + AD group (95% CI: –6.88, 0.45; *P*=0.088); therefore, 56 mg ESK + AD (95% CI: –7.67, -0.49; *P*=N/A), as well as other secondary endpoints, could not be formally evaluated.

Response and remission rates were numerically greater with esketamine + oral AD (56 mg and 84 mg) groups vs oral AD plus placebo nasal spray.

## Response and Remission Rates

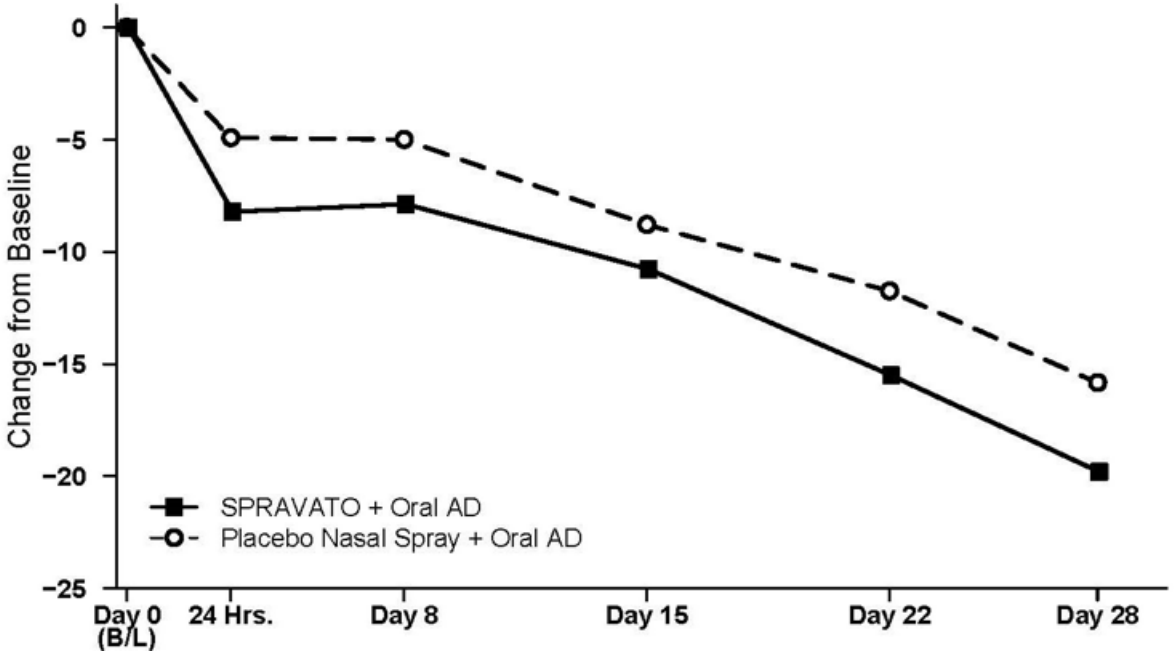



**Response: ≥50% improvement on MADRS from Baseline; Remission: MADRS Total Score ≤12**

Fedgchin M, et al. Poster presented at: *the 9th Biennial Conference of the International Society for Affective Disorders (ISAD);* September 20-22, 2018; Houston, TX

# Acute, flexible dose study (3002, TRANSFORM-2)

## LS Mean Change in MADRS Total Score Over Time in Double-blind Phase[2]




Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO™ dosage from 84 mg to 56 mg twice weekly.

**MADRS Total Score (LS Mean Change from Baseline to end of week 4):**

[2]Esketamine (56 mg or 84 mg) + oral AD: -19.8
oral AD + Placebo Nasal Spray: -15.8

**LS Mean difference: -4.0** (95% CI: -7.3, -0.6)

Esketamine + oral AD group showed a greater improvement from baseline to day 28 in mean MADRS total score compared to the oral AD + placebo group.

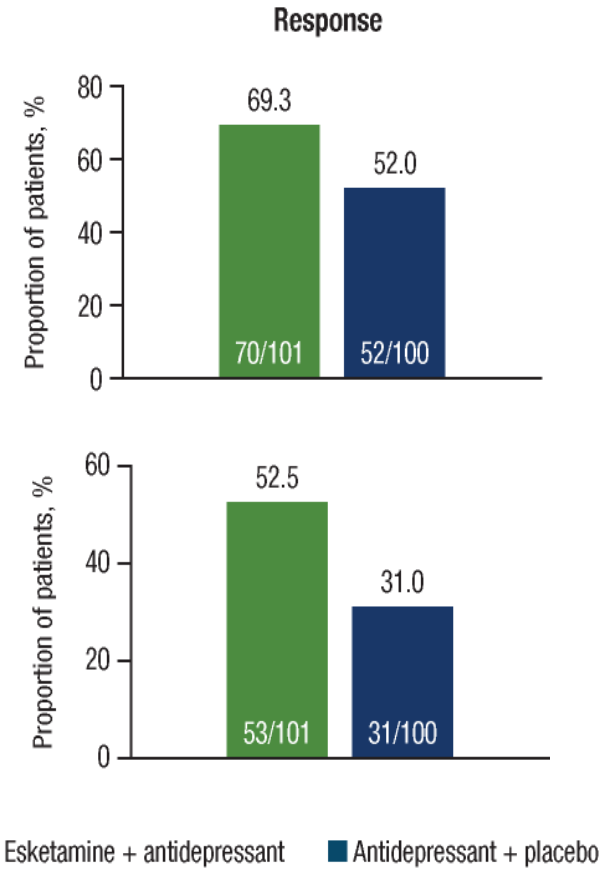
Most of esketamine's treatment difference (compared to placebo) was observed at 24 hours (*P*=0.321).

Between 24 hours and Day 28, there was continued improvement in both treatment groups: the difference between the groups generally remained but did not appear to increase over time through Day 28.

At day 28, 67% of patients randomized to esketamine were on 84 mg.

A greater proportion of patients treated with esketamine + oral AD demonstrated response and were in remission at the end of the 4-week double-blind induction phase than for oral AD plus placebo nasal spray.

## Response and Remission Rates




**Response: ≥50% improvement on MADRS from Baseline;**
**Remission: MADRS Total Score ≤12**


Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. 2.
SPRAVATO™ Prescribing Information Popova et al. Am J Psychiatry. 2019 May 21:appiajp201919020172. [Epub ahead of print]

# Response Can be Sustained with Repeated Treatments
## (3004, SUSTaIN 2)

DATA NOT PUBLISHED IN PEER REVIEWED JOURNAL

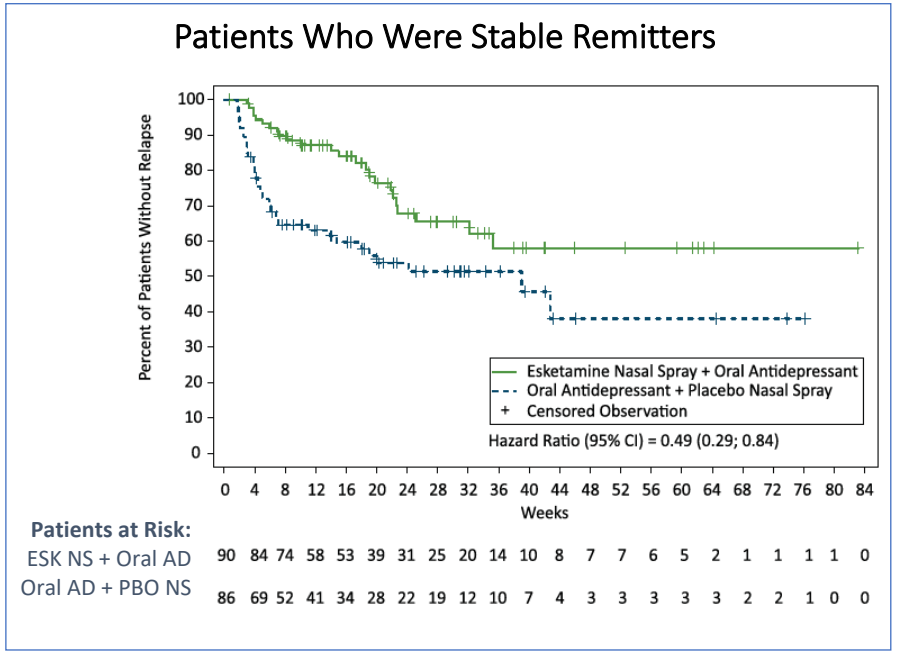
Data may be accessed here:

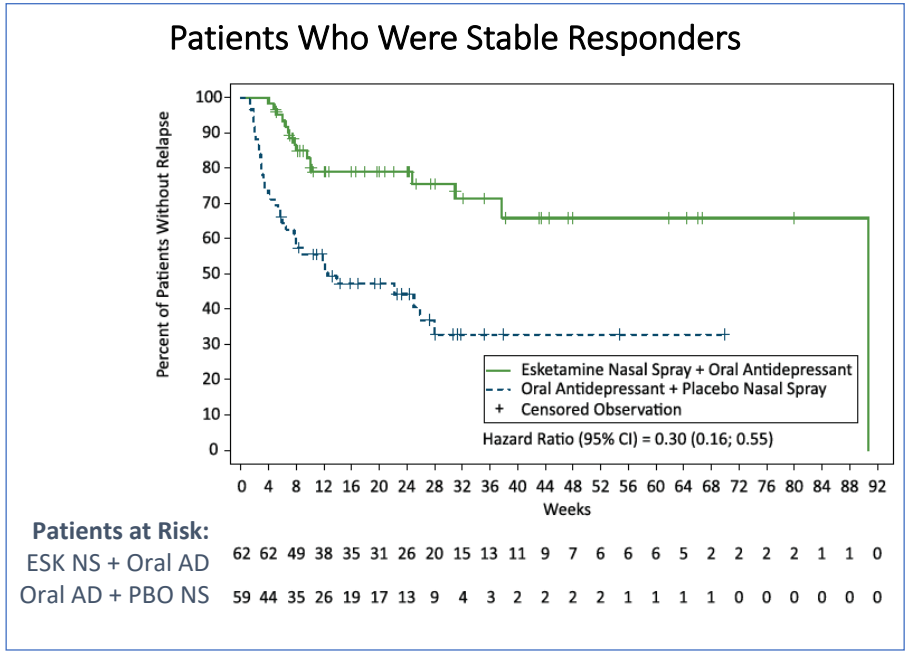
https://clinicaltrials.gov/ct2/show/NCT02497287

https://www.fda.gov/media/121379/download

Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.

# Abruptly Stopping Treatments Increased the Risk of Relapse Over Time (3003, SUSTAIN 1)




AD = anti-depressants; ESK = esketamine; HR: hazard ratio; NS = nasal spray; PBO = placebo

**Relapse Event :**
**ESK NS + Oral AD: 26.7%**
**Oral AD + PBO NS: 45.3%**

**51% reduction (HR: 0.49; 95% CI: 0.29, 0.84; *P*=0.003)**

**Median Time to Relapse:**
ESK NS + Oral AD: Not Estimable
Oral AD + PBO NS: 273 days

**Relapse Event :**
**ESK NS + Oral AD: 25.8%**
**Oral AD + PBO NS: 57.6%**

**70% reduction (HR: 0.30; 95% CI: 0.16, 0.55; *P* <0.001)**

**Median Time to Relapse:**
ESK NS + Oral AD: 635 days
Oral AD + PBO NS: 88 days



Daly EJ et al, *JAMA Psychiatry*, June 2019

# Elderly, acute, flexible dose study (3005, TRANSFORM-3)

DATA NOT PUBLISHED IN PEER REVIEWED JOURNAL

Data may be accessed here:

https://www.fda.gov/media/121379/download

Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL.

# Adverse Events of Interest
## (3004, SUSTaIN 2)

DATA NOT PUBLISHED IN PEER REVIEWED JOURNAL

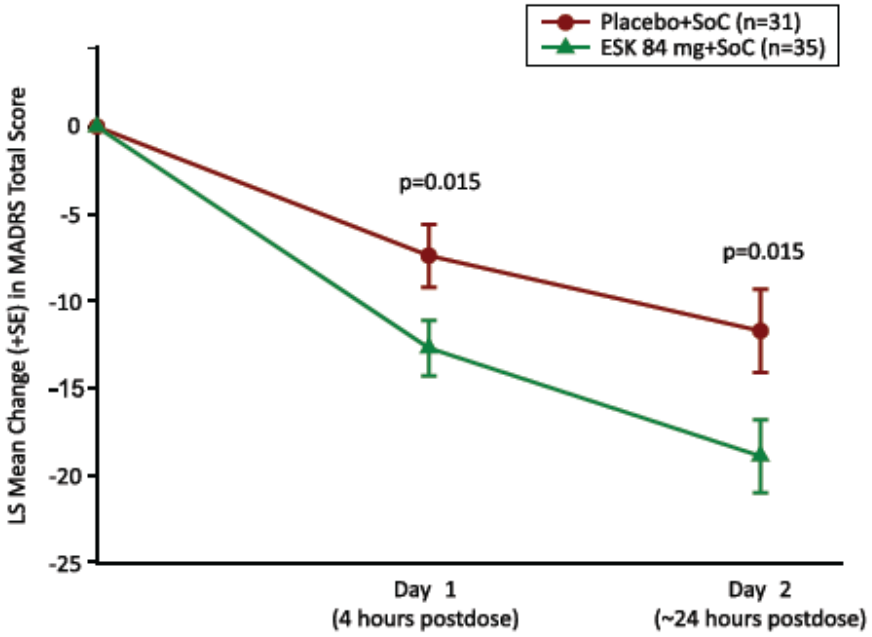
Data may be accessed here:

https://www.fda.gov/media/121379/download

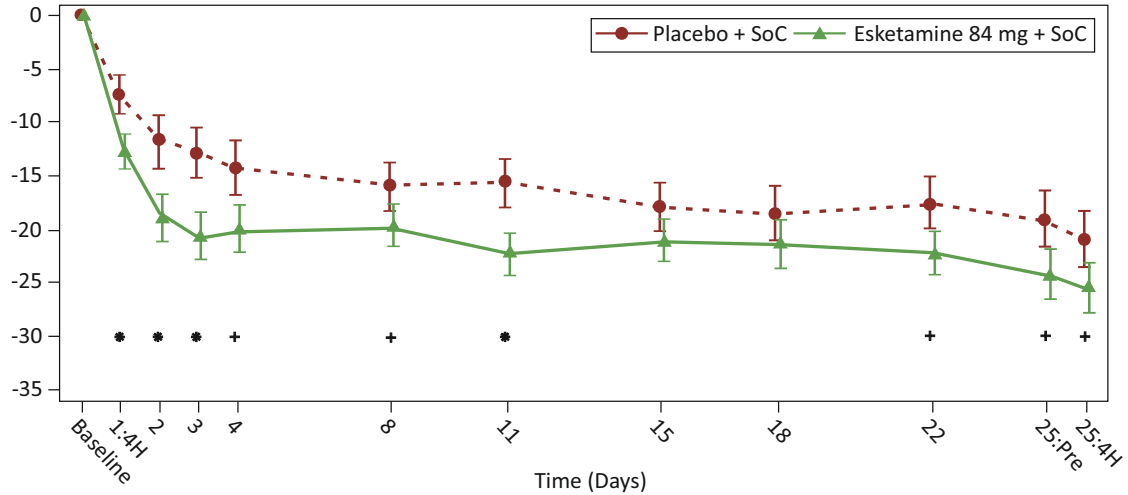
Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.

# Effects of Esketamine in Acutely Suicidal Patients (ASPIRE Studies)

**MADRS change from baseline to 4hr. and 24hr: ITT**




**MADRS change over 25 days**

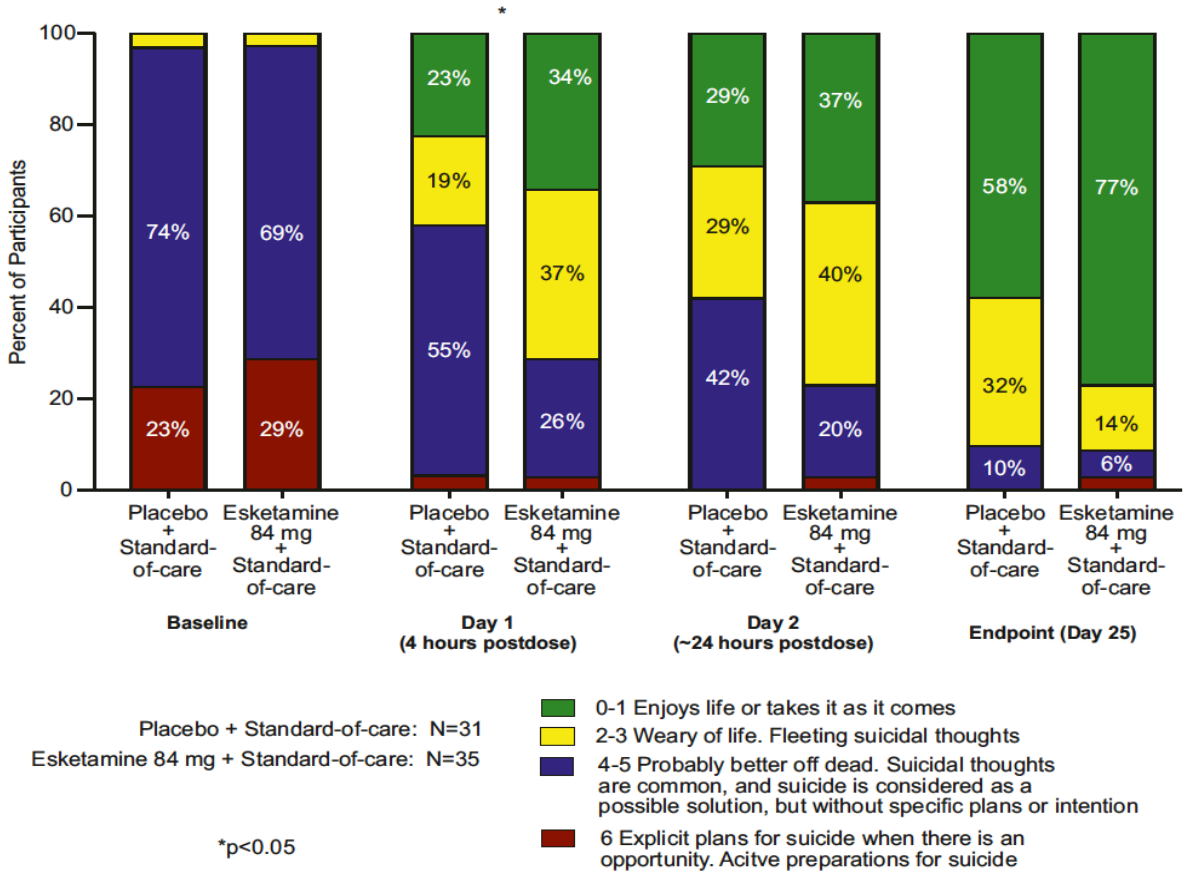



| Number of Participants | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + SoC | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 |
| Esketamine 84 mg + SoC | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |

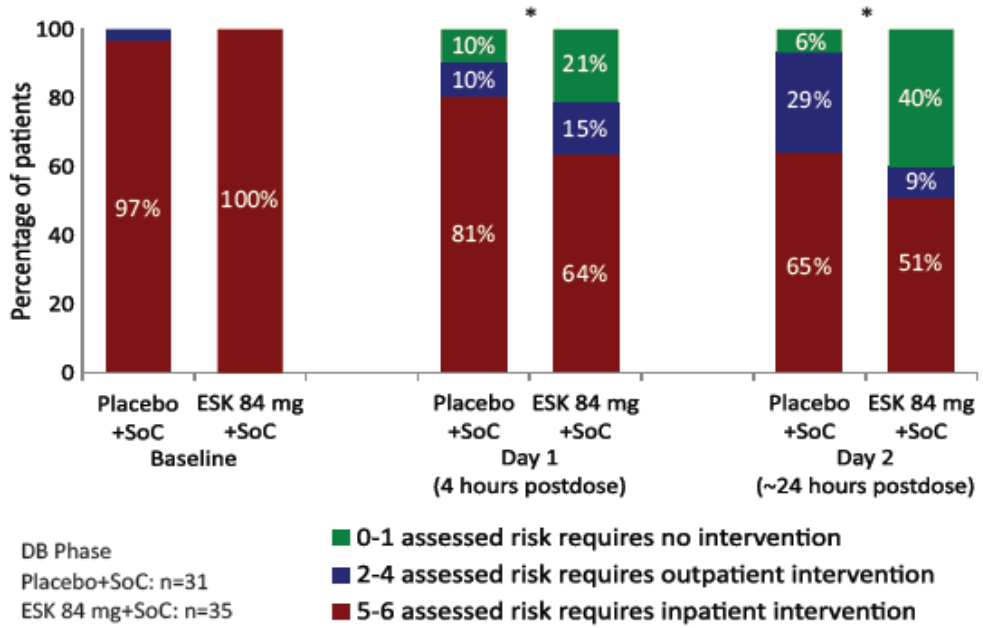
Canuso et al., *Am J Psychiatry*, 2018

# Effects of Esketamine in Acutely Suicidal Patients (ASPIRE Studies)

**Distribution of Responses to Item 10 (Suicide) of the MADRS**




**SIBAT: Frequency Distribution of Clinical Global Judgment of Suicide Risk at Baseline, day 1 (4Hr) and 24Hr: ITT**




Canuso et al., *Am J Psychiatry*, 2018

# Yale-IPS: Our experience with ketamine thus far. . .

- Fall 2014
- Initially single-infusion protocol
- In Spring 2015, we moved to 4-infusion protocol with growing evidence of multi-dose protocols [Singh et al., 2016; Murrough et al., 2013; Shiroma et al., 2014]
- Through Feb 2017:
  - 518 infusions total
  - 54 patients
  - 44 patients with mood disorders who underwent 4-infusion protocol
- Update through Dec 2017
  - 849 infusions
  - 72 patients

# Yale-IPS: Who are our patients?

| Variable | N/Mean (%/SD) |
|---|---|
| Age (SD) | 46.7 (18.0), range 16-87 |
| Male n (%) | 21 (38.9) |
| Marital Status n (%) | |
| Single | 25 (46.3) |
| Married | 18 (33.3) |
| Divorced/Separated | 5 (9.3) |
| Other | 6 (11.1) |
| Disabled, n (%) | 2 (4.7)* |
| Race n (%) | |
| White | 52 (96.3) |
| African American | 1 (1.9) |
| Other | 1 (1.9) |
| Diagnosis n (%) | |
| Major Depressive Disorder | 44 (81.5) |
| Bipolar Disorder | 6 (11.1) |
| Schizoaffective Disorder | 3 (5.6) |
| Catatonia | 1 (1.9) |
| History of Electroconvulsive Therapy, n (%) | 27 (55.1) |
| History of Hospitalization, n (%) | 40 (74.1) |
| History of Hospitalization for Suicidal Ideation or Attempt, n (%) | 35 (64.8) |
| History of Suicide Attempt, n (%) | 23 (46.9)** |
| Inpatient Status at First Infusion, n (%) | 21 (38.9) |
| Baseline QIDS-SR Score (SD) | 19.8 (6.0) |
| Baseline MADRS Score (SD) | 33.1 (6.9) |

# Typical Ketamine/Esketamine Treatment Course

## Initial Consult

- Pre-procedure workup
- Consent/registration in the Spravato™ REMS

## "Index" Series

- 6 *total treatments, IV ketamine – 8 total treatments, IN esketamine*
- Twice weekly (Tue/Thu)

## Maintenance Phase = *???*

- Exploratory
- Many patients will *stop* following a first index series and return after relapse/recurrence
- Many patients have begun "maintenance courses" similar to ECT with goal of treatment tapering to *qmonthly*

# Yale-IPS: Ketamine/Esketamine work-flow

- Initial evaluation in office
  - Indications: *treatment resistant major depressive disorder (failed at least two adequate medication trials), difficult to treat bipolar depression.*
  - Exclusions: Patients with active substance use or strong substance use histories
  - Avoid patients with psychotic disorders, unless MDD with psychotic features.
  - Ketamine vs. ECT?
  - *Extensive counseling regarding the "dissociative experience" – expectations lean both valences!*
- If appropriate for ketamine, sent to PCP for "pre-operative" evaluation
  - Labs
  - Urine toxicology
  - Physical exam
  - EKG
- Written informed consent
- Discussion regarding payment:
  - *Racemic ketamine not covered by most insurance companies! Insurers have begun contracting to reimburse to esketamine, but questions remains about procedural codes for actual dosing*
  - *Out of pocket: ~$6000 for a treatment course*
  - *Appropriate for a clinical trial?*

# Yale-IPS: Ketamine/Esketamine Treatment Day

Presentation for treatment

- Patient is NPO for 4 hours (solids), 2 hours (liquids)
- Evaluation with psychometric rating scales
  - Montgomery Asberg Depression Rating Scale (MADRS)
  - Quick Inventory of Depressive Symptomatology (QIDS)
- Insert IV or train with esketamine delivery device
- Vitals and rhythm EKG monitored throughout treatment
- IV: Mix 0.5mg/kg of ketamine in 500cc NS (dosing based on *ideal body weight)*
- IN: Select between 24mg, 56mg, 84mg doses (typically start 56mg vs 84mg)
- Last “pre-briefing” / anticipatory guidance

# Yale-IPS: Ketamine/Esketamine Treatment Day

During protocol – patient monitored by nursing

- Continuous pulse oximetry
- Continuous telemetry
- Blood pressure q15 minutes (IV), basline, 40min, 2 hours (IN)
- Maintain a low stimulus environment (lights dimed, quiet, soothing music)

Following Completion of Infusion

- Clinician Administered Dissociative State Scale (CADSS)
- Additional monitoring for at least 30 minutes (IV), ***mandatory 2 hour monitoring (IN)***
- Discharge readiness criteria:
  - Normal mental status
  - CADSS back to baseline
  - Vital signs normal

JAMA Psychiatry | Special Communication

# A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Gerard Sanacora, MD, PhD; Mark A. Frye, MD; William McDonald, MD; Sanjay J. Mathew, MD; Mason S. Turner, MD; Alan F. Schatzberg, MD; Paul Summergrad, MD; Charles B. Nemeroff, MD, PhD; for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments

- Important to consider limitations of the available data and the potential risks when considering off-label ketamine as treatment option.
- Comprehensive pre-procedural evaluation for appropriateness of off-label ketamine treatment, including urine toxicology and documentation of failed standard antidepressant therapies.
- Treatment facility should be equipped to rapidly assess and stabilize medical and behavioral emergencies should such arise, including established plan to address sustained alterations in cardiovascular function.
- Strongly advises *against at-home self-administration of ketamine.*

# Yale-IPS: Ketamine Side-Effects, AE's

- Anticipated side-effects:
  - Dissociation *during* treatment, often diminishes with repeated dosing.
  - Elevation in heart rate and blood pressure *during* treatment; patients counseled to take anti-hypertensives and anti-arrhythmics on treatment days.
  - Nausea and vomiting *during* treatment; pre-medication with anti-emetics is helpful.
  - Mild-headache and fatigue *post* treatment.

- Stopped infusions:
  - Once due to elevated blood pressure
  - Once due to intolerable dissociative effects
- Five patients did not complete full 4-protocol infusion
  - 4 withdrew early due to lack of efficacy
  - 1 withdrew early due to intolerable side effects
- 1 case of bradyphylaxis observed in 16y/o male
- 1 case of surreptitious cannabis abuse in 16y/o male
- 2 suicides, both by hanging, 6 and 10 months after last contact with IPS

# Spravato REMS

- REMS (Risk Evaluation and Management Strategies) to be implemented
- Drug safety program that FDA requires for certain medications with serious safety concerns to ensure benefits outweigh the risks
- Examples in psychiatry:
  - Clozapine
  - Suboxone (buprenorphine)
  - Vivitrol (naltrexone)
  - Zulresso (brexanolone)
  - Zyprexa Relprevv (olanzapine)

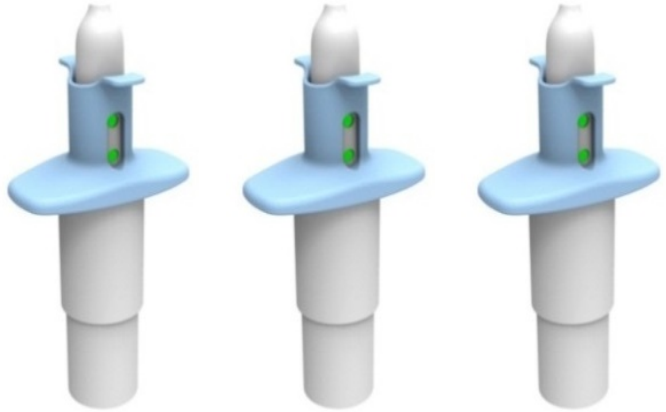
# Esketamine is *unique* among the psychotropic armamentarium

Schedule III / REMS (RMP) /
Secure Storage and Distribution


- Physicians pharmacies *must* be certified and patients registered in the Spravato™ REMS prior to administration.
- Specialty pharmacy vs. onsite storage.
- Significant documentation and reporting throughout a treatment course.

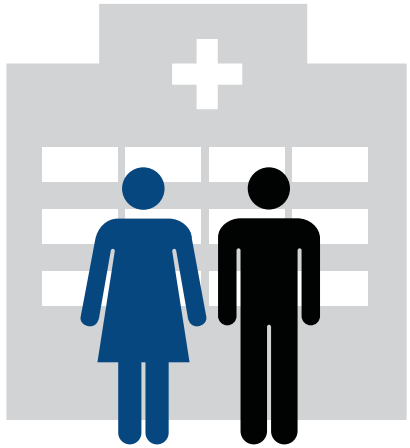
# Esketamine is *unique* among the psychotropic armamentarium

Delivered via an **intranasal device**/ most patients need **2-3 devices** per session



**Patient administered under HCP observation**: 2 sessions per week for 4 weeks, followed by weekly / every other week


Assistance required for **transportation** from site of care



- Administration must occur in a registered healthcare setting.
- The drug is *self-administered (CPT code?)* and monitored by a healthcare professional (HCP) for 2 full hours.
- Patients must not drive on the day of administration.

# Esketamine: Label highlights

- Indicated as ***augmentation*** an oral antidepressant (*not monotherapy*) for patients with treatment refractory depression

- Boxed Warning:
  - Risk for sedation/dissociation after administration
    - Monitor patients for at least 2 hours after administration
  - Potential for abuse and misuse
  - Increased risk of suicidal thoughts and behaviors in pediatric and young adults taking antidepressants

# Esketamine: Other other warnings and adverse events

- Impaired ability to drive/operate machinery
  - Cannot drive “until the next day following a restful sleep”
- Cognitive impairment
  - Short-term – wears off after 4 hours post-dose
  - Long-term – concerns of permanent impairment following ketamine following high-dose/high-frequency use.
    - No long-term effects seen with esketamine, but it has not been evaluated beyond 1 year
- Increase in blood pressure (8-17%)
  - Approximately 8-17% of patients see rise >40mmHg for systolic and/or >25mmHg diastolic
  - Peaks at 40 minutes post-dose

# Esketamine: Other other warnings and adverse events

- Ulcerative / Interstitial Cystitis
  - Ulcerative / interistitial cystitis have been reported following long-term, off-label use or abuse of ketamine
  - Higher rate of lower UT symptoms in esketamine patients compared to placebo patients
  - No cases of esketamine-related interstitial cystitis in any studies

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# Practical considerations in formulating candidacy

- Financial considerations
- Provider/geographic access
- Co-morbidities: poorly controlled HTN, active substance use issues
- Where
- What is the patient's preference?

# Role of the outpatient psychiatrist

- Finding a place to refer, know your local resources.
- Become a prescriber, but be aware of the extensive logistical and administrative considerations
  - Registering in the REMS, finding a specialty pharmacy to supply medications, is your practice setting capable of storing schedule III substances on site, is the care delivery model (2 hour monitoring per patient) fiscally sustainable for your practice (single vs. multiple provider)
- Working with the patient through their expectations of this new treatment
  - Themes:

1. The role of dissociation in the treatment response
2. Fear of the treatment failing them (recall 60-70% response and 50-60% remission rates), many patients see this as a ”stop-gap” on the road to ECT
3. What do response/remission mean *functionally*
4. Where does this fit in the overall plan for *recovery? Oral AD and psychotherapy should remain prominent features*
5. Is maintenance ketamine/esketamine reasonable or feasible?

# Role of the outpatient psychiatrist

- Communicating with the ketamine/esketmaine consultants:

1. You are the BEST source for providing context for the referral; collateral is invaluable throughout a ketamine course

2. Help the consultant understand the overall formulation, e.g. What is a reasonable treatment goal for this patient based on pre-morbid functioning?

3. Provide further augmentation support via psychotropic optimization *and/or* psychotherapy

4. Providing a comprehensive past-psychiatric history, especially with past medication trials and description of response

5. Provide ongoing support in evaluating whether the patient needs an alternative therapy

6. Work with the patient on a relapse prevention plan

JAMA Psychiatry | Special Communication

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- Strongly advises *against at-home self-administration of ketamine.*

# Acknowledgements


## Yale-Interventional Psychiatric Service/Yale Depression Research Program:

- Gerard Sanacora, MD, PhD
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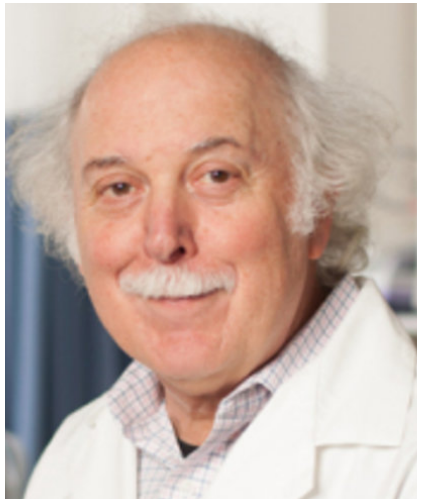
- Ryan Webler, BA
- Christina Elder, BS
- Tyler Khilnani, BS

Referral Inquiries:

Clinical Treatment, ECT/ketamine/rTMS:

(203) 281-4106, extension 10

Clinical Trials, Yale Depression Research Program:

(203) 764-9131

Opportunities for CME and CEU's in ECT:

Yale-IPS Mini-Fellowship (2.5 day experience)

*Please contact me! brandon.kitay@yale.edu*

Yale NewHaven Health

Yale New Haven Psychiatric Hospital