Crossing the Goal Line; Bringing Ketamine Treatments to the Clinic

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Disclosures

- Consulting fees: Dr. Sanacora has received fees from Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Intra-Cellular Therapies, Janssen, Merck, Naurex, Navitor Pharmaceuticals, Novartis, Noven Pharmaceuticals, Otsuka, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, and Vistagen therapeutics over the last 36 months.

- Research contracts: AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., Johnson & Johnson (Janssen), Hoffman La-Roche, Merck & Co., Naurex and Servier over the last 5 years. Free medication was provided to Dr. Sanacora for an NIH sponsored study by Sanofi-Aventis.

- In addition Dr. Sanacora holds equity in BioHaven Pharmaceuticals and is a co-inventor on a US patent (#8,778,979) held by Yale University and is a co-inventor on U.S. Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018 by Yale University Office of Cooperative Research OCR 7451 US01 Abdallah, C, Krystal, JH, Duman, R, Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases.

- Yale University has a financial relationship with Janssen Pharmaceuticals, and may in the future receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

Topics Discussed

1. Brief History of the discovery of ketamine's rapid onset of antidepressant effects

2. Early clinical evidence of ketamine's antidepressant properties

3. Outline the key clinically relevant questions related to the use of ketamine

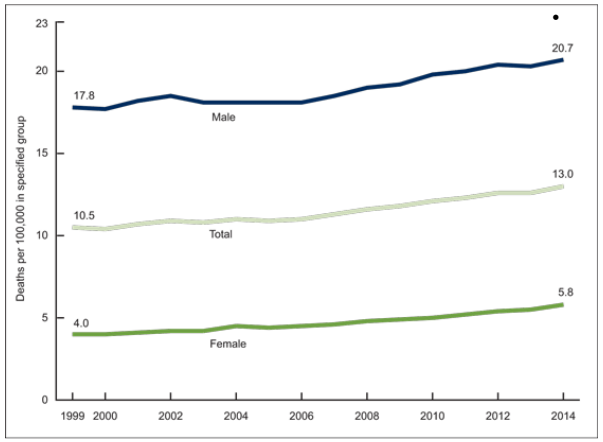
4. Results from a series of studies conducted over the past couple of years that attempt to address some of the critically import questions related to ketamine's use in the clinic and the development of rapidly acting antidepressants

Is There Really a Need for New Antidepressant Treatments?

World Health Organization

Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease.

Suicide is increasing in the United States



Centers for Disease Control and Prevention. www.cdc.gov/violenceprevention/suicide/statistics/. Accessed September 1, 2015.

Table 1. Results at Each Level of Treatment in STAR*D[a]

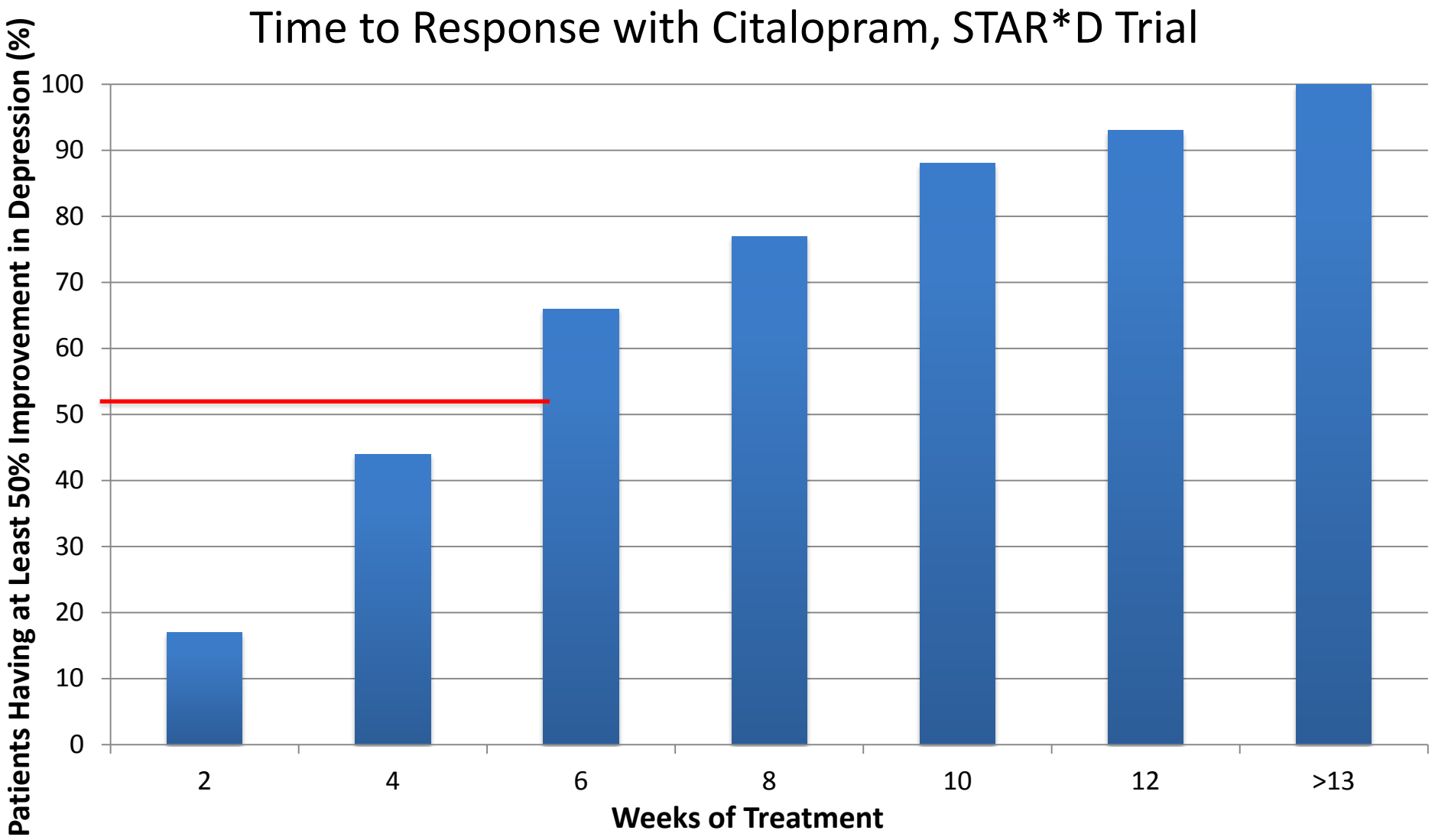
Level	Remission Rate (%)	Intolerance Rate (%)[b]	Relapse During 1-Year Follow-Up (%)
1			
Citalopram monotherapy	36.8	16	40
2			
Any level 2 treatment	30.6	19	55
Any switch	27	23	
Bupropion SR	26	27	
Sertraline	27	21	
Venlafaxine XR	25	21	
CT	31	17	
Any combination/augmentation	35	16	
Bupropion SR + citalopram	39	13	
Buspirone + citalopram	33	21	
CT + citalopram	31	9.2	
3			
Any level 3 treatment	13.7	26	65
Any switch	11	32	
Mirtazapine	8	32	
Nortriptyline	13	33	
Any combination/augmentation	21	15	
Lithium + prior ADT	15	21	
Triiodothyronine + prior ADT	26	10	
4			
Any level 4 treatment (switch)	13.0	34	71
Tranylcypromine	15	40	
Mirtazapine + venlafaxine XR	16	20	

ADT = antidepressant treatment; CT = cognitive therapy; STAR*D = Sequenced Treatment Alternatives to Relieve Depression; SR = sustained release; XR = extended release.

Zisook S, et al. *J Clin Psychiatry*. 2008;69(7):1184-1185.

A large percentage of patients do not receive an adequate response to current antidepressant Medications

There is a Clear Unmet Need for Medications with a Faster Onset of Action



STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

The Discovery of Rapid Onset of Antidepressant Activity has been The Holy Grail in the field of mood disorders for Several decades

Onset of Activity

Practicing clinicians know that the mood-elevating effect of antidepressant medication usually begins about 1 to 2 weeks after initiation of treatment. The clinical rule of thumb is that a patient must be treated with an adequate dosage for at least 6 weeks before the clinician considers changing the treatment. However, the synaptic effects of these drugs occur within hours after the patient ingests the drug. Because many of the early adverse effects have the same time course as the early synaptic effects, such synaptic effects of antidepressants can be related to certain adverse effects and drug interactions (as discussed subsequently). In treating a patient with severe depression, the clinician would like to prescribe a drug that begins to work in the same time course as the synaptic effects. This rapid onset of activity would be one characteristic of the ideal antidepressant. However, no drug appears to work more rapidly than another, and the time course is generally prolonged.

ELLIOTT RICHELSON., Mayo Clin Proc. 2001;76:511-527

Now the Field is now Replete with Putative Rapidly Acting Antidepressant Treatments

Review Article

Rapid-Acting Antidepressants

Jeffrey M. Witkin*, Daniel E. Knutson, Gabriel J. Rodriguez, Samuel Shi.

Current Pharmaceutical Design, 2018

CONCLUSION:

The preclinical and clinical literature strongly suggests that rapid-acting antidepressants are the current focus of antidepressant drug discovery..

F1000Research 2018, 7(F1000 Faculty Rev):659 Last updated: 24 MAY 2018

Check for updates

REVIEW

Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide [version 1; referees: 3 approved]

Ronald S. Duman

Department of Psychiatry, Laboratory of Molecular Psychiatry, Yale University School of Medicine, New Haven, CT 06508, USA

The discovery of ketamine and its unique mechanisms heralds a new era with tremendous promise for the development of novel, rapid, and efficacious antidepressant medications.

TABLE 1

Potential antidepressant compounds in development[a]

	Compound, route of administration	Pharmacology	Sponsor	Phase	Comments
	Ketamine, various	Nonselective, noncompetitive NMDAR antagonist	Multiple	N/A	Several small trials from academia; unlikely to be studied as a monotherapy in Phase III clinical trials required to receive FDA approval
*	Esketamine, intranasal	Nonselective, noncompetitive NMDAR antagonist	Janssen	III	Breakthrough Therapy Designation in 2013 for TRD and Breakthrough Therapy Designation in 2016 for MDD with imminent risk of suicide; 4–5 x NMDAR-binding potency compared with (*R*)-ketamine; several positive studies reported, with one study among older patients that did not meet statistical significance for its primary endpoint
	Lanicemine/AZD-6765, intravenous	Low trapping NMDAR antagonist	AstraZeneca/ BioHaven	IIb	Mixed results in two Phase II studies
	Traxoprodil/CP-101,606, intravenous	NMDAR antagonist at NR2B subunit	Pfizer	II	Positive Phase II study reported; no additional studies registered
	EVT-101	NMDAR antagonist at NR2B subunit	Evotec/La Roche	II	Phase II trial terminated early, placed on clinical hold by FDA (clinicaltrials.gov)
	Rislenemdaz/CERC-301/ MK-0657, oral	NMDAR antagonist at NR2B subunit	Cerecor	II	At least one Phase II trial did not show separation from placebo
	AVP-786, oral	Nonselective antagonist of NMDAR	Avanir/Otsuka	II	Combination of dextromethorphan and quinidine. Phase II trial completed in February 2016; no additional studies for mood disorders registered as of March 2018.
	AXS-05, oral	Nonselective antagonist of NMDAR	Axsome	III	Combination of dextromethorphan/ bupropion; Fast Track Designation by FDA
	Rapastinel/GLYX-13, intravenous	Partial functional agonist at glycine site of NMDAR	Allergan	III	Fast Track Designation for MDD in 2014; Breakthrough Therapy designation in 2016
	Apimostinel/NRX-1074/ AGN-241660, oral	Reported to be a functional antagonist at Glycine B site of NMDAR	Allergan	II	Company press release reports that NRX-1074 showed rapid antidepressant efficacy in initial single-dose Phase II study in patients with MDD
	AV-101, oral	Selective agonist at glycine site of NMDAR NR1 subunit	VistaGen	II	Fast Track Designation for MDD in 2018
	NRX-100/NRX-101, oral	Partial NMDAR agonist at glycine site	NeuroRx	III	Ketamine (NRX-100) followed by D-cycloserine plus lurasidone (NRX-101) to sustain effects in suicidal bipolar depression
	AGN-241751	NMDAR modulator	Allergan	II	Fast Track Designation by FDA in 2018
	Basimglurant/ RO4917523, oral	Negative allosteric modulator of $mGluR_5$	Hoffmann-La Roche	IIb	Phase IIb study did not show separation from placebo
	Decoglurant/RG1578/ RO4995819	Negative allosteric modulator of $mGluR_{2/3}$	Hoffmann-La Roche	II	Removed from Roche pipeline as reported by company in 2015
	Tulrampator/CX-1632/S-47445	Positive allosteric modulator of AMPAR	RespireRx	II	Completed Phase 2 trial in TRD; no results reported to date.
	Riluzole, oral	Glutamate release inhibitor/ up take facilitator	Multiple	II	Mixed results, among randomized clinical trials: three negative studies (incl. NCT00376220); one positive study
*	Brexanolone/SAGE-547, intravenous	Positive allosteric modulator of $GABA_A$ receptor	Sage	III	PPD with two positive Phase III trials; Breakthrough Designation for MDD
	Ganaxolone, intravenous	Positive allosteric modulator of $GABA_A$ receptor	Marinus	II	Treatment of PPD
	SAGE-217, oral	Positive allosteric modulator of $GABA_A$ receptor	Sage	II	Fast Track Designation by FDA in 2017 with a positive Phase II trial

Abbreviations: NMDAR, N-methyl-D-aspartate receptor; FDA, Food and Drug Administration; TRD, treatment-resistant depression; PPD, post-partum depression; GABA, gamma-ar acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR, metabotropic glutamate receptor; NAM, negative allosteric modulator; PAM, positive allosteric m

*Now with FDA indication

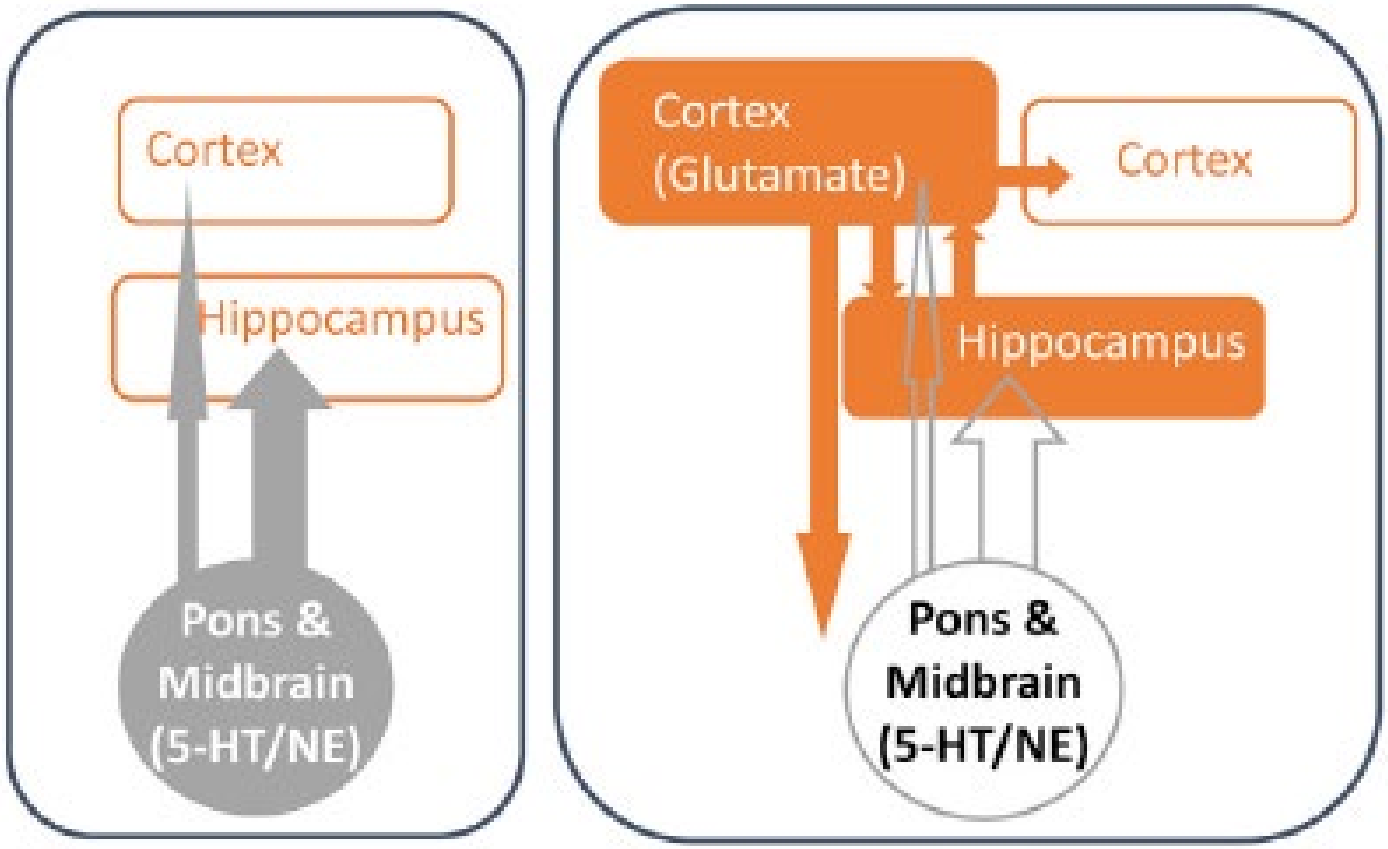
Wilkinson and Sanacora, 2018

What was the Rationale for trying ketamine?

Changing Theories of Mood Disorder Pathophysiology

Historically dominant monoaminergic theory

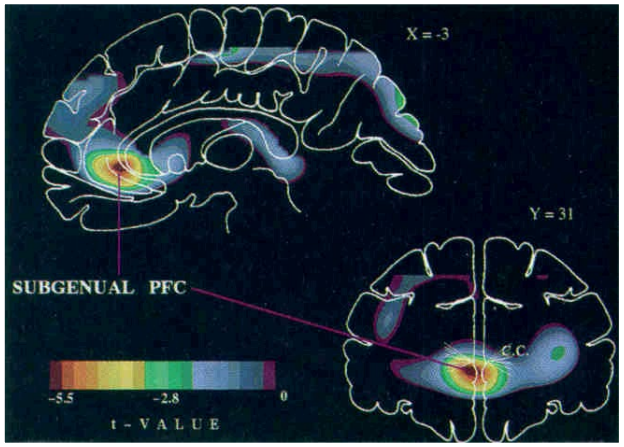
Shift to cortical and limbic pathology



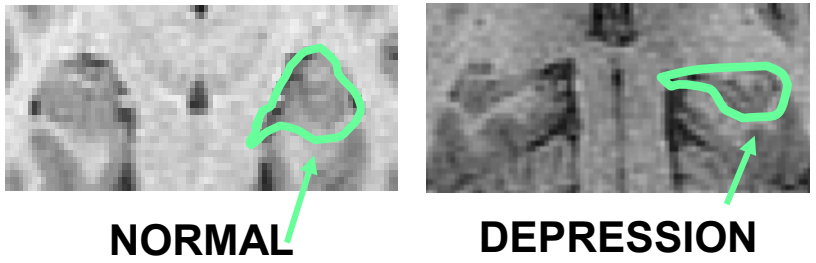
"If one viewed depression as a disorder of cortico-limbic function, then glutamatergic and GABAergic signaling would be implicated. This perspective shift led us to test the effects of the NMDA glutamate receptor antagonist as a probe of alterations in glutamate signaling associated with depression."

Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Neuron. 2019 Mar 6;101(5):774-778

Emerging Evidence of Structural and Cellular Abnormalities in MDD

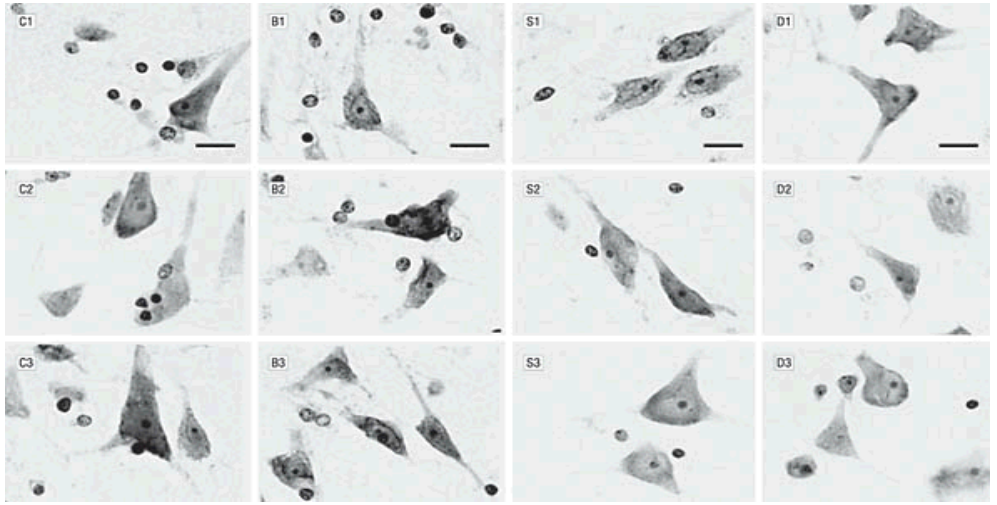


Drevets W, et al. *Nature*. 1997;386:824–827; 2.



Bremner 2000
Sheline 2003.

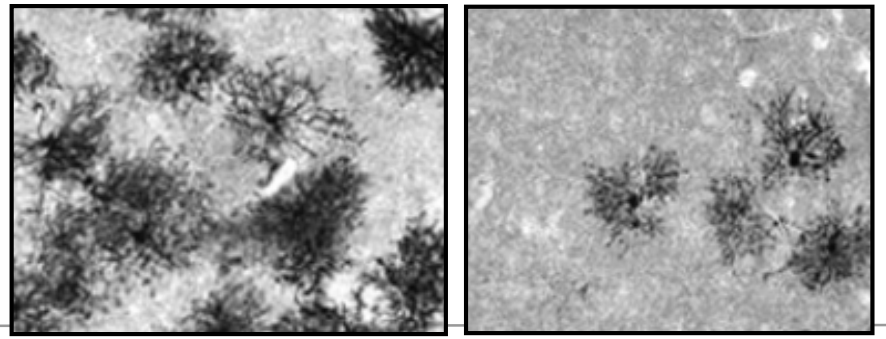
Anterior Cingulate Cortex



Control Bipolar Schizophrenia MDD

Glial (GFAP) immunoreactivity in the prefrontal cortex[1]

Control (27 years old) MDD (32 years old)



1. Rajkowska G, et al. *CNS Neurol Disord Drug Targets*. 2007;**6**:219–233. Copyright © 2007 Bentham Science Publishing Ltd. 2. Rajkowska G, et al. *Biol Psychiatry*. 1999;**45**:1085–1098. 3. Ongür D, et al. *Proc Natl Acad Sci USA*. 1998;**95**:13290–13295. 4. Si X, et al. *Neuropsychopharmacol.* 2004;**29**:2088–2096. 5. Miguel-Hidalgo et al. J Affect Disord. 2010 Dec;127(1-3):230-40. 6. Altshuler, et al. Bipolar Disord 2010: 12: 541–549. 7. Gittins and Harrison PJ.,J Affect Disord. 2011 Sep;133(1-2):328-32

Mounting Evidence of Glutamate's Contribution to the Pathogenesis and Pathophysiology of MDD

The Possibility of Neurotoxicity in the Hippocampus in Major Depression: A Primer on Neuron Death

Robert M. Sapolsky

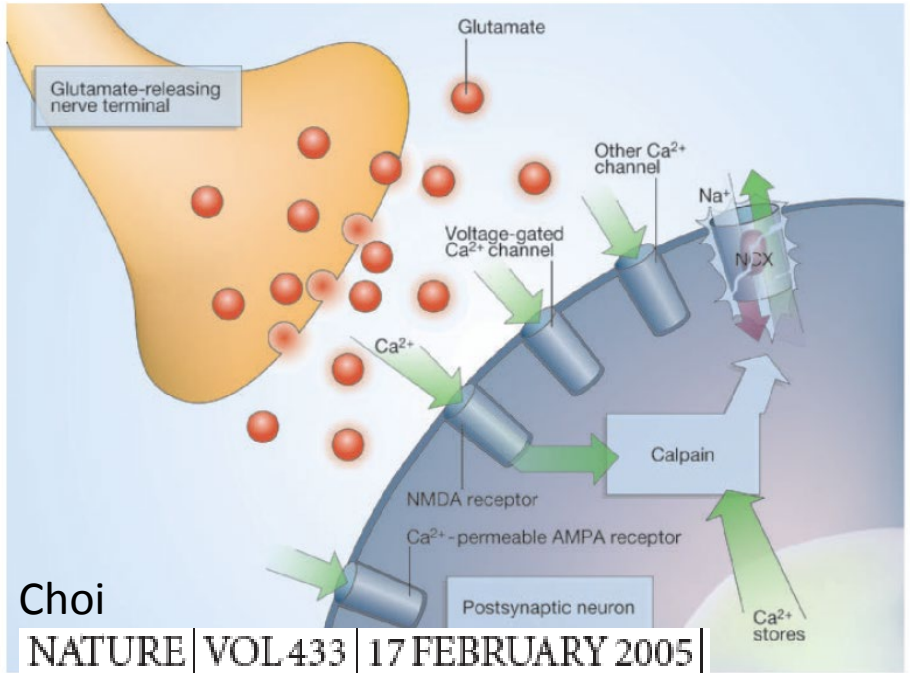
A number of studies indicate that prolonged, major depression is associated with a selective loss of hippocampal volume that persists long after the depression has resolved. This review is prompted by two ideas. The first is that overt neuron loss may be a contributing factor to the decrease in hippocampal volume. As such, the first half of this article reviews current knowledge about how hippocampal neurons die during insults, focusing on issues related to the trafficking of glutamate and calcium, glutamate receptor subtypes, oxygen radical generation, programmed cell death, and neuronal defenses. This is meant to orient the reader toward the biology that is likely to underlie any such instances of neuron loss in major depression. The second idea is that glucocorticoids, the adrenal steroids secreted during stress, may play a contributing role to any such neuron loss. The subtypes of depression associated with the hippocampal atrophy typically involve significant hypersecretion of glucocorticoids, and the steroid has a variety of adverse effects in the hippocampus, including causing overt neuron loss. The second half of this article reviews the steps in this cascade of hippocampal neuron death that are regulated by glucocorticoids. Biol Psychiatry 2000;48:755–765 © *2000 Society of Biological Psychiatry*

REVIEW

Stress Activation of Glutamate Neurotransmission in the Prefrontal Cortex: Implications for Dopamine-Associated Psychiatric Disorders

Bita Moghaddam

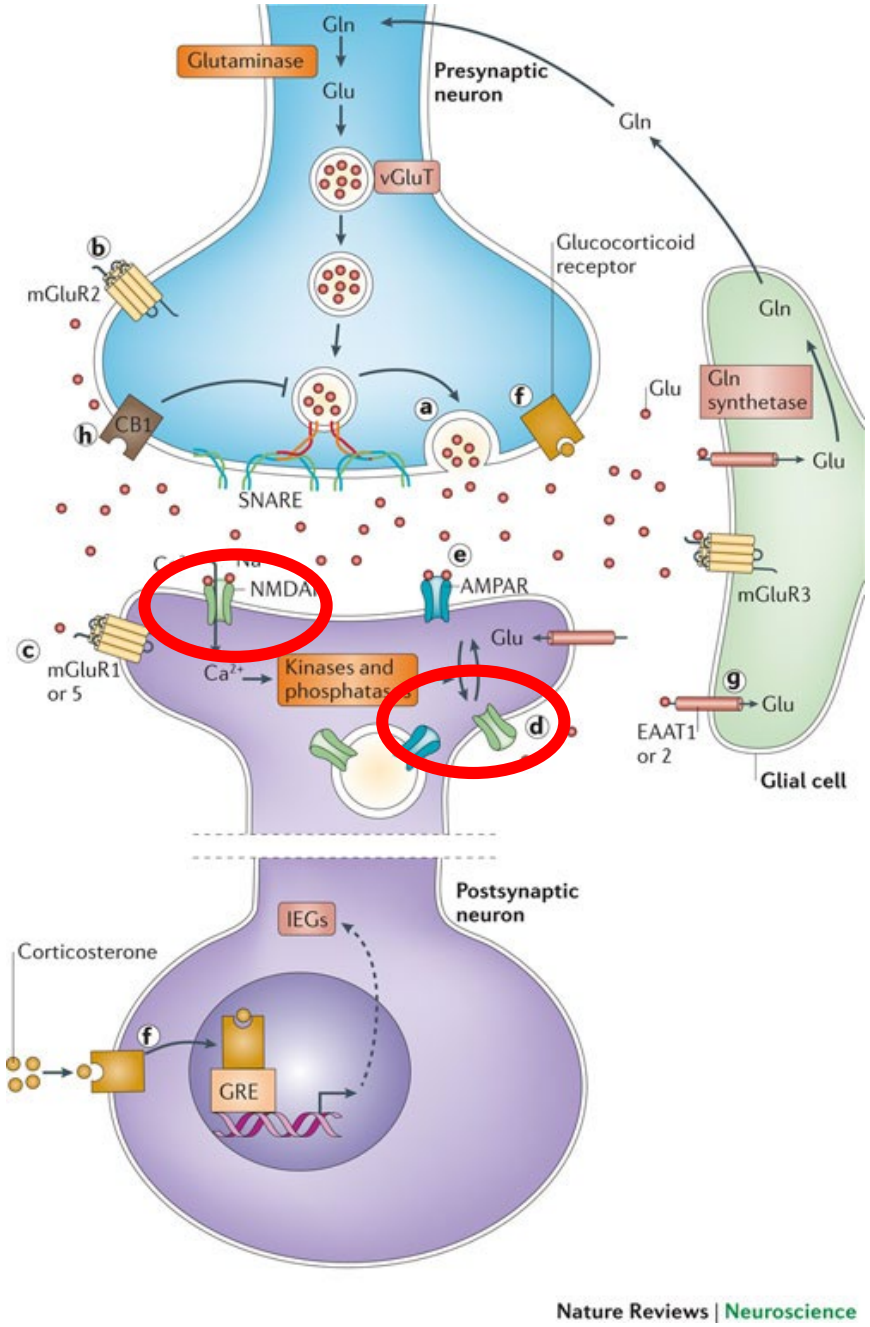
Biological Psychiatry
Volume 51, Issue 10, 15 May 2002, Pages 775-787



Choi

NATURE | VOL 433 | 17 FEBRUARY 2005

Identifying Glutamatergic Targets for Antidepressant Drug Development



Popoli, Yan, McEwen and Sanacora et al. *Nat Rev Neurosci*. 2012;13(1):22-37.

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

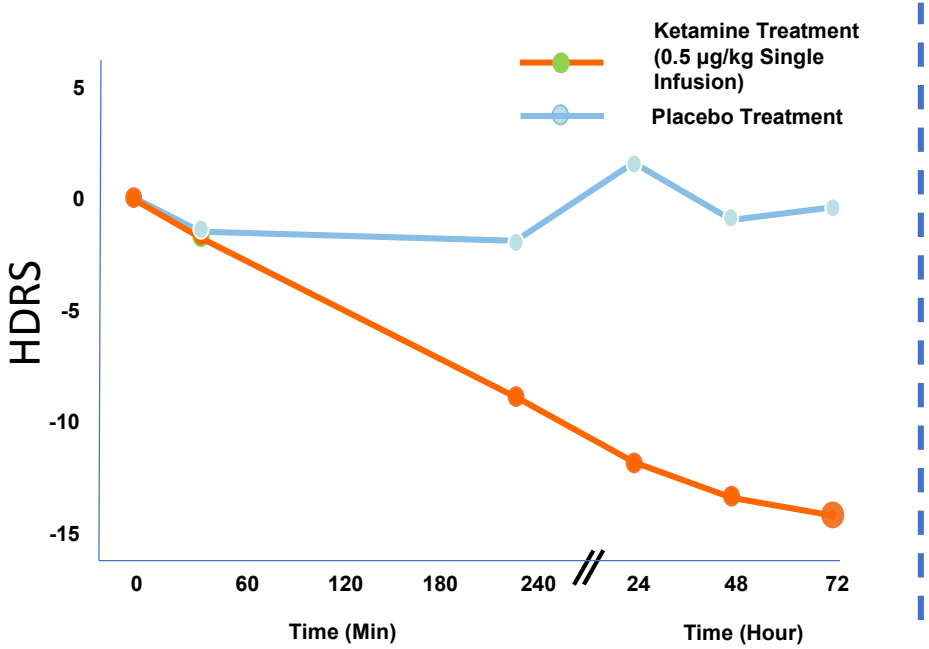
Laboratory of Neuroscience, National Institutes of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, U.S.A.

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.

Initial Reports of Ketamine's Rapid Antidepressant

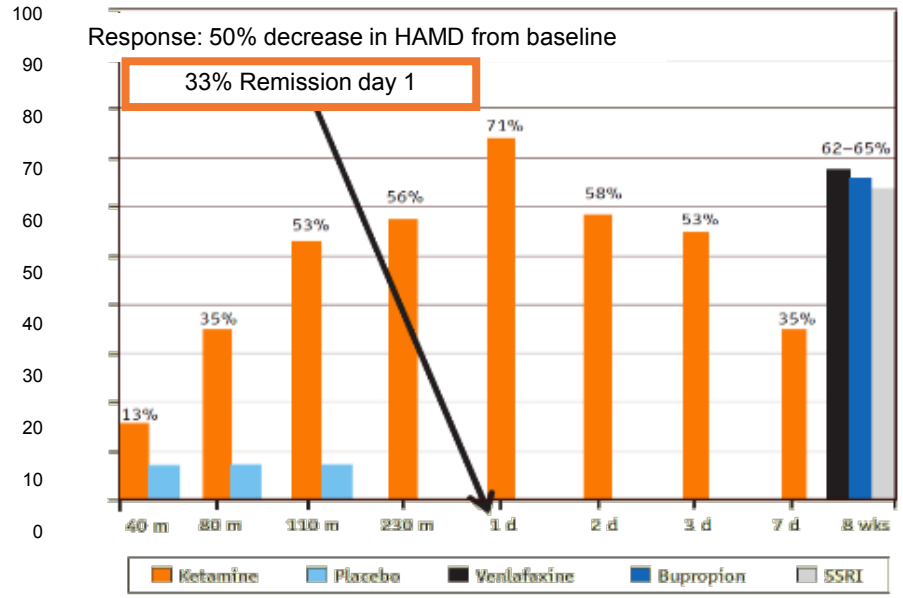
"To the amazement of our patients and ourselves, we found that ketamine produced rapid, profound, and surprisingly durable antidepressant effects that were temporally dissociated from the brief acute behavioral effects of the drug" Krystal JH, et al. Neuron. 2019 Mar 6;101(5):774-778



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.

Confirmatory Reports of Ketamine's Rapid Antidepressant

THE AMERICAN JOURNAL OF PSYCHIATRY

From: Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

The APA Council of Research Task Force on Novel Biomarkers and Treatments

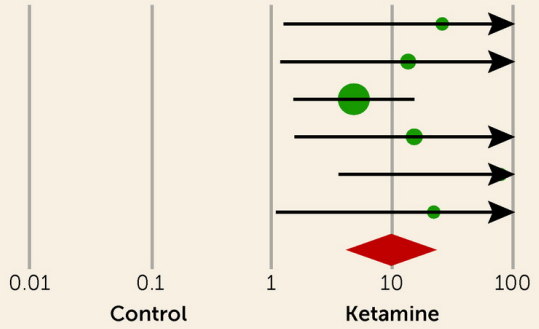
American Journal of Psychiatry, Newport et al. 2015; 172:950–966

A

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	26.053	1.359	499.339	2.164	0.030
Lapidus et al. (84)	13.600	1.238	149.455	2.134	0.033
Murrough et al. (87)	4.833	1.578	14.803	2.759	0.006
Sos et al. (91)	15.294	1.610	145.305	2.374	0.018
Zarate et al. (88)	79.545	3.762	1681.833	2.811	0.005
Zarate et al. (86)	22.176	1.133	434.158	2.042	0.041
	9.865	4.366	22.293	5.503	0.000

Statistics for Each Study

Odds Ratio and 95% CI

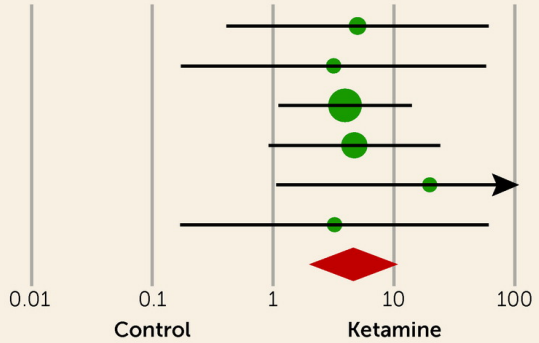


B

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	1.999	0.046
Zarate et al. (86)	3.222	0.176	58.849	0.789	0.430
	4.610	2.076	10.236	3.754	0.000

Statistics for Each Study

Odds Ratio and 95% CI



a The A) top plot shows results one day after initiation of ketamine (heterogeneity: $\chi 2=4.27$, df=4, p=0.51, I2=0%). The B) bottom plot shows results one week after initiation of ketamine (heterogeneity: $\chi 2=1.14$, df=5, p=0.95, I2=0%).

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

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

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

BBC NEWS HEALTH

News | Sport | Weather | Capital | Future | Shop

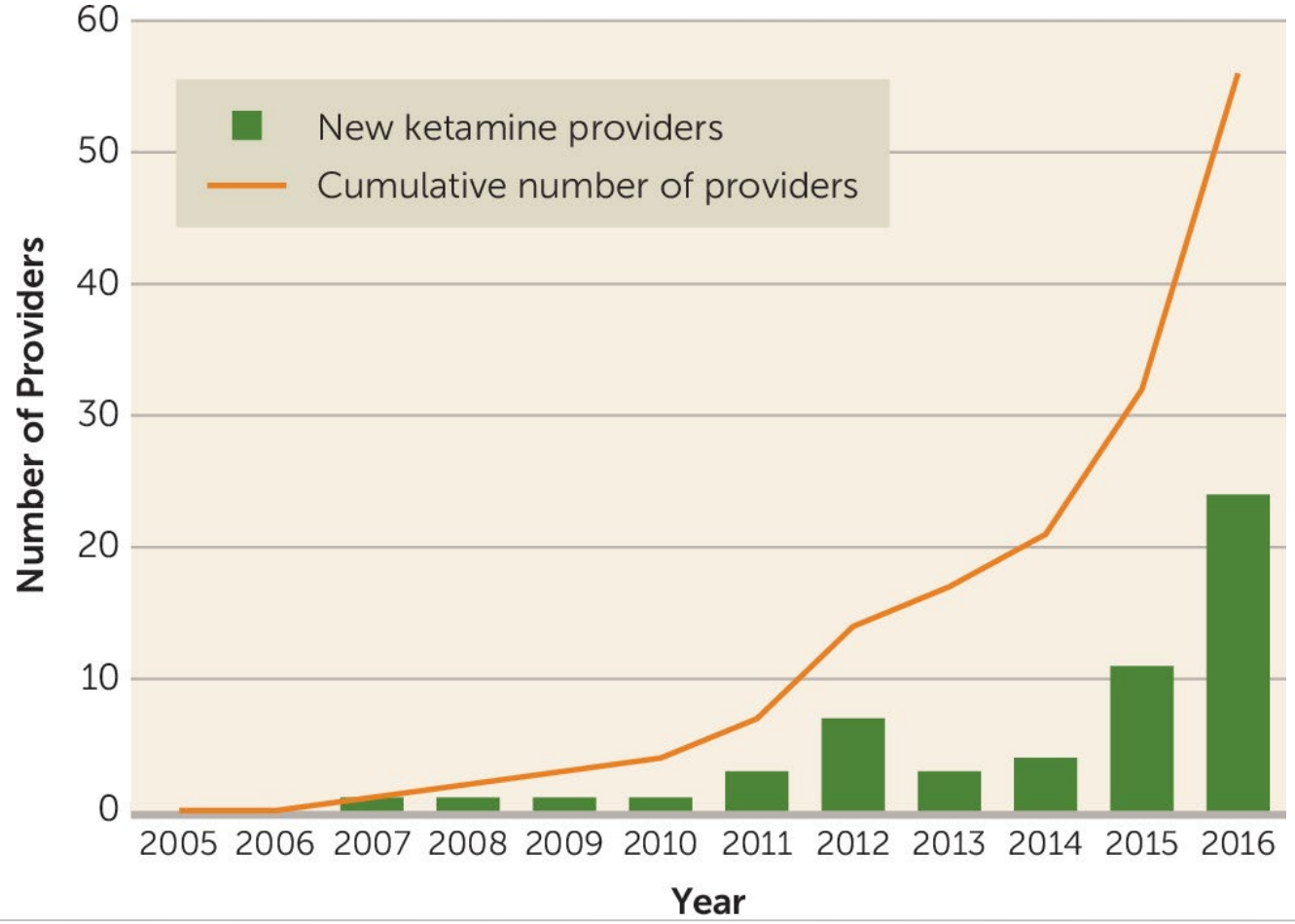
Ketamine 'exciting' depression therapy

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 Ketamine for the Treatment of Psychiatric Disorders

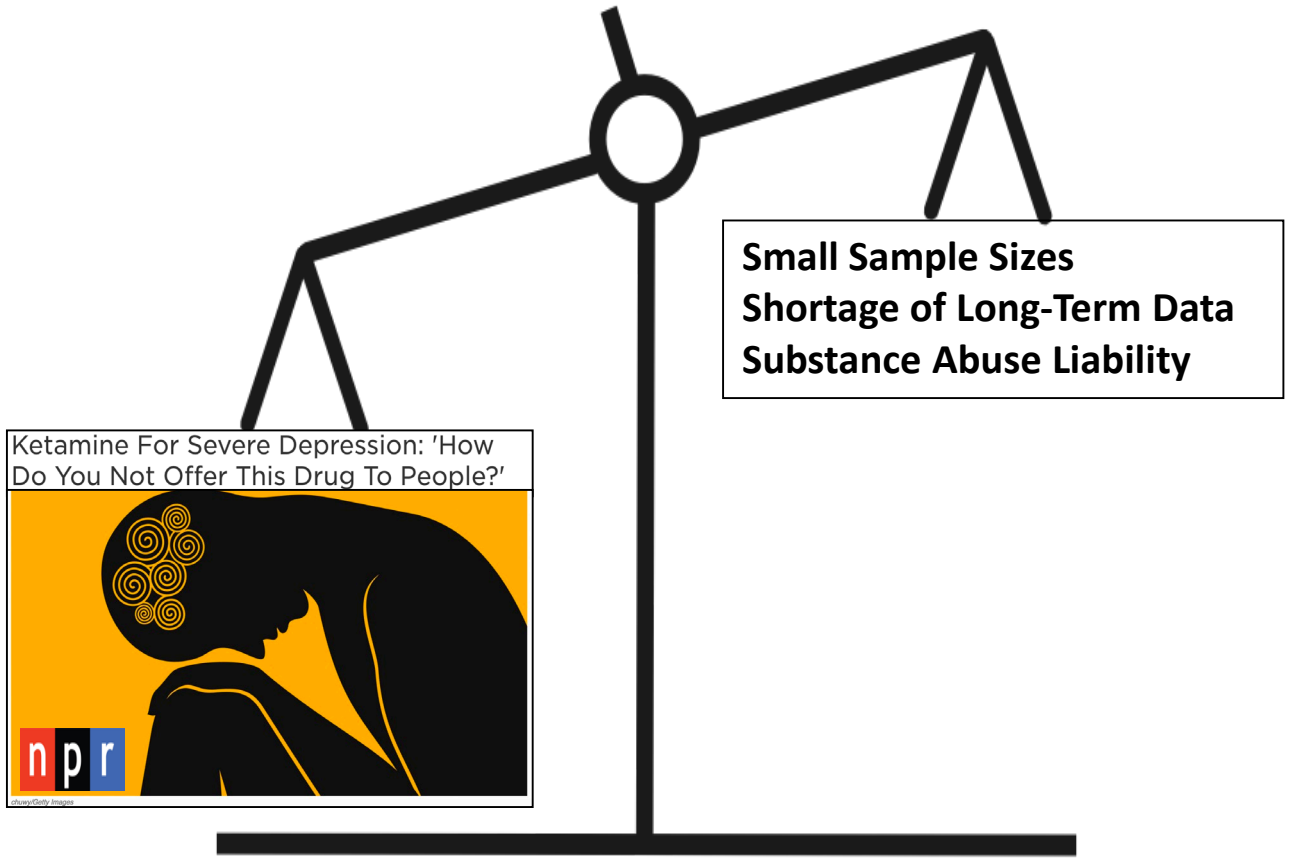
A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders



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

Balancing the Potential Benefits with the Current Knowledge and Potential Risks of Ketamine Treatment



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

IMPORTANCE Several studies now provide evidence of ketamine hydrochloride's ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders.

OBSERVATIONS This review and consensus statement provides a general overview of the data on the use of ketamine for the treatment of mood disorders and highlights the limitations of the existing knowledge. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option.

CONCLUSIONS AND RELEVANCE The suggestions provided are intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provides information on potentially important issues related to the off-label treatment approach that should be considered to help ensure patient safety.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2017.0080
Published online March 1, 2017.

Invited Commentary
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments members are listed at the end of this article.

Corresponding Author: Gerard Sanacora, MD, PhD, Yale University School of Medicine, 100 York St, Ste 2J, New Haven, CT 06511 (gerard.sanacora@yale.edu).

Addressing the Key, Clinically Relevant Questions Regarding Ketamine's Rapid Onset Antidepressant Effects

- **Immediate Clinical Relevance**
  - What is the Optimal Dosing Strategy for Ketamine (dose, route, and frequency)?
  - What is the Longer-term effectiveness of the treatment
  - What is Longer-term safety of the treatment approach
  - What are the Critical Moderators of response of adverse effects
    - Dx Subtype, genetic, or endophenotypic differences in response
    - Drug-drug interactions (regarding both safety and efficacy)

- **Longer-Term Relevance to Drug Development**
  - What are the Mediators of Response (Mechanisms of Antidepressant Action)
    - Proximal effects
      - Pharmacological Targeting
      - Biological Activity
      - Non-specific Effects
    - Downstream effects
      - Neuroplastic Changes
        - Synapses
        - Circuits
        - Behavior and Cognition

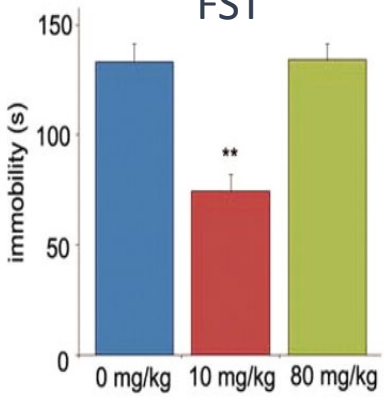
- **Can Similar Drugs be Developed**

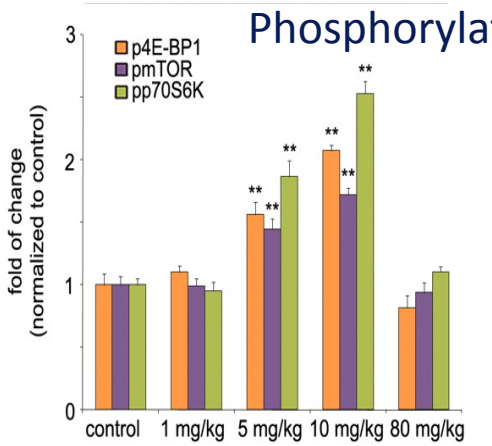
What is the Optimal Dose and Dosing Strategy?

"The dose and manner of ketamine infusion in our depression study (0.5 mg/kg ketamine infused intravenously over 40 min) was derived from our psychosis studies. In those studies, we selected a dose and rate of infusion that produced transient schizophrenia-like symptoms and cognitive impairments without producing delirium or an anesthetized state."

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

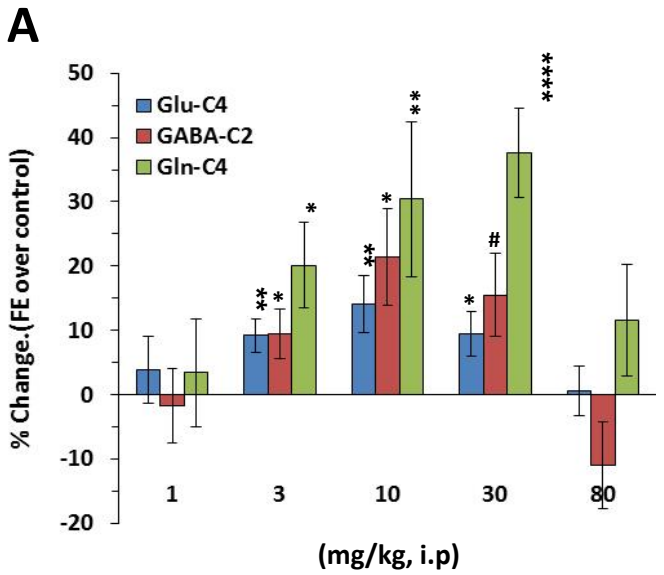
Dose dependence of ketamine effects on physiology and antidepressant-like behavior in rodent models

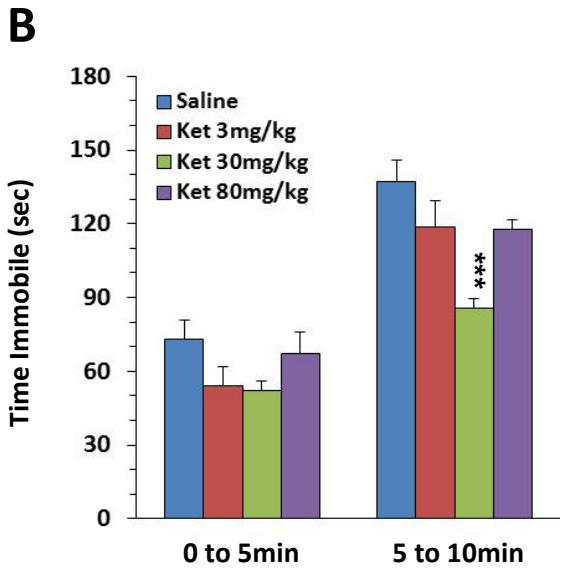




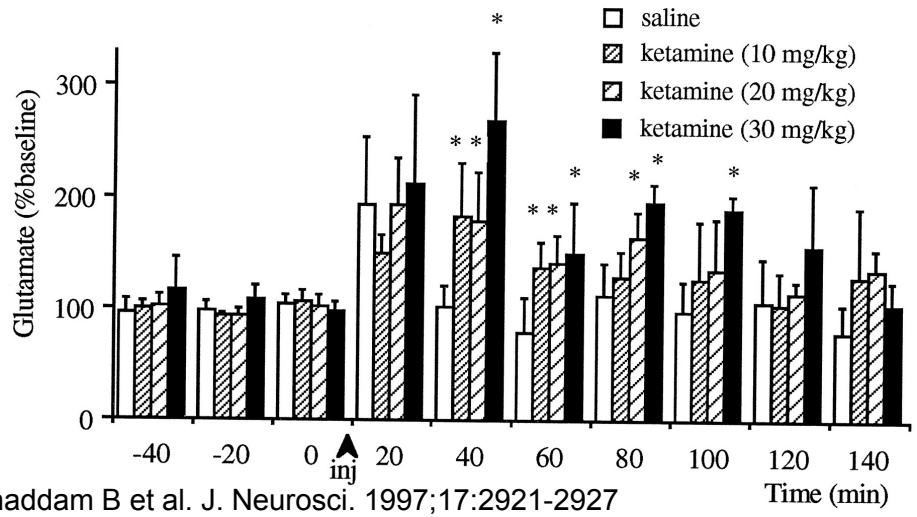
****P < .01, ANOVA. FST = forced swim test.**

Li N, et al. *Science*. 2010;329(5994):959-964.

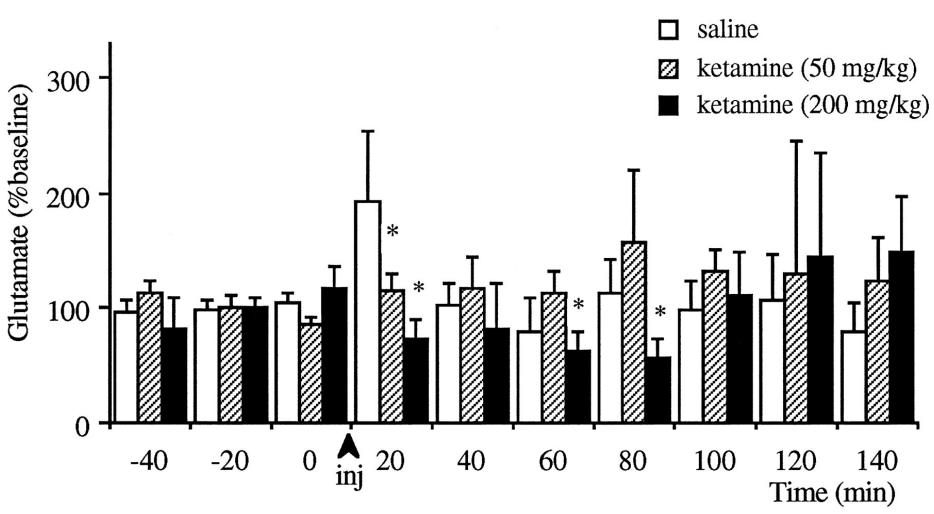




Chowdhury et al. Mol Psychiatry. 2017

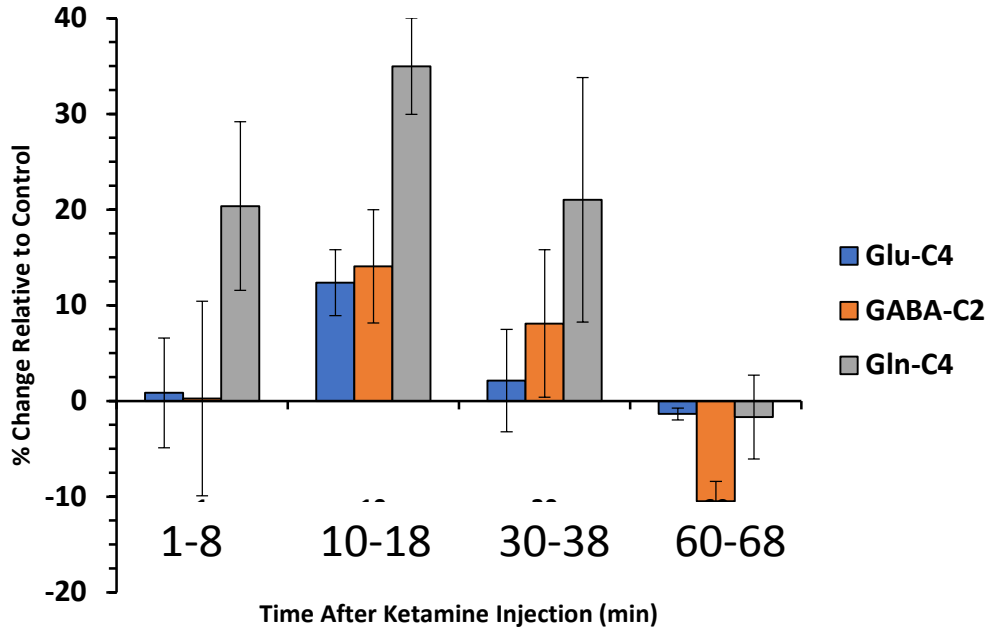


Moghaddam B et al. J. Neurosci. 1997;17:2921-2927



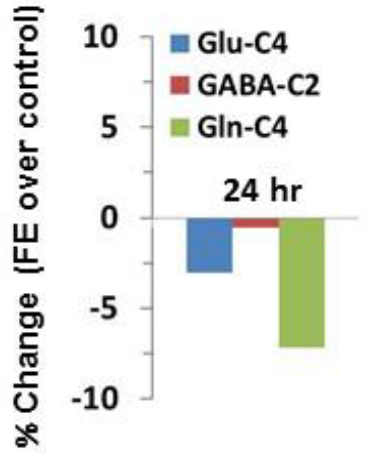
Time course of ketamine's effects on cycling

Ketamine (30 mg/kg) 10, 30 and 60 mins Post-Injection Time Response



Chowdhury et al. Mol Psychiatry. 2017

Ketamine (10 mg/kg) 24 hour Post-Injection Time Response

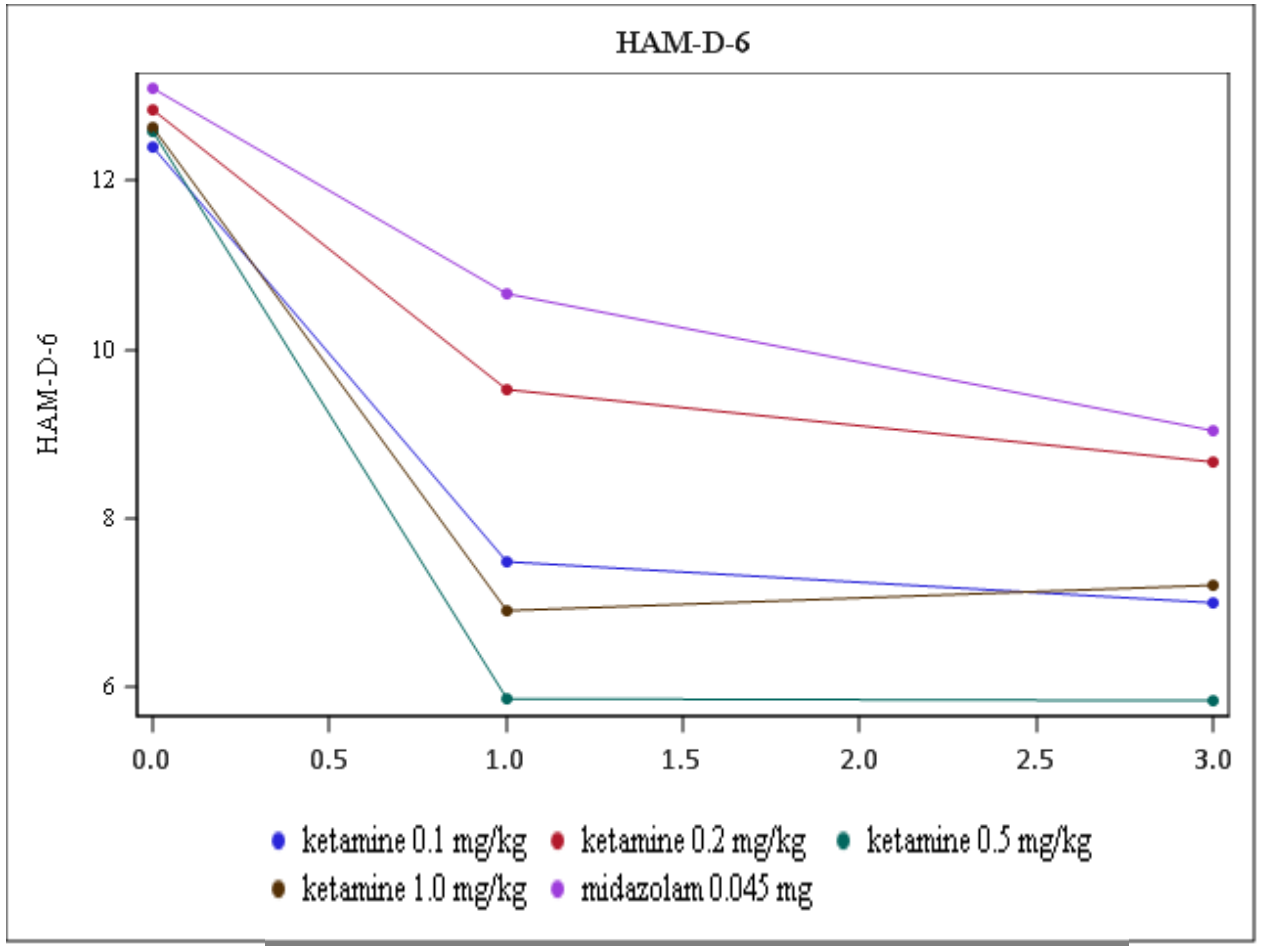


{NS} p= .65, .93, .44 respectively

What about in the Clinic?

Double-Blind, Placebo-Controlled, Dose-Ranging Trial of Intravenous Ketamine as Adjunctive Therapy in Treatment-Resistant Depression (TRD)

Differences in HAM-D-6 Scores Between Doses of Ketamine and Midazolam (Primary outcome)



Pairwise Comparisons of MADRS Changes Between Ketamine Doses and Midazolam

Group	Day	Estimated MADRS Change Difference	Raw p	Adj. p	Cohen's d
2-Group Comparison					
Ketamine comb.	1				
Ketamine comb.	3	-5.47	0.04	0.04	-0.60
5-Group Comparison					
ketamine 0.1 mg/kg	1				
ketamine 0.2 mg/kg	1				
ketamine 0.5 mg/kg	1				
ketamine 1.0 mg/kg	1				
ketamine 0.1 mg/kg	3	-5.15	0.16	0.33	-0.48
ketamine 0.2 mg/kg	3	-2.16	0.53	0.53	-0.20
ketamine 0.5 mg/kg	3	-9.85	0.00	0.02	-1.03
ketamine 1.0 mg/kg	3	-7.72	0.03	0.08	-0.70

Fava et [RAPID Study Group] Molecular, Psychiatry 2018

What is the Optimal Dosing Frequency?

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

Ketamine
69% Responders
38% Remitters

Ketamine
55% Responders
23% Remitters

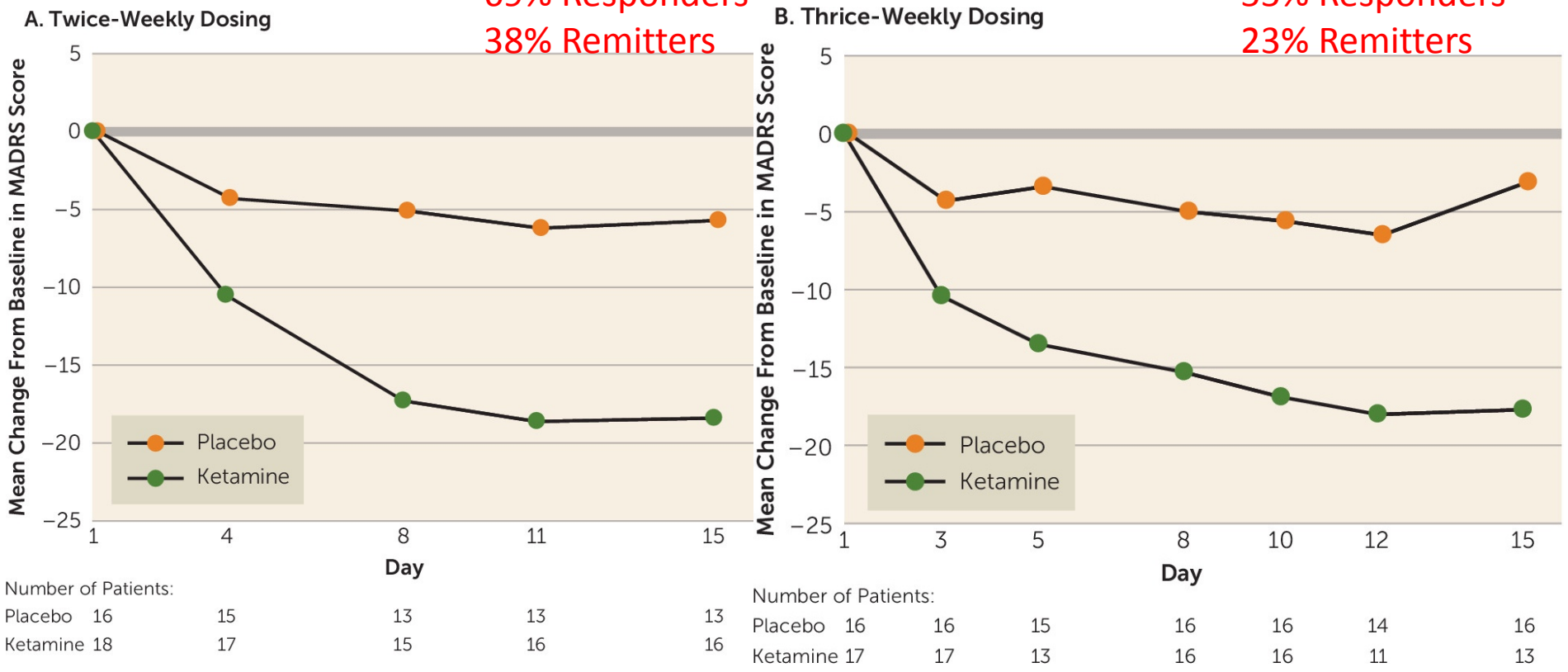
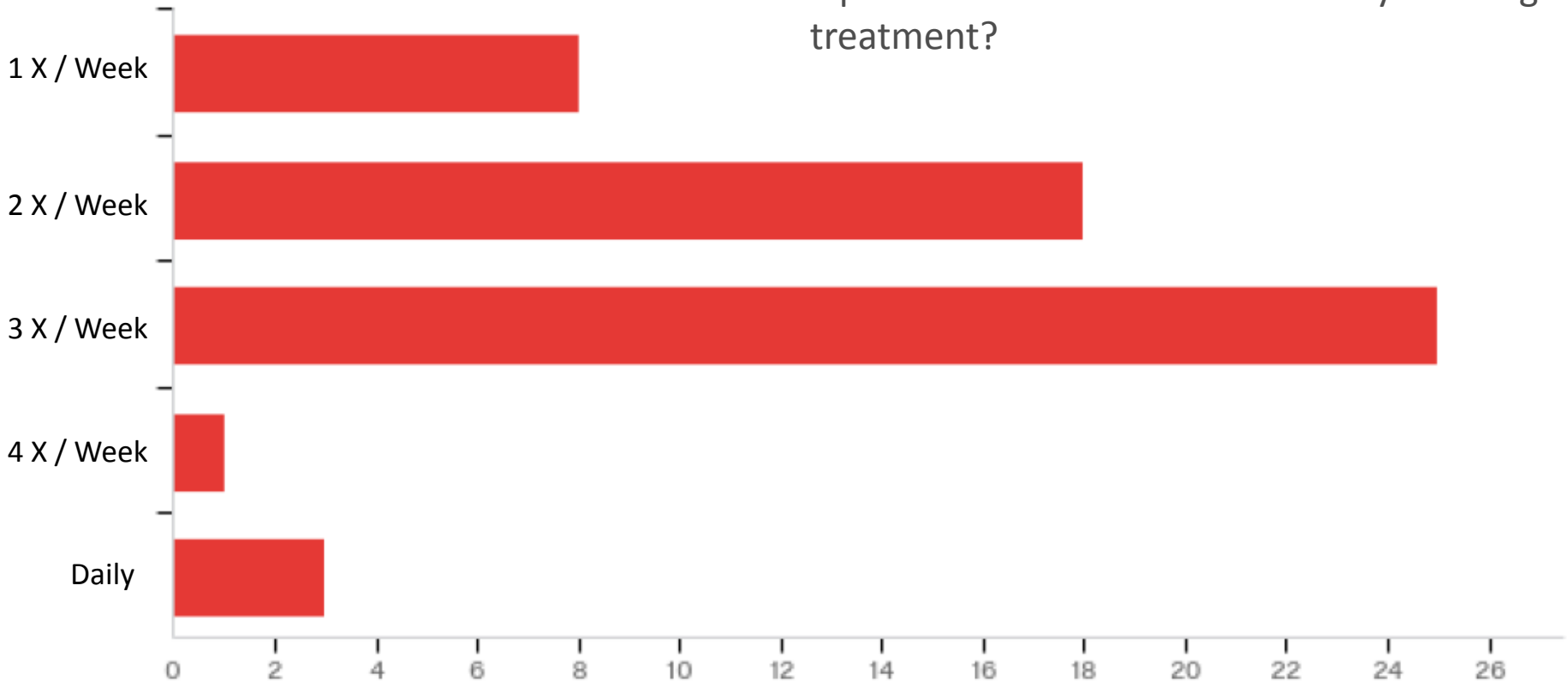


FIGURE 2. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Score, by Dose Frequency, From Baseline Through Day 15 of the Double-Blind Phase in a Study of Intravenous Ketamine in Treatment-Resistant Depression

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

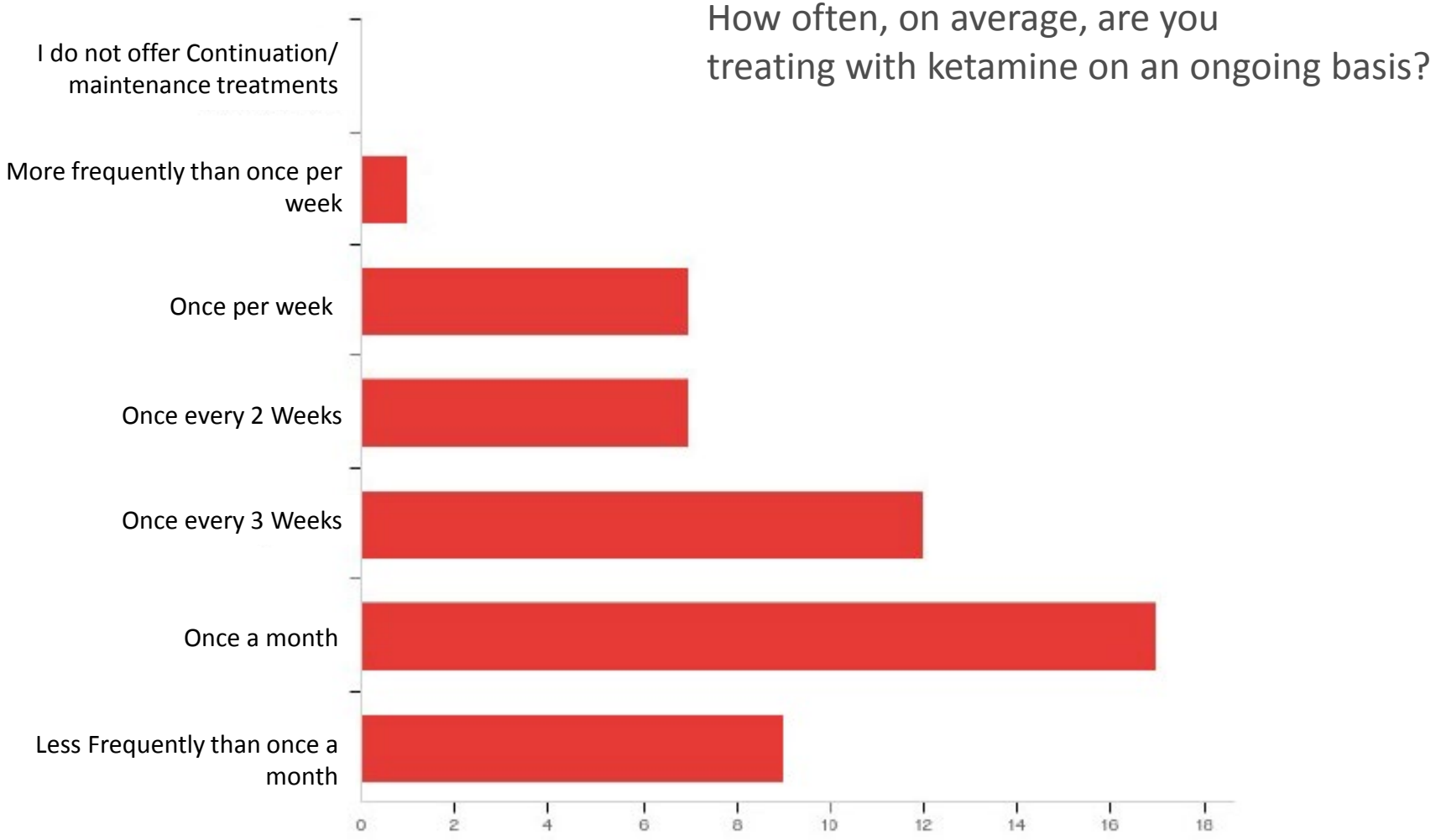
How is Ketamine Being Used in Clinical Practice?

How many times per week do you usually treat a patient with ketamine when they first begin treatment?



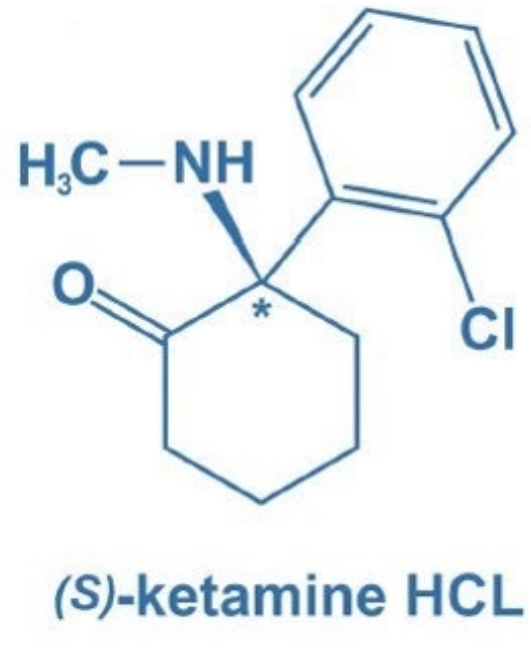
Data from a Survey of 54 Ketamine Providers in North, Wilkinson et al. Am. J. Psychiatry 2017

How Frequently is Ketamine Being Dosed for Continuation Treatment in Clinical Practice?

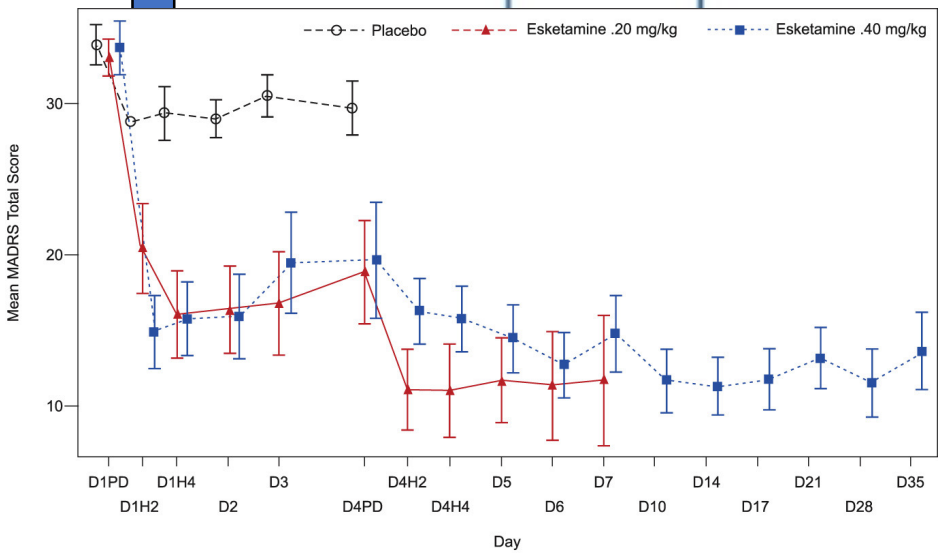


Data from a Survey of 54 Ketamine Providers in North, Wilkinson et al. Am. J. Psychiatry 2017

EsKetamine



The (S) enantiomer has a greater affinity for the NMDA glutamate receptor. This allows for a greater amount of NMDA receptor blocade with lower doses of the drug. (White et al.. (1980) Pharmacology of ketamine isomers in surgical patients. Anesthesiology 52: 231–239., Oye et al. . Effects of ketamine on sensory perception: evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther. 1992;260:1209–13)

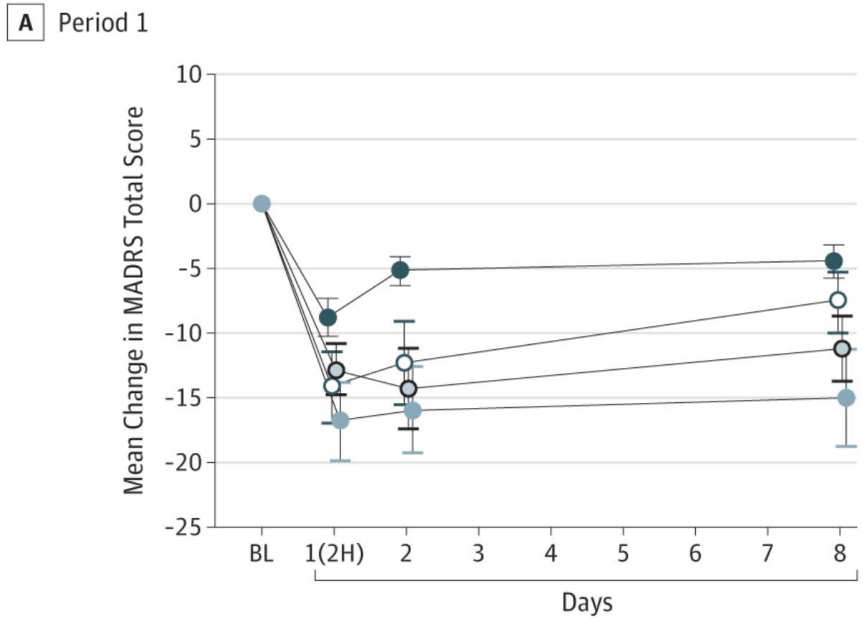


Number of Subjects																
Placebo	10	10	10	10	10	10										
Esketamine .20 mg/kg	9	9	9	9	9	9	9	9	9	9	9					
Esketamine .40 mg/kg	11	11	11	11	11	11	20	20	20	19	20	29	29	27	29	28	27

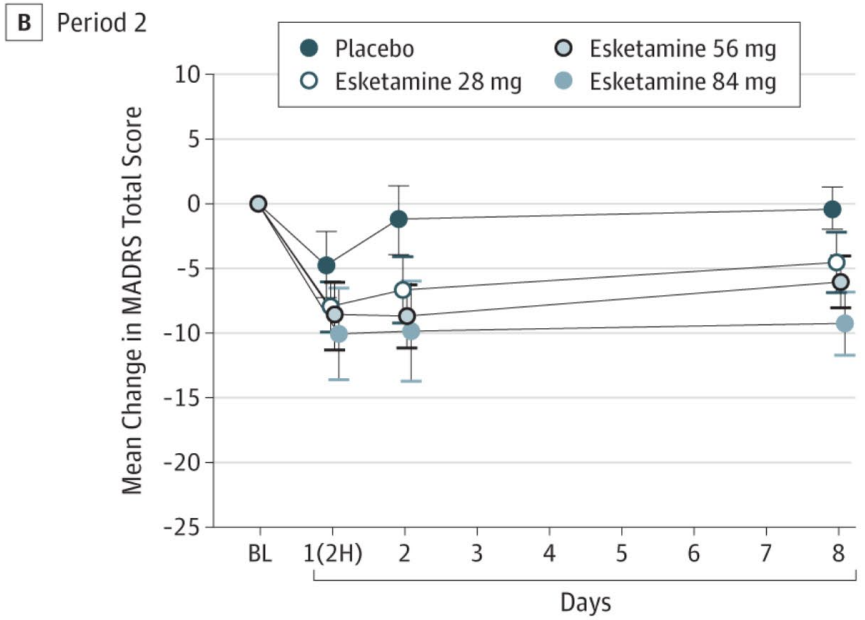
Singh et al. Biol Psychiatry. 2016 Sep 15;80(6):424-431

Antidepressant effects of esketamine delivered intravenously

Efficacy of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression



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

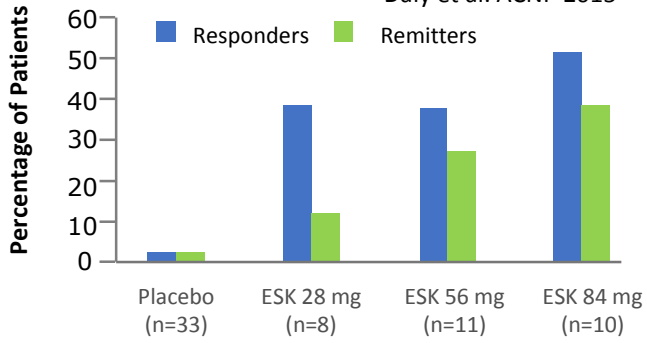


No. of participants				
Placebo	6	6		6
Esketamine 28 mg	8	8		8
Esketamine 56 mg	9	9		9
Esketamine 84 mg	5	5		5

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

Response and Remission with Single Dose Intranasal Esketamine

Daly et al. ACNP 2015

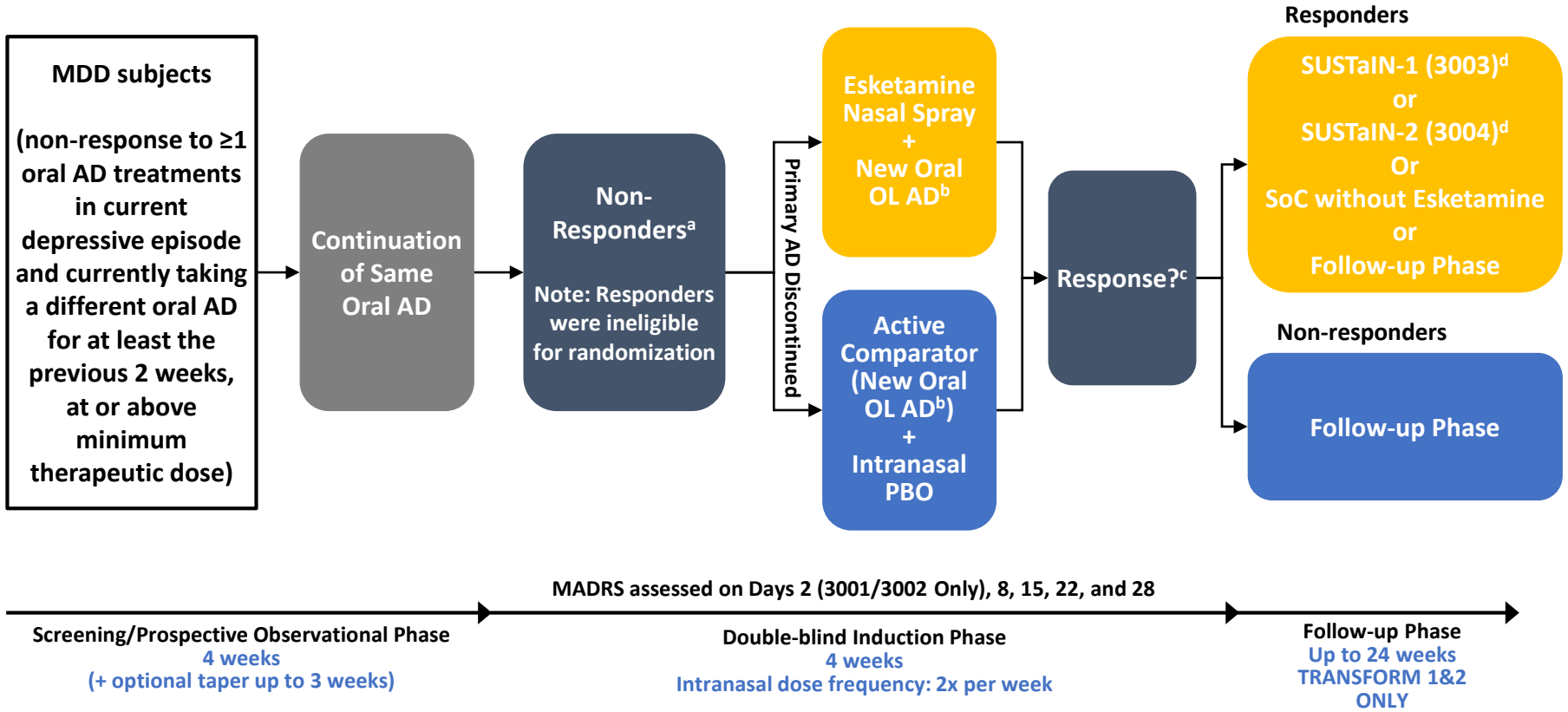


Esketamine Phase 3 Clinical Development Program in Treatment-Resistant Depression (TRD)

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

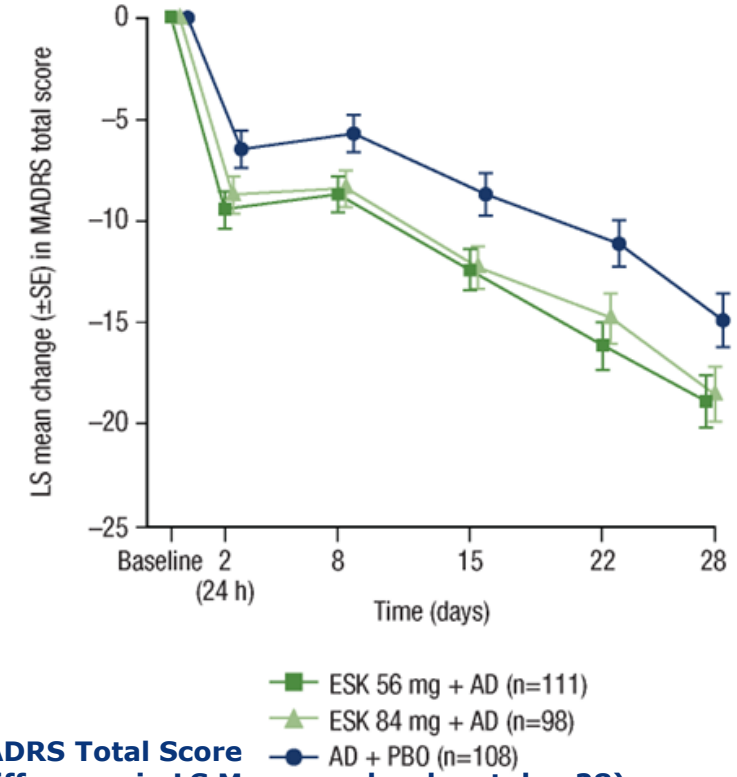


AD, antidepressant; MADRS, Montgomery-Asberg depression Rating Scale; MDD, major depressive disorder; OL, open label; PBO, placebo.
a. Non-response at end of screening (3001 and 3002) = ≤ 25% improvement in MADRS total score from week 1 to week 4 and a MADRS total score ≥ 28 at weeks 2 and 4; Non-response 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):

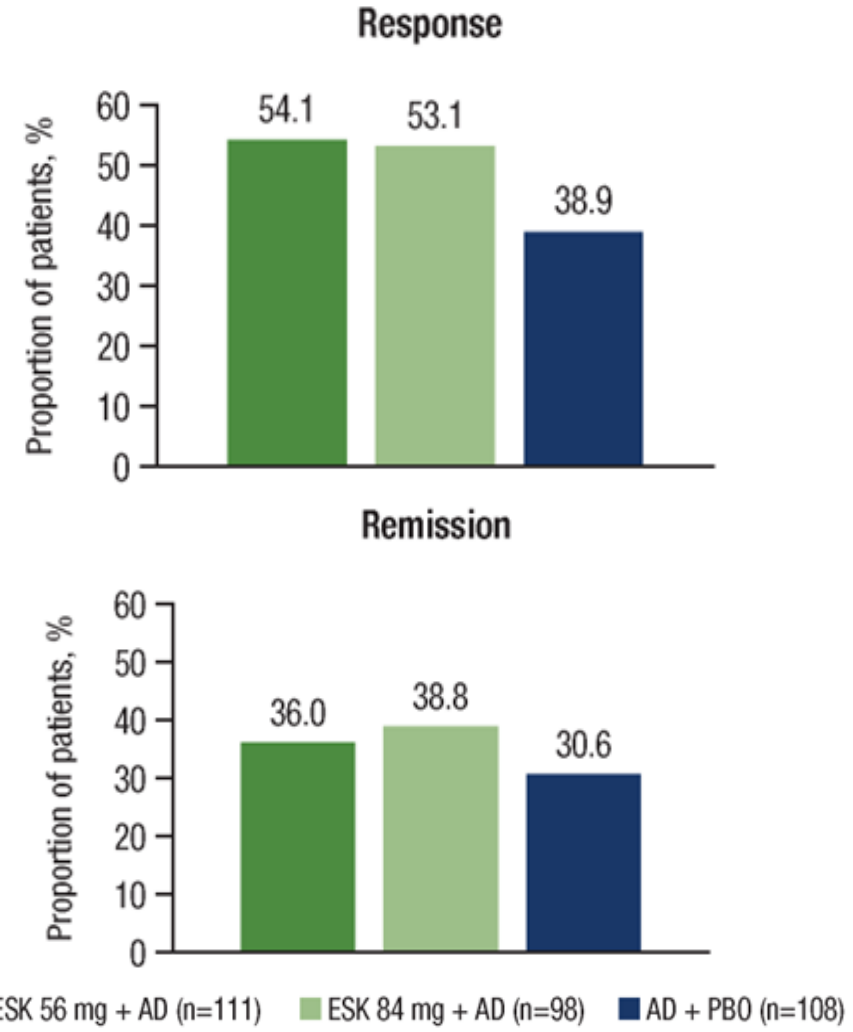
Esketamine 56 mg + oral AD: -4.1
Esketamine 84 mg + oral AD: -3.2

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

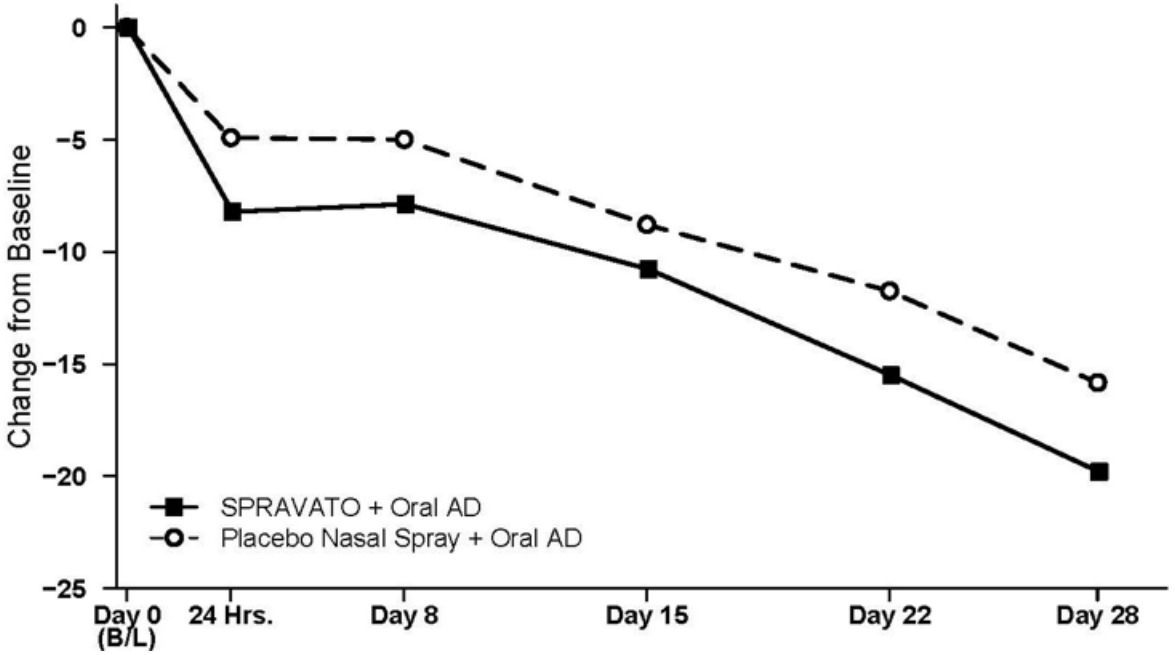


Response: ≥50% improvement on MADRS from Baseline; Remission: MADRS Total Score ≤12

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.

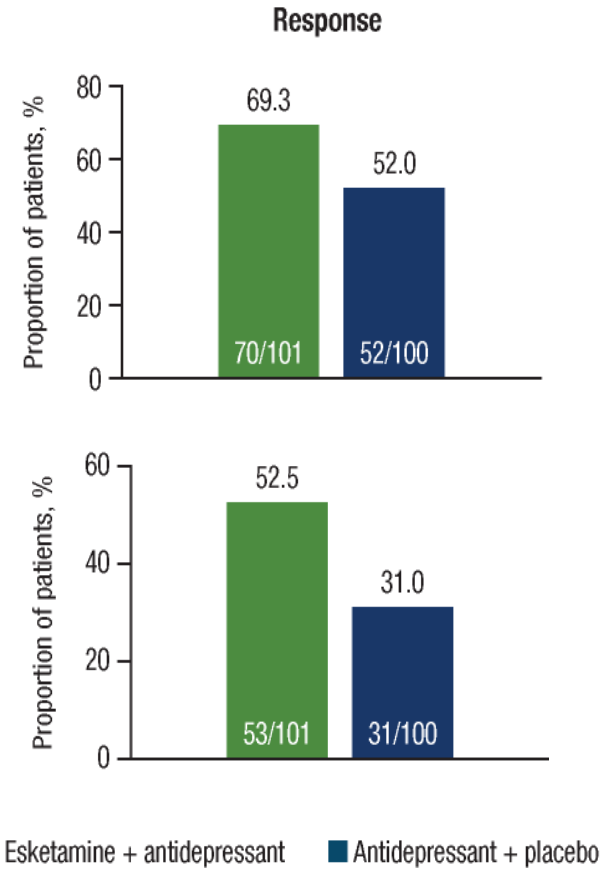
Most of esketamine's treatment difference (compared to placebo) was observed at 24 hours (*P*=0.321).

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

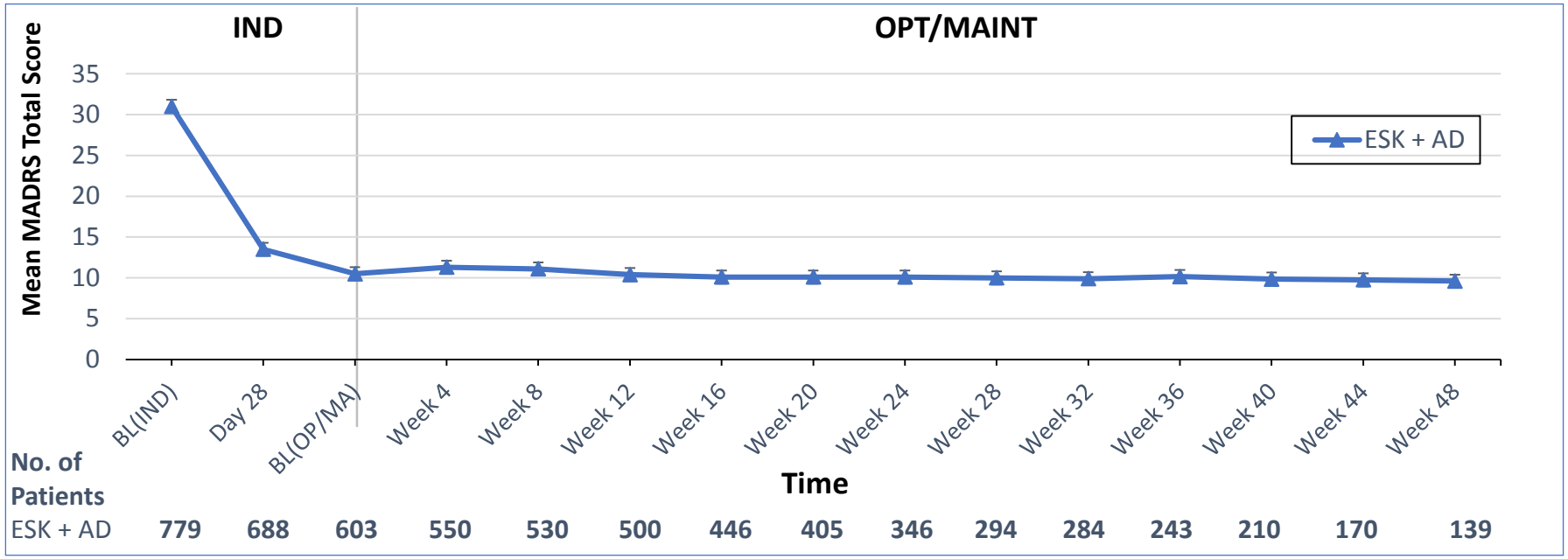


Response: ≥50% improvement on MADRS from Baseline;
Remission: MADRS Total Score ≤12

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

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

Mean Montgomery-Asberg Depression Rating Scale Total Score Over Time
(full analysis set [IND and OP/MAINT]; observed case analysis)



IND Endpoint:
Responders: 78.4% (593/756)
Remitters: 47.2% (357/756)

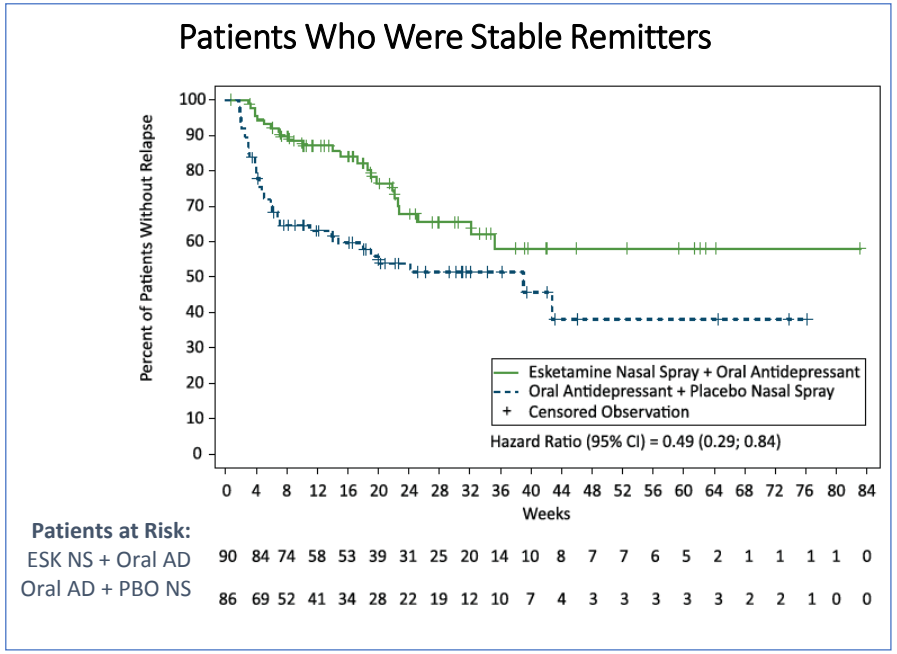
OP/MAINT Endpoint:
Responders: 76.5% (461/603)
Remitters: 58.2% (351/603)

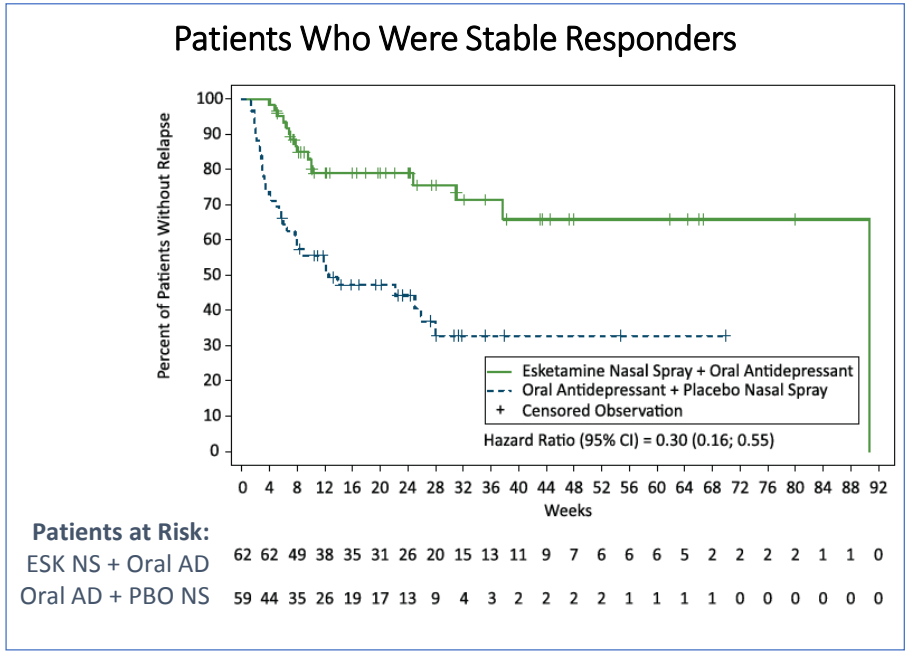
Responders (≥50% reduction in the MADRS total score); Remitters (MADRS total score ≤12)

Full analysis sets: All patients who received ≥1 dose of nasal spray study medication or oral antidepressant in the open-label IND or OP/MAINT phases.
AD = oral antidepressant; ESK = esketamine; IND = induction phase; MADRS = Montgomery-Asberg Depression Rating Scale; OP/MAINT = optimization/maintenance phase; SE = standard error.

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. Poster presented at *the European College of Neuropsychcopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.

Is Repeated Dosing Safe?

Shorter-Term Risks of Ketamine Treatment?

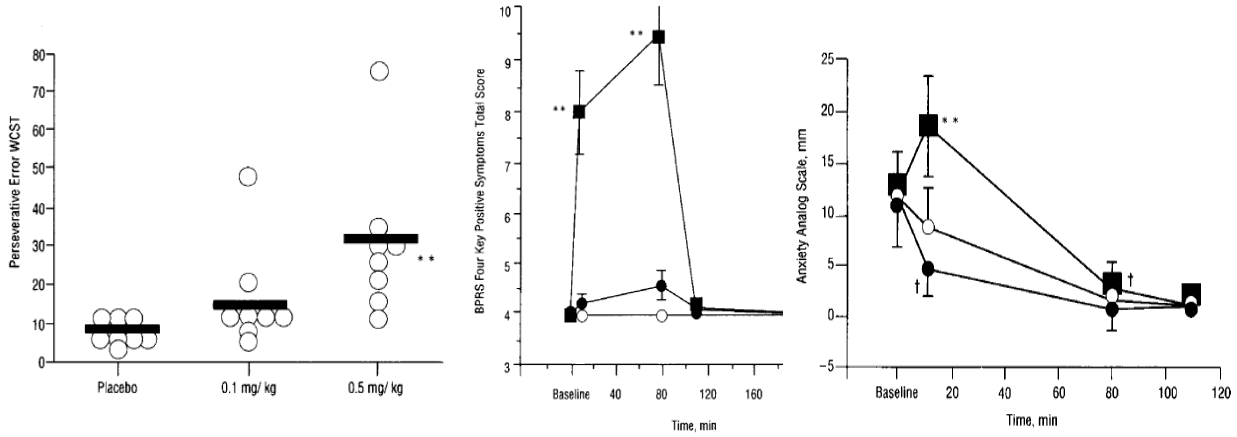
Physiological: Increases in cardiovascular demand and concern for loss of consciousness and respiratory depression

- Individuals can become nonresponsive to verbal stimuli, but all remained medically stable during the infusion and none required any form of respiratory assistance. No episodes of respiratory depression
- Increases in systolic and diastolic blood pressure , with blood pressure levels occasionally exceeding 180/100 mm Hg or heart rates exceeding 110 beats per minute in the patients treated.

(Perry et al. Psychopharmacology (Berl). 2007;192(2):253-260.) (Wan et al. J Clin Psychiatry. 2015;76(3):247-252)

Psychological: Acute Cognitive and Perceptual Alterations, with Accompanying Anxiety

Transient changes in Cognition, Perception and Anxiety have long been reported following sub-anesthetic doses of ketamine



Cognition Perception Anxiety

Krystal et al. (Arch Gen Psychiatry. 1994;51:199-214)

Animal Studies Suggest Repeated and Early Administration of Ketamine May Have Toxic Effects

Ketamine-induced Neuroapoptosis in the Fetal and Neonatal Rhesus Macaque Brain

Ansgar M. Brambrink, M.D., Ph.D.,* Alex S. Evers, M.D.,†
Michael S. Avidan, M.B.B.Ch., F.C.A.S.A.,‡ Nuri B. Farber, M.D.,§ Derek J. Smith, B.A.,‖
Lauren D. Martin, D.V.M.,# Gregory A. Dissen, Ph.D.,** Catherine E. Creeley, Ph.D.,††
John W. Olney, M.D.§ Brambrink et al. Anesthesiology. 2012 Feb;116(2):372-84.

Neuron

Article

Imaging Patients with Psychosis and a Mouse Model Establishes a Spreading Pattern of Hippocampal Dysfunction and Implicates Glutamate as a Driver

Scott A. Schobel,[1,4,8] Nashid H. Chaudhury,[4,9] Usman A. Khan,[2,5] Beatriz Paniagua,[6] Martin A. Styner,[6,7] Iris Asllani,[3]
Benjamin P. Inbar,[4] Cheryl M. Corcoran,[1,4] Jeffrey A. Lieberman,[1,4] Holly Moore,[1,2,*] and Scott A. Small[2,*]

***Neuron*. 2013;78(1):81-93**

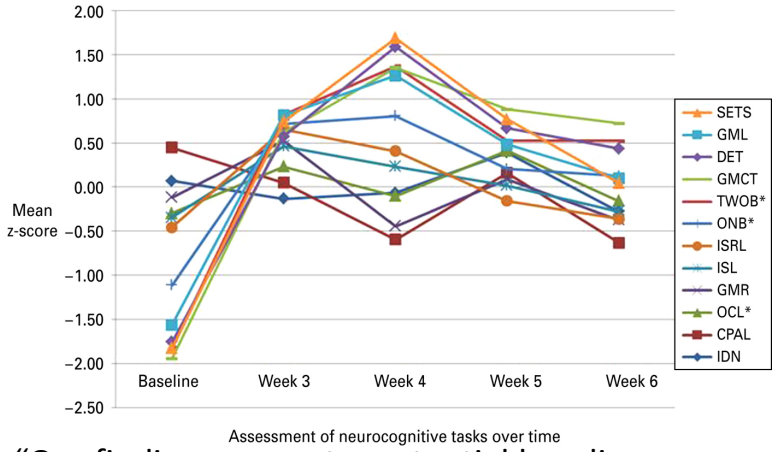
Is it Safe to Dose Repeatedly?
Possible Cognitive Effects of Chronic Ketamine Abuse

- Frequent ketamine use (at least 3Xweek for the past year) is associated with impairments in various forms of memory and aspects of executive function
- Reduced regional brain activity activation memory tasks.
- Ketamine users also exhibited schizotypal and dissociative symptoms that were related to hippocampal activation.

- 'Recreational' ketamine use does not appear to be associated with distinct cognitive impairments, although increased levels of delusional and dissociative symptoms were observed.
- The cognitive impairments observed in the frequent ketamine abusers appeared to be reversible upon cessation of ketamine use, although delusional symptoms persist."**.**

Morgan CJ, et al. *Addiction*. 2009;104(1):77-87. Morgan CJ, et al. Front Psychiatry. 2014 Dec 4;5:149

Short-Term Effects of Repeated Ketamine on Neurocognition among TRD Participants



"Our findings suggest a potential baseline neurocognitive predictor of ketamine response and the apparently lack of short-term neurocognitive impairment after completion of six ketamine infusions in TRD." **Shiroma PR, et al. *Int J Neuropsychopharmacol*. 2014**

****P* < .05. Mean z-score of neurocognitve tasks at baseline and at follow-up visits post-ketamine treatment among participants with TRD. Attention: Identification Task (IDN). Working Memory: One Back Task (ONB); Two Back Task (TWOB); Groton Maze Learning Test (GML). Visual Memory: Continuous Paired Associate Learning Task (CPAL); One Card Learning Task (OCL); Groton Maze Learning Test – Delayed Recall (GMR). Verbal Memory: International Shopping List Task (ISL); International Shopping List Task: Delayed Recall (ISRL). Speed of Processing: Groton Maze Chase Test (GMCT); Detection Task (DET). Set shifting: Set-Shifting Task (SETS).**

.

"The results suggest that ketamine does not cause memory deficits when given on up to six occasions. Confidence in this conclusion is enhanced by the fact that the two measures of autobiographical memory function and a measure of episodic memory function concur, as does an assessment of subjective memory." **Diamond PR, et al. *J Psychopharmacol*. 2014;28(6):536-544.**

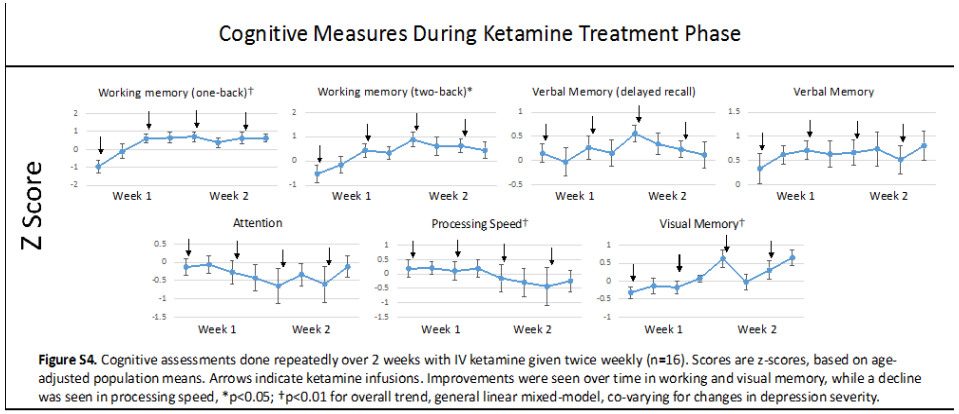


Figure S4. Cognitive assessments done repeatedly over 2 weeks with IV ketamine given twice weekly (n=16). Scores are z-scores, based on age-adjusted population means. Arrows indicate ketamine infusions. Improvements were seen over time in working and visual memory, while a decline was seen in processing speed, *p<0.05; †p<0.01 for overall trend, general linear mixed-model, co-varying for changes in depression severity.

Improvements seen in working and visual memory replicated those from a prior study, though our study showed these effects over a shorter time period (24-72 hours v. 3 weeks) and survived adjustment for changes in depression severity. We observed a decline in processing speed over time, which was unexpected and is in contrast with prior research,

Wilkinson et al, In Press Psychotherapy and Psychosomatics 2017

Yale's Early Clinical Experience

History of electroconvulsive therapy	27 (50.0)
History of hospitalization	40 (74.1)
History of hospitalization for suicidal ideation or attempt	35 (64.8)
History of suicide attempt	23 (46.9)
Inpatient status at first infusion	21 (38.9)
Baseline QIDS-SR score, mean (SD)	19.8 (6.0)
Baseline MADRS score, mean (SD)	33.1 (6.9)

We calculated dichotomous outcomes from the sample of patients with mood disorders who began a 4-infusion protocol (n = 44).

First infusion, 31.8% of patients (n = 14) responders*

Fourth infusion, 45.5% of patients (n = 20) responders*

*(50% or greater improvement in QIDS-SR).

14 patients received continuation/maintenance ketamine treatments for at least 14 weeks

The average patient received 25.1 (Median 27, range, 12–45 treatments) treatments (range, 12–45 treatments).

Cognitive Outcomes of Long-Term (>3mos) Ketamine Treatment (n = 14)

The median time between assessments was 331 days (range, 49–522 days).

Cognitive Domain	Mean Paired Difference Between First and Most Recent Cognitive Assessment (age-adjusted *z*-score)	Correlation Between Paired Difference (age-adjusted *z*-score) and No. of Ketamine Treatments	
		r^2 Value	*P* Value
Processing speed	0.330	0.035	.538
Attention	–0.187	0.042	.500
Visual memory	0.126	0.008	.771
Verbal memory	0.361	0.021	.635
Verbal memory, delayed recall	0.316	0.099	.297
Working memory	0.807	0.143	.203

[a]Paired differences between the first and most recent cognitive assessments were calculated for each subject and then correlated with the total number of treatments between assessments. A positive difference indicates improved performance at second assessment compared to baseline. Tasks included are as follows: Identification Task (attention), One-Back Task (working memory), One Card Learning Task (visual memory), International Shopping List and Delayed Recall (verbal memory, with delayed recall), and Detection Task (processing speed). Further description of these tasks can be found elsewhere.[23,24]

Wilkinson et al. J. Clinical Psychiatry 2018

Treatment-Emergent Adverse Events (3004, SUSTaIN 2)

Most common TEAEs (≥10% of Patients in the Combined Phases Group)			
n (%)	4-week IND Phase (N=779)	48-week OP/MAINT Phase (N=603)	IND and OP/MAINT Phases (N=802)
Dizziness	228 (29.3)	135 (22.4)	264 (32.9)
Dissociation	182 (23.4)	113 (18.7)	221 (27.6)
Nausea	157 (20.2)	84 (13.9)	201 (25.1)
Headache	137 (17.6)	114 (18.9)	200 (24.9)
Somnolence	94 (12.1)	85 (14.1)	134 (16.7)
Dysgeusia	77 (9.9)	54 (9.0)	95 (11.8)
Hypoesthesia	79 (10.1)	40 (6.6)	95 (11.8)
Vertigo	68 (8.7)	43 (7.1)	88 (11.0)
Vomiting	56 (7.2)	45 (7.5)	87 (10.8)
Viral upper respiratory tract infection	19 (2.4)	70 (11.6)	82 (10.2)

Overall, 90.1% of patients in the induction (IND) and optimization/maintenance (OP/MAINT) phases experienced ≥1 TEAE which were primarily mild or moderate in intensity, occurred on dosing days and resolved on the same day.

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

Adverse Events of Interest (3004, SUSTaIN 2)

- There were **no** reported cases of **interstitial or ulcerative cystitis**.
  - 65 (8.1%) patients experienced UTI during the treatment phases; 5 (0.6%) patients reported cystitis that were mostly mild in intensity and resolved during ongoing esketamine treatment.

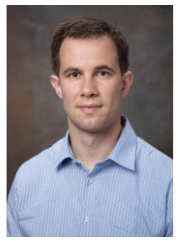
- **Blood pressure** increases were reported 40 minutes post-dose and returned to baseline values by 1.5 hours.
  - Thirty-three patients (**4.1%**) experienced systolic blood pressure **≥180 mm Hg or diastolic blood pressure ≥110 mm Hg**.

- **Dissociative** and perceptual changes, as measured by the CADSS, peaked at 40 minutes post dose and resolved by 1.5 hours. The magnitude of change attenuated with repeated dosing.

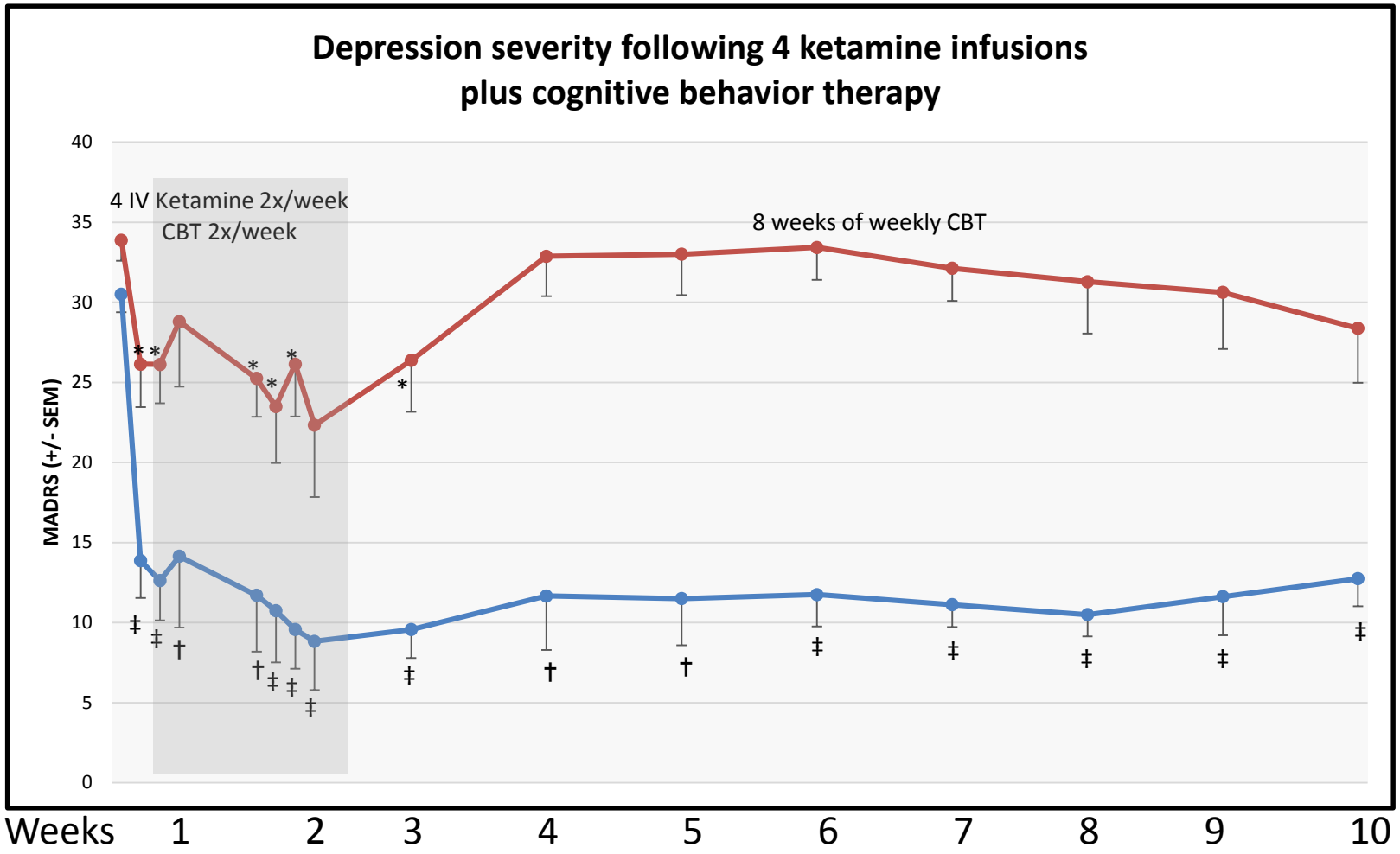
- **Nasal tolerability** was acceptable (≥99% of patients had a normal nasal examination).
  - Based on a nasal symptoms questionnaire, few patients reported moderate to severe symptoms (≤11%).
  - Taste disturbance (IND, 10.2%; OP/MAINT, 11.0%) and postnasal drip (IND, 9.9%; OP/MAINT, 11.0%) were most commonly reported.

- Performance on multiple **cognitive** domains either **improved or remained stable** throughout the study post baseline for the entire study population. Likewise, performance on memory and spatial/executive tests remained stable in both elderly (≥65 years) and younger patients.

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



Can we use Augmentation/Combination Therapies to Extended the Benefits of Ketamine?



Wilkinson et al, Psychotherapy and Psychosomatics 2017

Who is the appropriate Ketamine patient?

or

What do we know about moderators of the effect?

Does gender/sex matter?

Rodent data suggests a possible gender effect for ketamine's efficacy

Table 1. In vitro and in vivo experiments using ketamine treatment.

Publication	Test Subject	Study Design	Antidepressant-Like Effect	Molecular Mechanism
Franceschelli et al., 2015 [64]	Male and female C57/BL6J mice	KET in naïve and CMS animals: female and male mice (FST)	KET effect: Female mice > male mice	Effects on excitatory amino acids (glutamate and aspartate), serotoninergic activity.
Saland et al., 2018 [65]	Male and female Sprague-Dawley rats	KET metabolism and distribution		↑ level of KET and NK in both brain and plasma
Ho et al., 2018 [66]	Human iPSC-derived astrocytes	Oestrogen + KET in vitro	Oestrogens augmented the effect of KET	↑ level of AMPA receptor subunit and ERα. Oestrogens: ↑ level of CYP2A6 and CYP2B6.
Dossat et al., 2018 [67]	Male and female C57/BL6J mice	Oestrogen and Progesterone receptor agonist and KET (FST)	Female in proestrus + KET: sensitive to lower dose.	Proestrus female ↑ p-Akt and p-CaMKIIα.
Sarkar et al. 2016 [28]	Male and female Sprague-Dawley rats	KET and social isolation stress (behaviour and synaptic protein level)	IS: male depression like behaviour at 8 weeks while female at 11 weeks. KET rescued the phenotype.	Decline in spine density and synaptic proteins reversed by KET only in male but not female

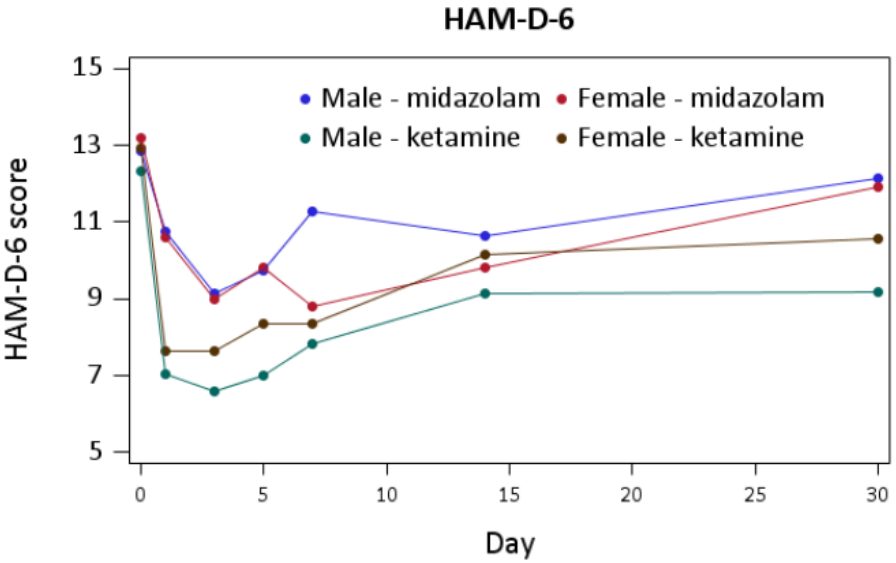
We list relevant, ketamine-associated publications with significant impact in the field. *KET* ketamine, *CMS* chronic mild stress, *FST* forced swim test, *NK* norketamine, *iPSC* induced Pluripotent Stem Cells, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *CYP* Cytochrom P 450 Enzyme, *IS* Isolation Stress.

Herzog et al. Int. J. Mol. Sci. 2019, 20, 949

(Carrier and Kabbaj, 2013, Celia Moreira Borella et al., 2016, Coyle and Laws, 2015, , Guo et al., 2016, van den Buuse et al., 2015, Wright et al., 2017)

No Clear Effect of Gender in the NIH sponsored RAPID study

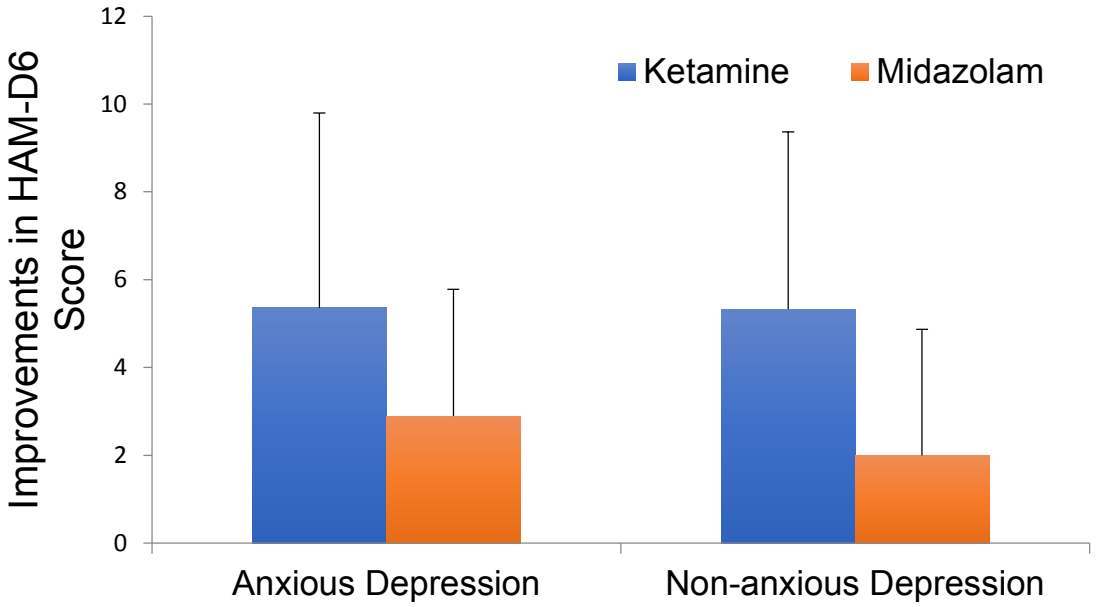
One-time use of ketamine appears to have similarly effective and tolerable treatment for TRD for both women and men, and pre- and postmenopausal women.



Effect	Num DF	Den DF	F Value	Pr > F
GROUP	1	180	7.25	0.01
DAY	1	180	54.51	<.0001
GENDER	1	180	0.24	0.63
GROUP*DAY	1	180	8.00	0.01
GROUP*GENDER	1	180	0.16	0.69
DAY*GENDER	1	180	0.05	0.83
GROUP*DAY*GENDER	1	180	0.06	0.80

Freeman et al [RAPID], J Psychiatr Res., 2019 Mar;110:166-171

or Anxious Depression

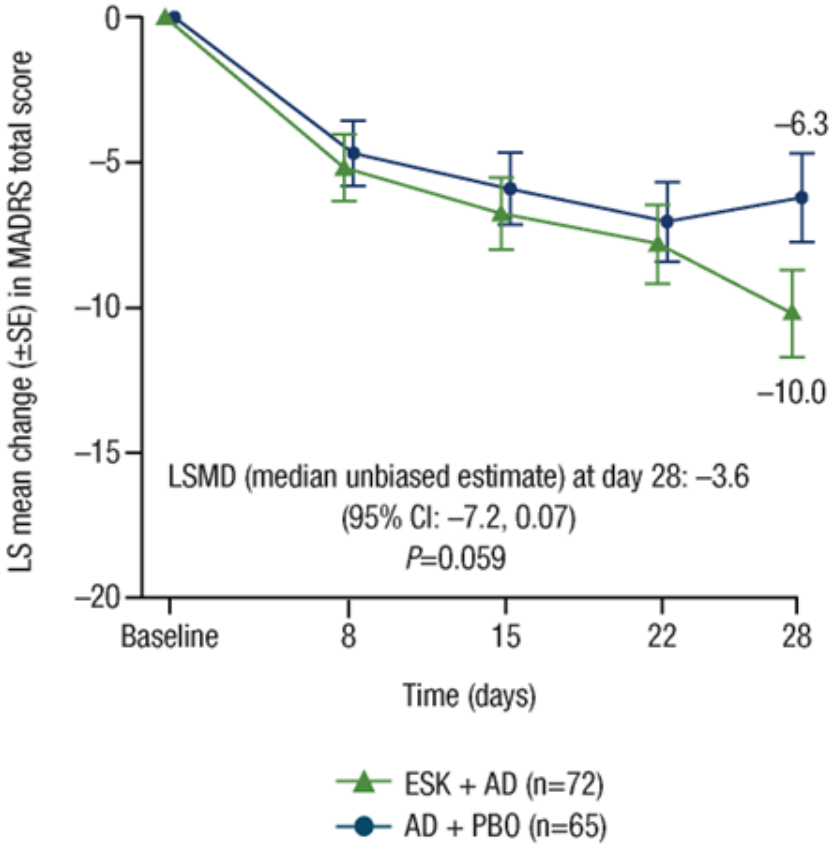


Salloum et al [RAPID]Depression & Anxiety 2018

Does age matter?

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

LS Mean Change in MADRS Total Score Over Time in Elderly Patients; Primary Outcome



Median unbiased LS difference estimate between esketamine nasal spray + oral AD vs placebo nasal spray + oral AD at Day 28:

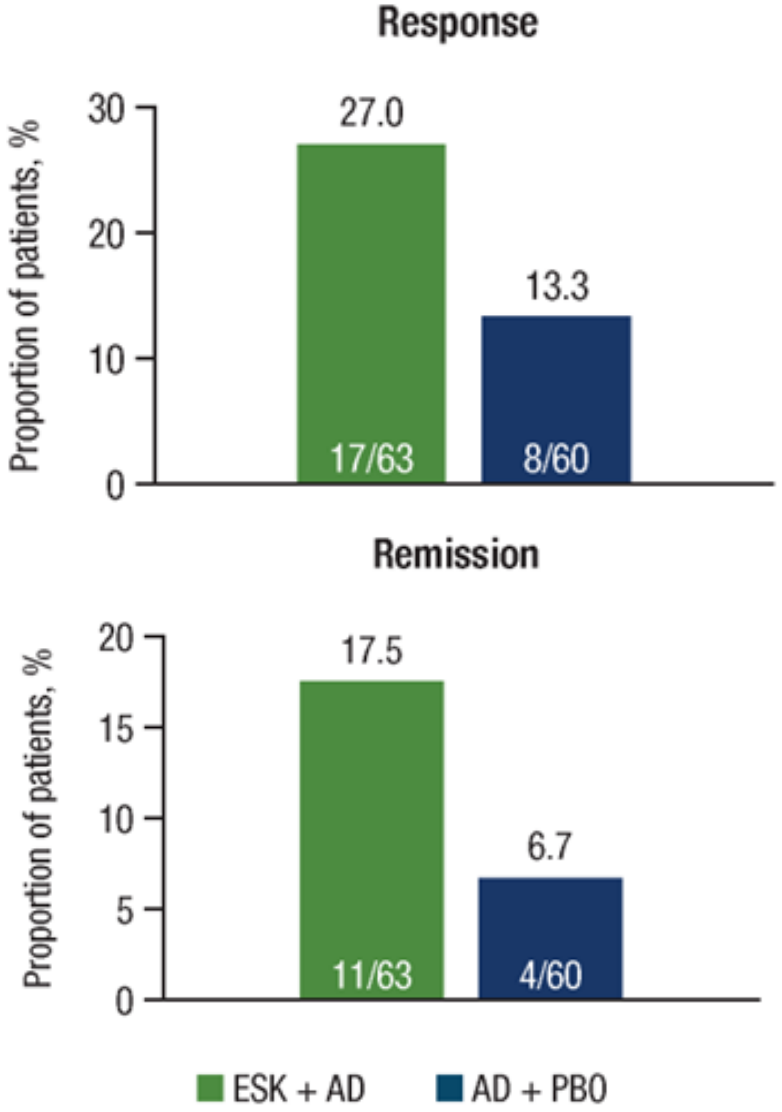
Total Study Population: -3.6 (*P*=0.059)

Primary outcome was not statistically significant. However, the ESK + oral AD group showed a numerically greater improvement in the MADRS total score from baseline to day 28 compared to the oral AD + PBO group.

Overall response rates at day 28 favored the intranasal ESK + oral AD group (17 of 63 [27.0%] subjects) compared with the oral AD + PBO group (8 of 60 [13.3%] subjects).

At Day 28, 11 of 63 (17.5%) subjects in the ESK + oral AD group and 4 of 60 (6.7%) subjects in the oral AD + PBO group were in remission.

Response and Remission Rates

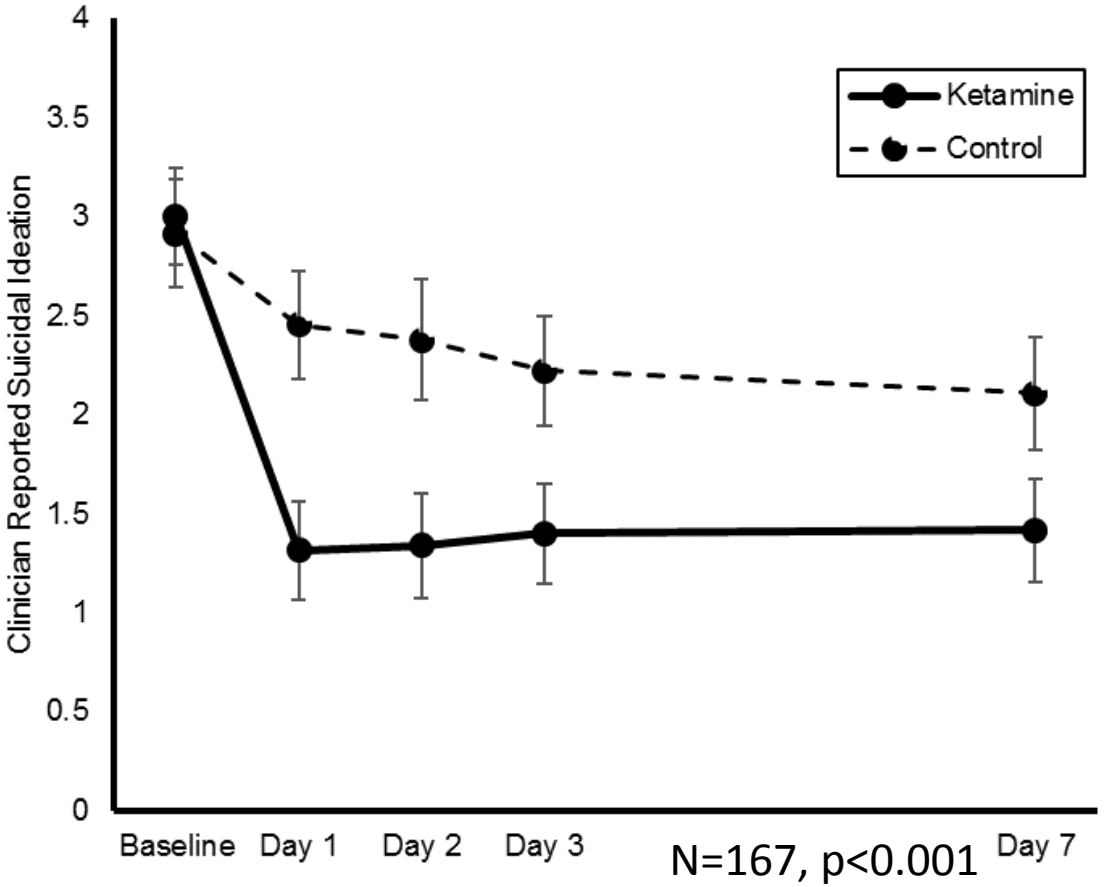


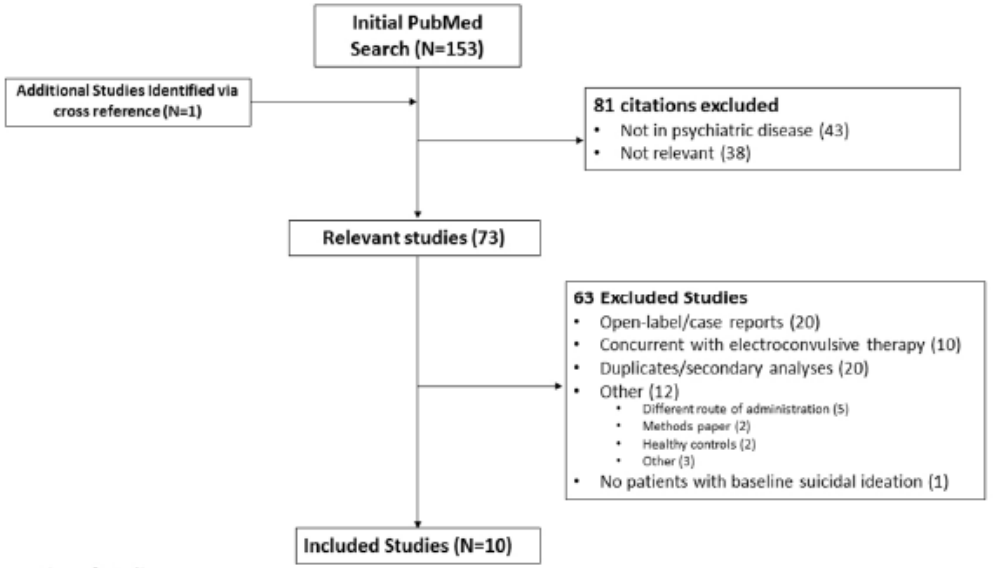
Response: ≥50% improvement on MADRS from Baseline; Remission: MADRS Total Score ≤1

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.

Does ketamine/esketamine have rapid effects on suicidal ideation?

Individual patient level data Meta-analysis of Effects of Single Ketamine Treatment on Suicidal Ideation





ction of studies.

Proportion without suicidal ideation after single dose of ketamine, clinician-reported outcomes

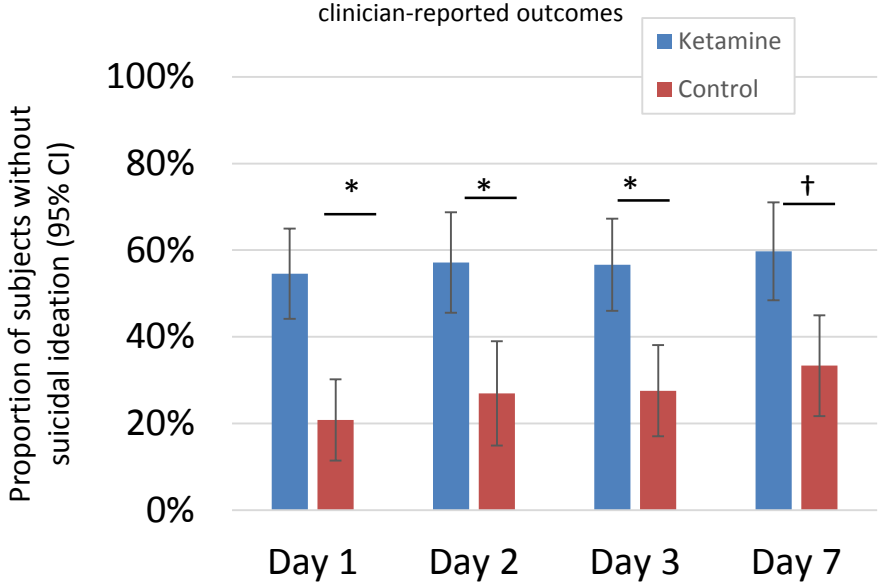
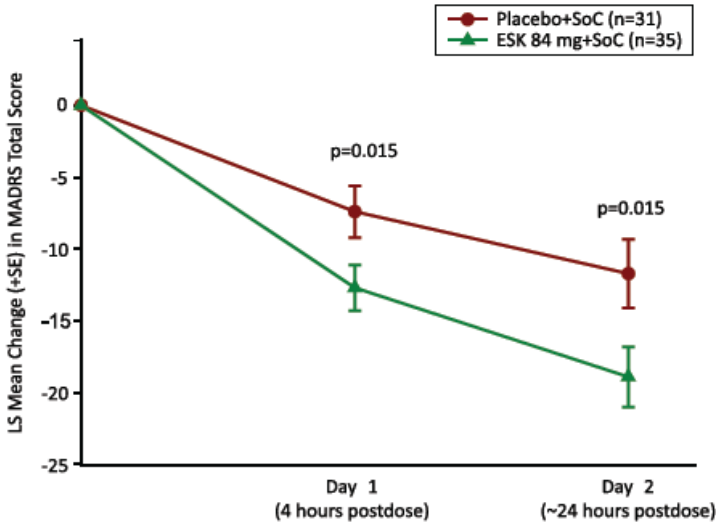


Figure 4A. Proportion of subjects without suicidal ideation (95% confidence intervals) at each time point post-dose using clinician-reported outcomes (Montgomery-Asberg Depression Rating Scale or Hamilton Depression Rating Scale; *p<0.001, †p<0.01).

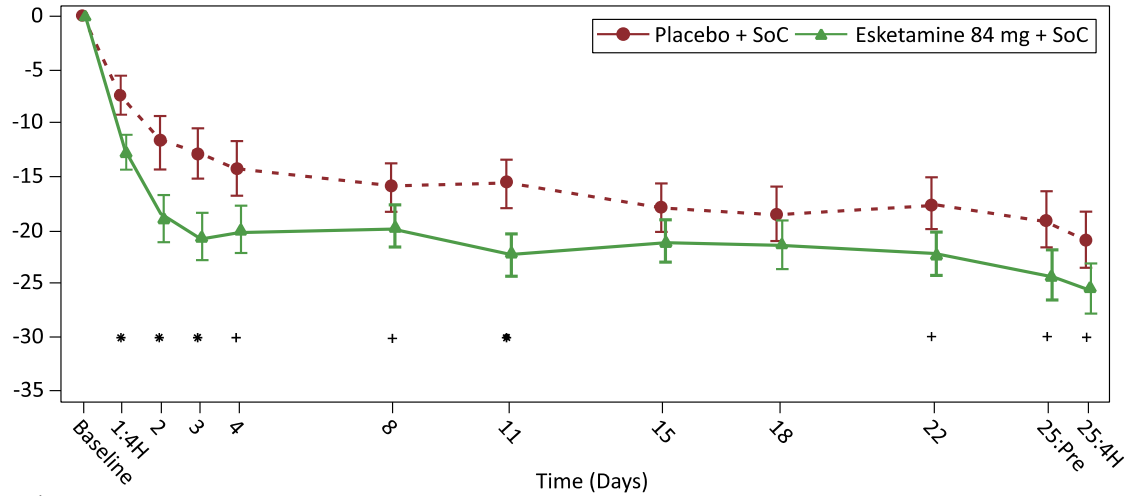
Wilkinson, Ballard et al., Am. J. Psychiatry 2018

Effects of Esketamine in Acutely Suicidal Patients

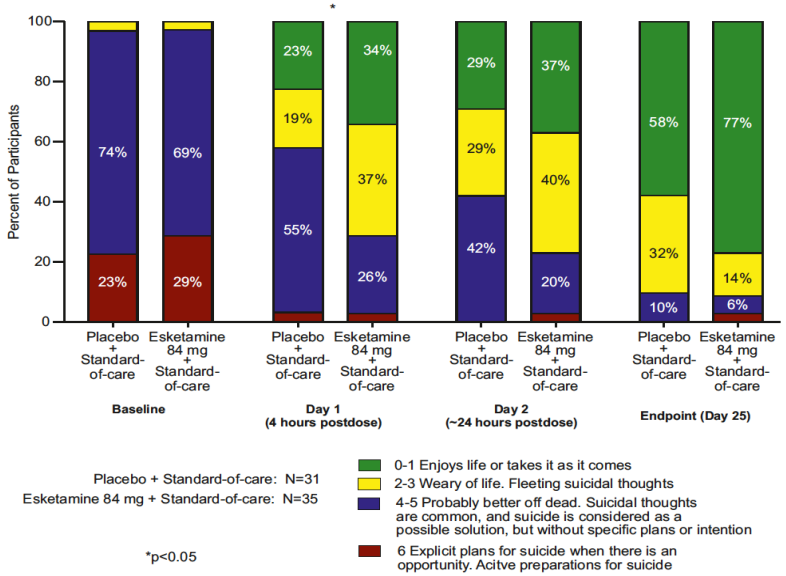
MADRS change from baseline to 4hr. and 24hr: ITT



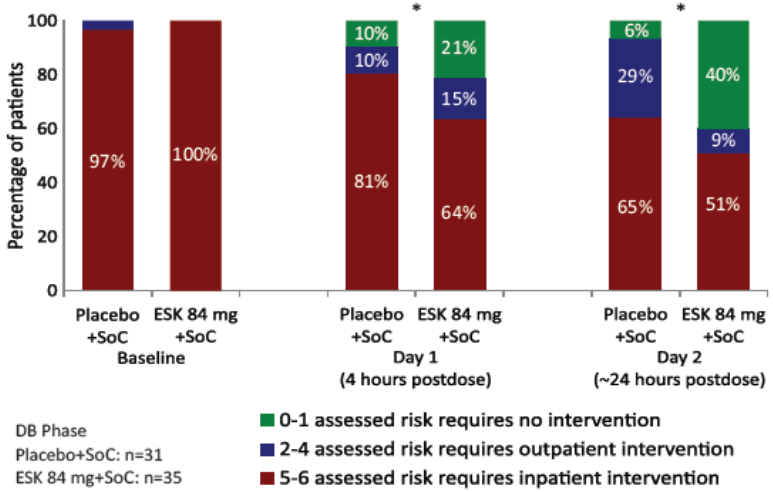
MADRS change over 25 days



Number of Participants												
Placebo + SoC	31	31	31	31	31	31	31	31	31	31	31	31
sketamine 84 mg + SoC	35	35	35	35	35	35	35	35	35	35	35	35



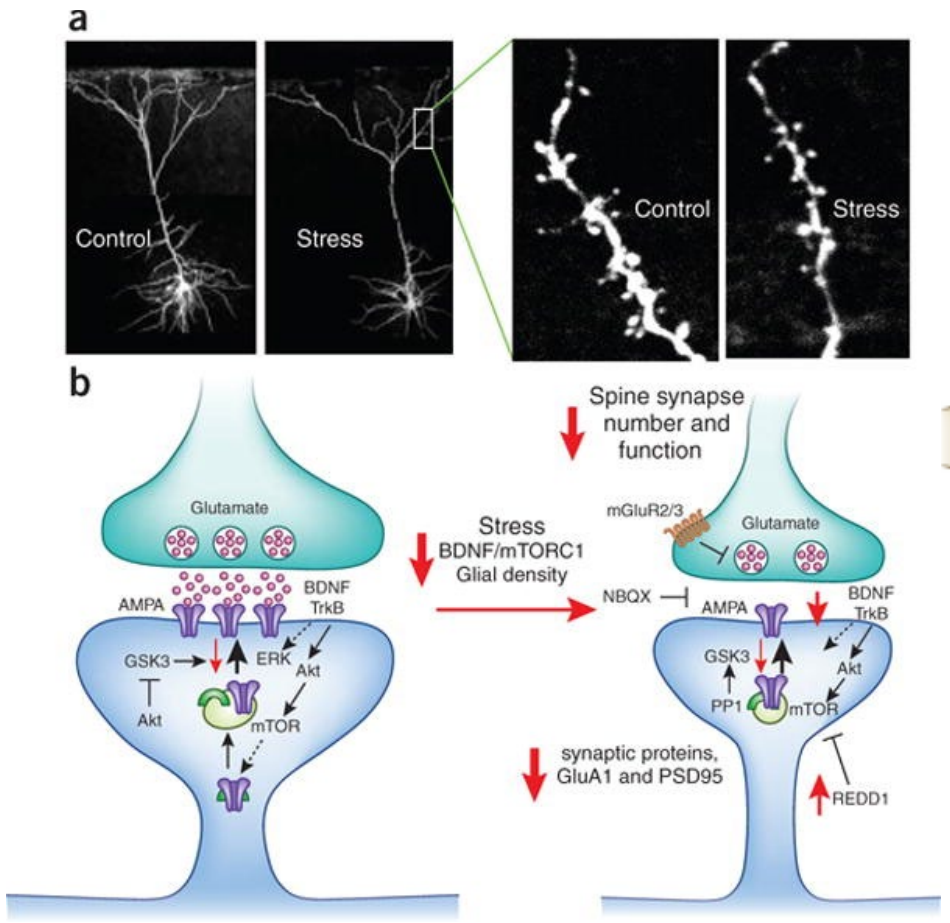
SIBAT: Frequency Distribution of Clinical Global Judgment of Suicide Risk at Baseline, day 1 (4Hr) and 24Hr: ITT



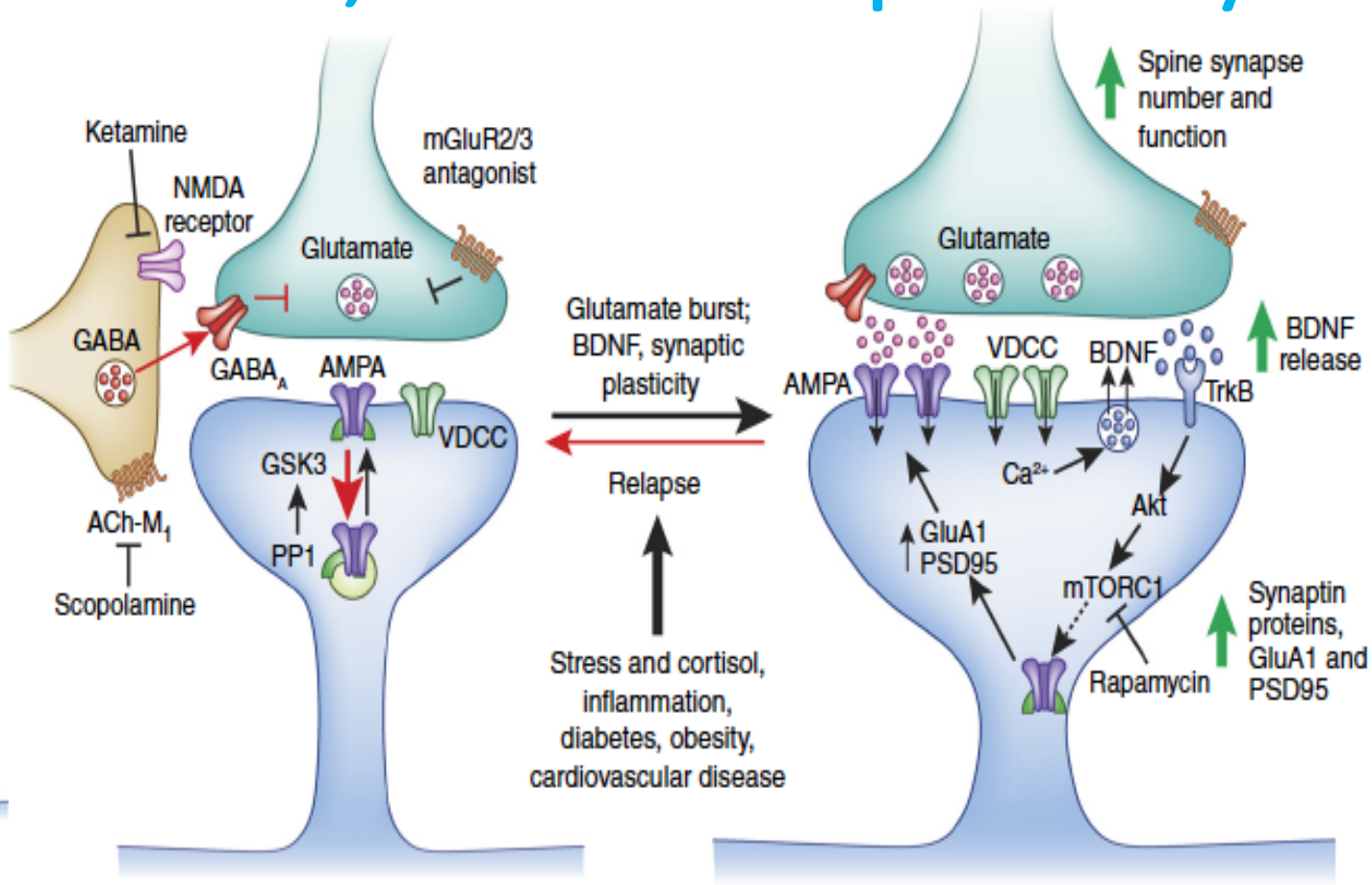
Canuso et al. Am J Psychiatry. 2018

What is the mechanism of action?

NMDA Receptor, Glutamate Burst, and Neuroplasticity



Duman, Aghajainian, Sanacora, and Krystal Nat Med. 2016 Mar; 22(3): 238–249.



Duman, Aghajainian, Sanacora, and Krystal Nat Med. 2016 Mar; 22(3): 238–249.

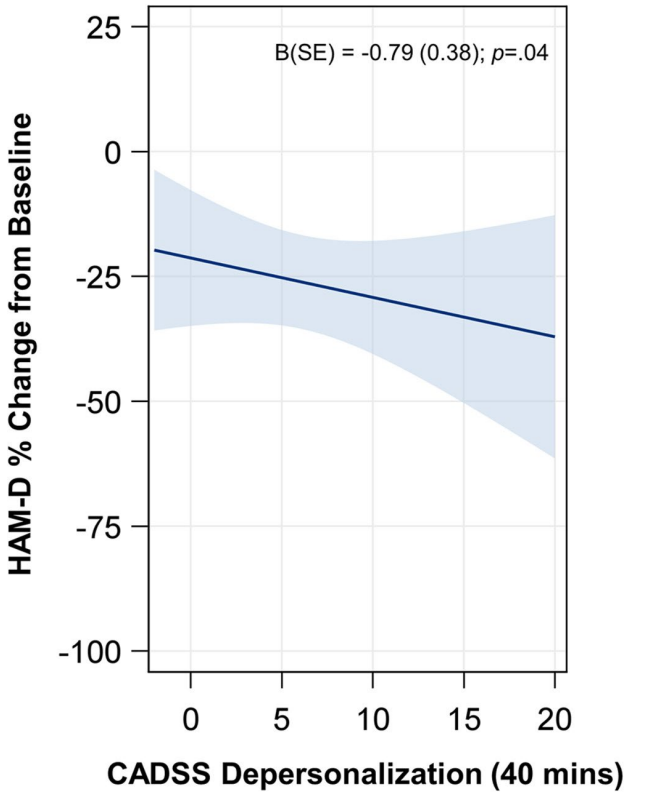
Other Possible Mechanisms of the Treatment

- Monoaminergic
- Effects on Neuroinflammation
- Effects on Opioid Systems

Non-Specific Effects of the Treatment

- Hope
- Unique Psychological / Spiritual Experience
- Positive Social Interactions

What is the relationship between "Dissociation" and Antidepressant response?



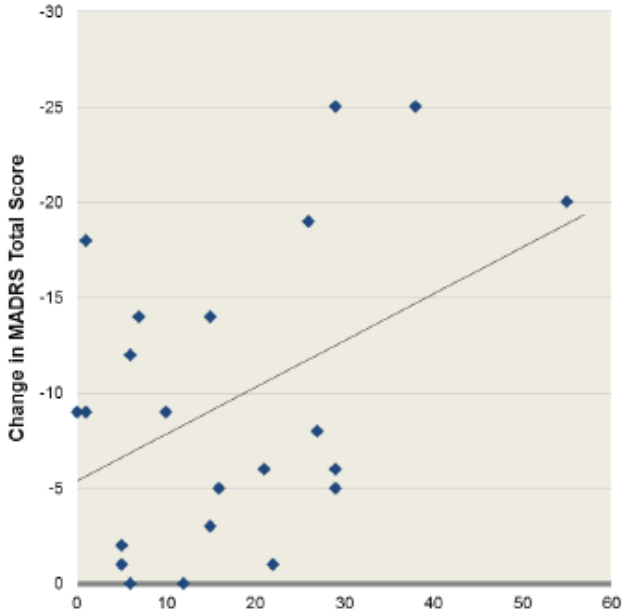
Niciu et al. J Affect Disord. 2018 May;232:310-315

Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital

Fifty-four patients with severe treatment resistant mood disorders received ketamine, with 518 total infusions performed. A subset of 44 patients with mood disorders initiated the 4-infusion protocol,of whom 45.5% responded and 27.3% remitted by the fourth infusion.

CADSS was not found to moderate the effect of time on the MADRS or QIDS-SR scores

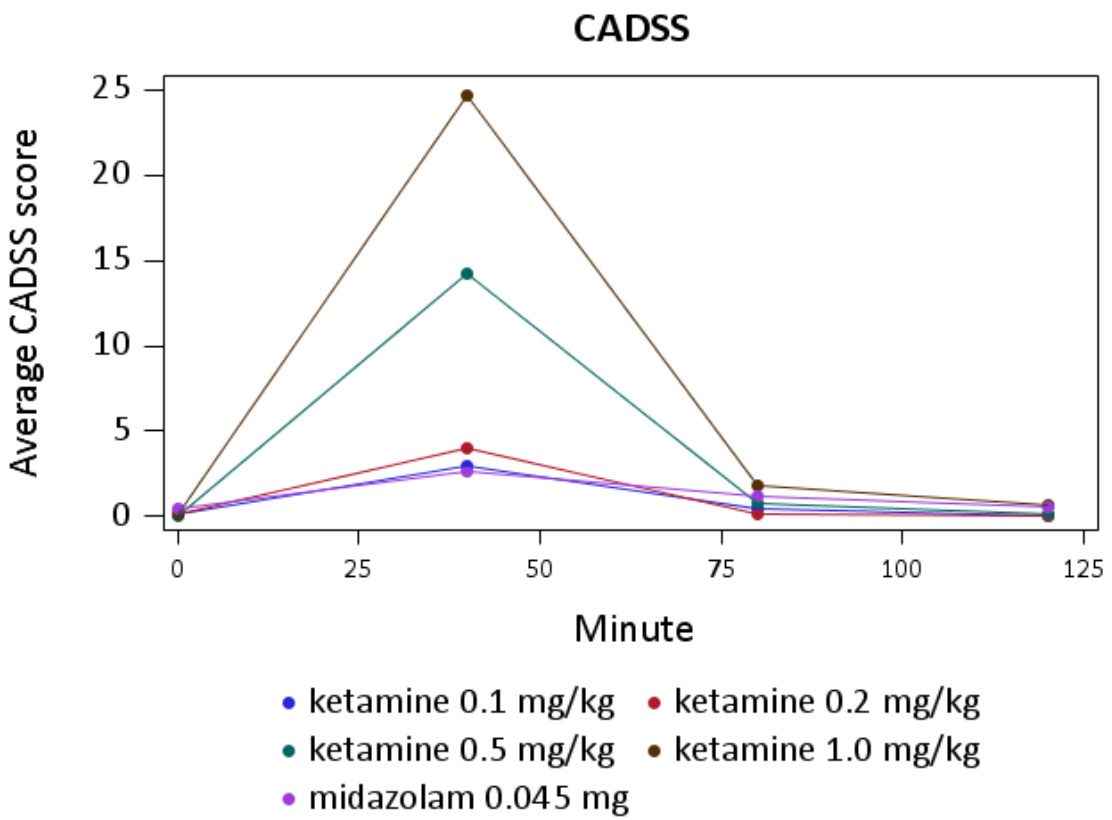
Wilkinson et al. J. Clinical Psychiatry 2018



"In the present study, although participants' initial antidepressant response to ketamine was associated with dissociative experience, dissociation decreased with repeated infusions despite increasing therapeutic benefits"

Phillips et al. Am J Psychiatry. 2019 May 1;176(5):401-409.

What is the relationship between “Dissociation” and Antidepressant response?



MADRS Changes at day 3

Group	Day	Estimated MADRS Change Difference	Raw p	Adj. p	Cohen’s d
5-Group Comparison					
ketamine 0.1 mg/kg	3	-5.15	0.16	0.33	-0.48
ketamine 0.2 mg/kg	3	-2.16	0.53	0.53	-0.20
ketamine 0.5 mg/kg	3	-9.85	0.00	0.02	-1.03
ketamine 1.0 mg/kg	3	-7.72	0.03	0.08	-0.70

It’s Complicated

and very unlikely to be linear

Fava et RAPID Study Group Molecular Psychiatry 2018

Novel Medications in Development

Compound, Route of Administration	Pharmacology	Sponsor	Phase
Ketamine, various	Non-selective, non-competitive NMDA receptor antagonist	Multiple	--
Esketamine, IN	Non-selective, non-competitive NMDA receptor antagonist	Janssen	III *Now with FDA indication
Lanicemine/ AZD-6765, IV	Low trapping NMDAR antagonist	AstraZeneca/Biohaven	IIb
Traxoprodil/ CP-101,606, IV	NMDAR antagonist at NR2B subunit	Pfizer	II
EVT-101	NMDAR antagonist at NR2B subunit	Evotec/La Roche	II
Rislenemdaz/ CERC-301/MK-0657, oral	NMDAR antagonist at NR2B subunit	Cerecor	II
AVP-786, oral	Non-selective antagonist of NMDAR	Avanir/ Otsuka	II
AXS-05, oral	Non-selective antagonist of NMDAR	Axsome	III
Rapastinel/ GLYX-13, IV	Partial functional agonist at glycine site of NMDA receptor	Allergan	III
Apimostinel/ NRX-1074/AGN-241660, oral	Reported to be a functional antagonist at Glycine B site of the NMDA receptor	Allergan	II

Wilkinson and Sanacora, Drug Discov Today. 2019 Feb;24(2):606-615

Compound, Route of Administration	Pharmacology	Sponsor	Phase
AV-101, oral	Selective agonist at glycine site of NMDA receptor NR1 subunit	VistaGen	II
NRX-100/NRX-101, oral	Partial NMDAR agonist at glycine-site	NeuroRx	III
Basimglurant/ RO4917523, oral	NAM of $mGluR_5$	Hoffmann- La Roche	IIb
Decoglurant/RG1578/ RO4995819	NAM of $mGluR_{2/3}$	Hoffmann- La Roche	II
Tulrampator/ CX-1632/S-47445	PAM of AMPA receptor	RespireRx	II
Riluzole, oral	Glutamate release inhibitor/up take facilitator	NIMH Tehran University of Medical Sciences	II
Brexanolone/ SAGE-547, IV	PAM of $GABA_A$ receptor	Sage	III
Ganaxolone, IV	PAM of $GABA_A$ receptor	Marinus	II
SAGE-217, oral	PAM of $GABA_A$ receptor	Sage	II

*Now with FDA indication

Wilkinson and Sanacora, Drug Discov Today. 2019 Feb;24(2):606-615

Take Home Messages

1. There is now clear evidence demonstrating the ability to produce a rapid onset of antidepressant effects using a treatment that does not directly target the monoaminergic neurotransmitter systems.
2. Ketamine and now Esketamine have repeatedly been demonstrated to induce clinical improvement in a substantial proportion of previously treatment resistant depressed patients within 24hrs of initiating treatment.
3. Increasing evidence demonstrates the ability to sustain the response with repeated dosing.
4. There does appear to be dose related effects clinical response in rodents and in clinical studies.
5. There is now studies of sufficient size and duration (especially with Esketamine) to give a much better idea of the ability to sustain the response and the safety of repeated dosing.
6. There is early evidence to suggest the treatments may have rapid effects producing decreases in suicidal ideation.
7. While the safety profile appears to be generally favorable, there are still both short-term and longer-term risks associated with the treatments that require the drugs to be administered under medical supervision in a facility that can provide care if necessary and monitor drug dispensing.
8. Future studies are required to better determine the whether it can be used as monotherapy, for other disorders, safely in patients with comorbid substance use disorders, and directly to treat suicidal ideation.

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NIMH, NARSAD, VA REAP, CT DMHAS

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