Rapid Acting Ketamine and Esketamine: Changing the Neurobiology of Depression

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Consulting Activities, Advisory Board, Speakers Bureau (past 36 months):

Avanir Pharmaceuticals, Johnson and Johnson, Janssen Pharmaceuticals, Neurocrine Biosciences, Otuska Pharmaceuticals, Lundbeck Pharmaceuticals, PsychU, Teva Pharmaceuticals, New Hope Clinical Research, Centers of Psychiatric Excellence, and Continuous Precision Medicine.

Demands for Treatment

- In 2003, spending on prescription medications totaled $179.2 billion - 11% of national health expenditures
- 1996 to 2001, spending on psychotropics almost tripled from $5.9 million to $14.7 million, more rapidly than other class
- In 2000-2001, sales for antidepressants grew faster than retail sales for any other therapeutic class
- By 2011, GSK, AstraZeneca and Novartis announced closures of neuroscience divisions globally
- All available FDA approved antidepressants (until recently) target monoamine systems and require 2-3 weeks to work
- Given the suicide rate with mood disorders better treatments are needed

So we may have novel targets, and novel ways of going after these targets……..but targets for what?

The need for Translational Endophenotypes

Unmet medical need

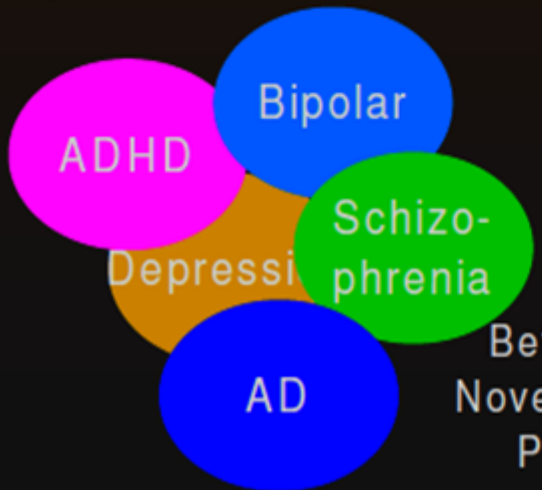
Cognition	Mood disorders	Psychosis

Symptomatic Improvement (versus current standards)

Disease Modification (neuroplasticity/trophism/neurodegeneration

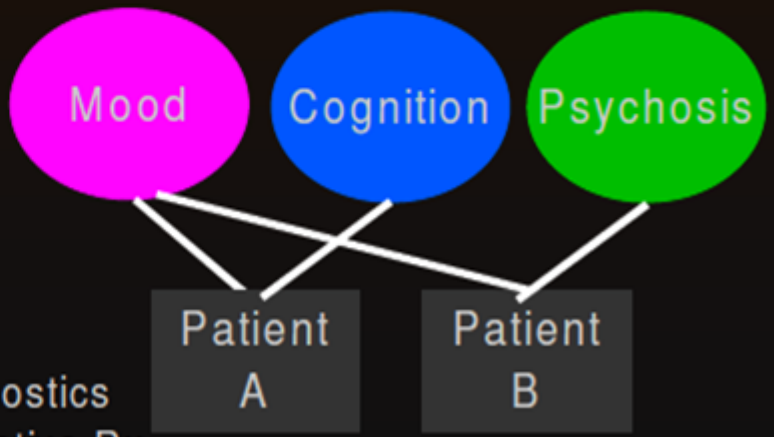
CURRENT

- Complex diseases → Syndromes
- Multiple-target drugs
- Population-based treatments



FUTURE

- Phenotypic quantitative traits
- Individual-Personalized Medicine



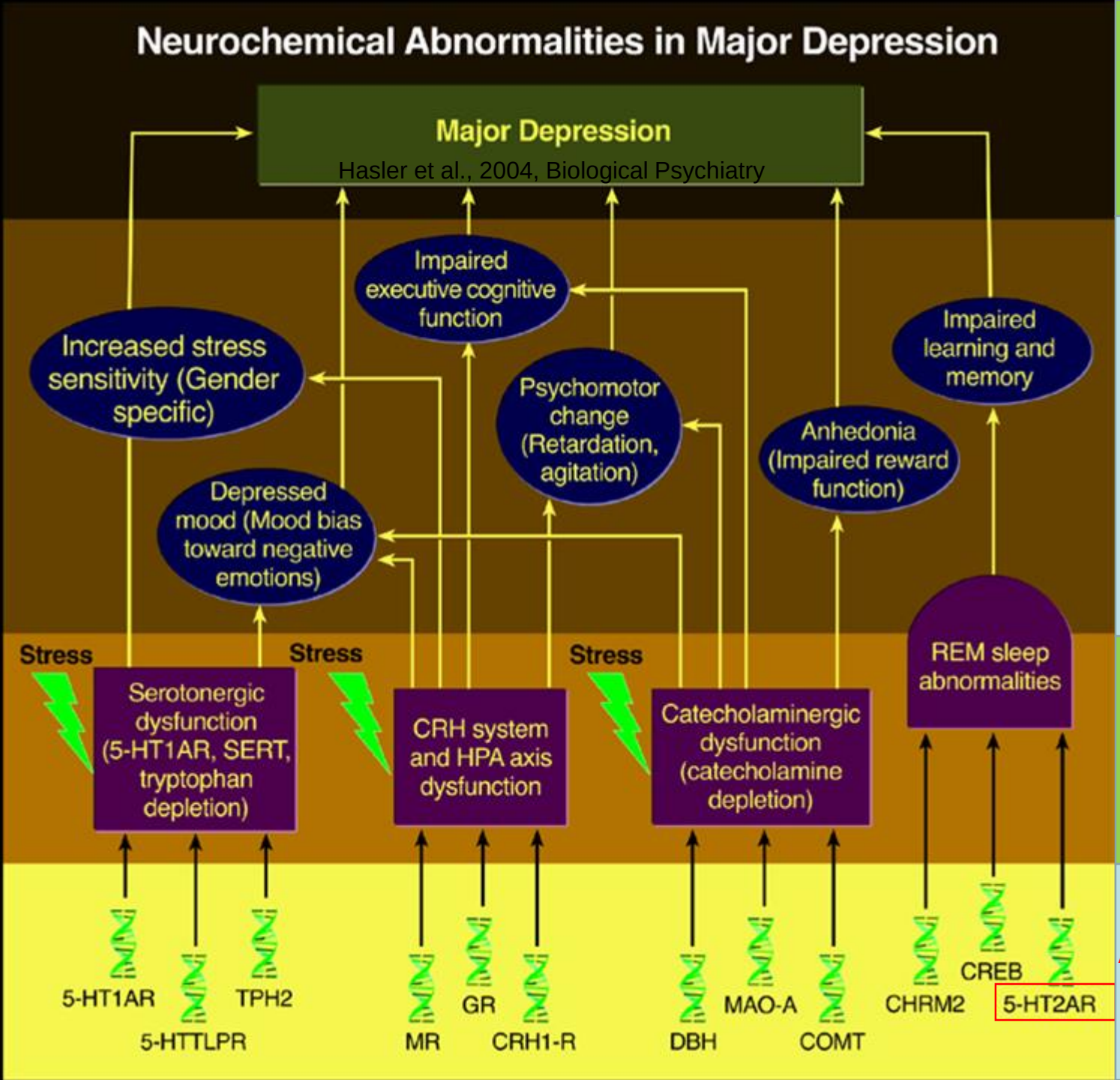
Better & early diagnostics
Novel targets→ Innovative Rx
Personalized medicine

Depression: A Major Cause of Disability

- 10% of the American population suffer from depression/yr
- 2.3 million people suffer from bipolar disorder
- 4th leading cause of worldwide disease burden in 1990; ahead of ischemic heart disease, cerebrovascular, and TB
- Expected to be of the highest causes of disability by 2020
- Mood and cognitive changes relate to a syndrome that effects the body through hormonal and ANS changes
- Doubling of the death rate at any age independent of suicide, smoking, or other risk factors

The Mortality of Mood Disorders: Suicide

- 8th leading cause of death in the U.S.; > 30,000 deaths/yr
- 80% of severely depressed patients have suicidal ideation
- ~ 15% of Major Depression and Bipolar Disorder patients will die by suicide
- Patients who die by suicide are untreated or undertreated
- Many patients do not respond adequately to monoamine antidepressants



Better Care

Diagnostics/ Monitoring

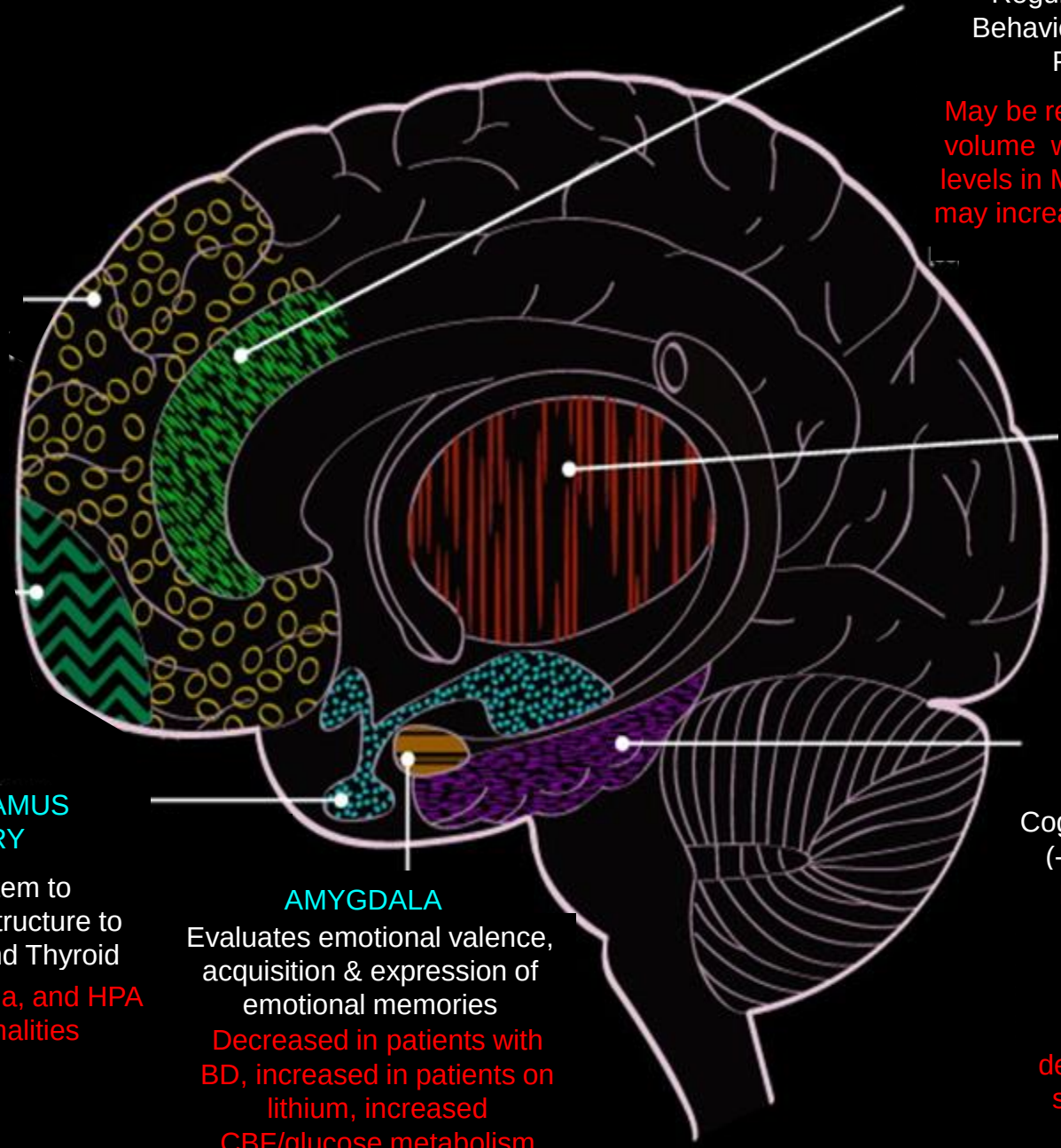
Neurophysiology
(fMRI, Pupilometry)

Biologics
(Microbiome)
(Metabolomics)

Experimental Manipulation
(Stress Paradigms)
(Depletion Studies)
(Drug Challenge)

Human Genetics/ Animal Engineering
(Transgenic Mice)
(Optogenetics)

Mood Disorders



ANTERIOR CINGULATE

Regulates Emotional Behavior and Emotional Processing

May be reduced in grey matter volume with altered glutamate levels in MDD and BD. Lithium may increase grey matter in BD.

MEDIAL PREFRONTAL

Emotion Regulation, Connects to Limbic Areas, Hippocampus & Amygdala

Altered CBF and Glucose Metabolism in Depression

THALAMUS

Sensory relay connects limbic with mood areas

Increased metabolism/CBF In BD + MDD

ORBIFRONTAL

Multi-modal Stimuli Integration, Value-Reward to Stimuli, Extinction of Unreinfornced Responses.

Volume Reduction and Increased Metabolism

HIPPOCAMPUS

Learning-Memory, Cognition, Neurogenesis, (-) Regulation of HPA

Reduction in Grey Matter in BD, Increased Grey Matter to Lithium Treatment in BD, decreased number of synapses, synaptic proteins

HYPOTHALAMUS PITUITARY

Nervous System to Endocrine, Key structure to control of HPA and Thyroid

Hypercortisolemia, and HPA axis abnormalities

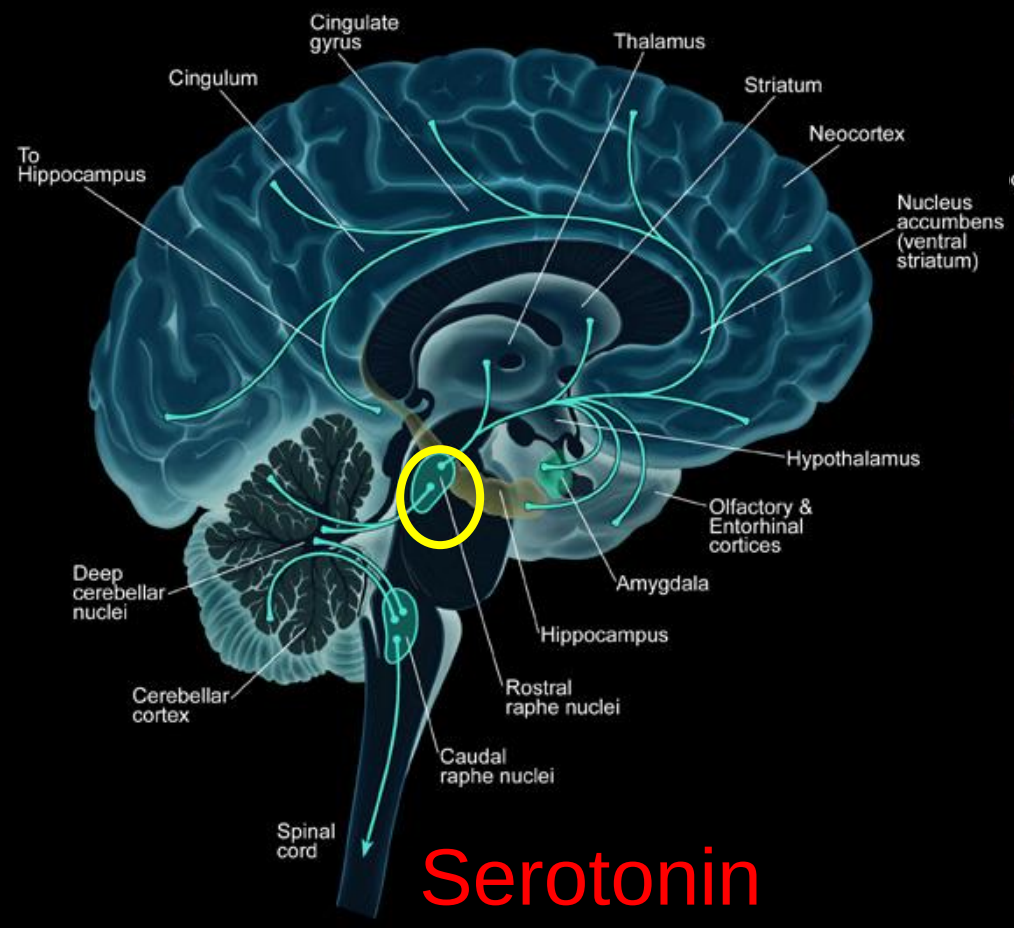
AMYGDALA

Evaluates emotional valence, acquisition & expression of emotional memories

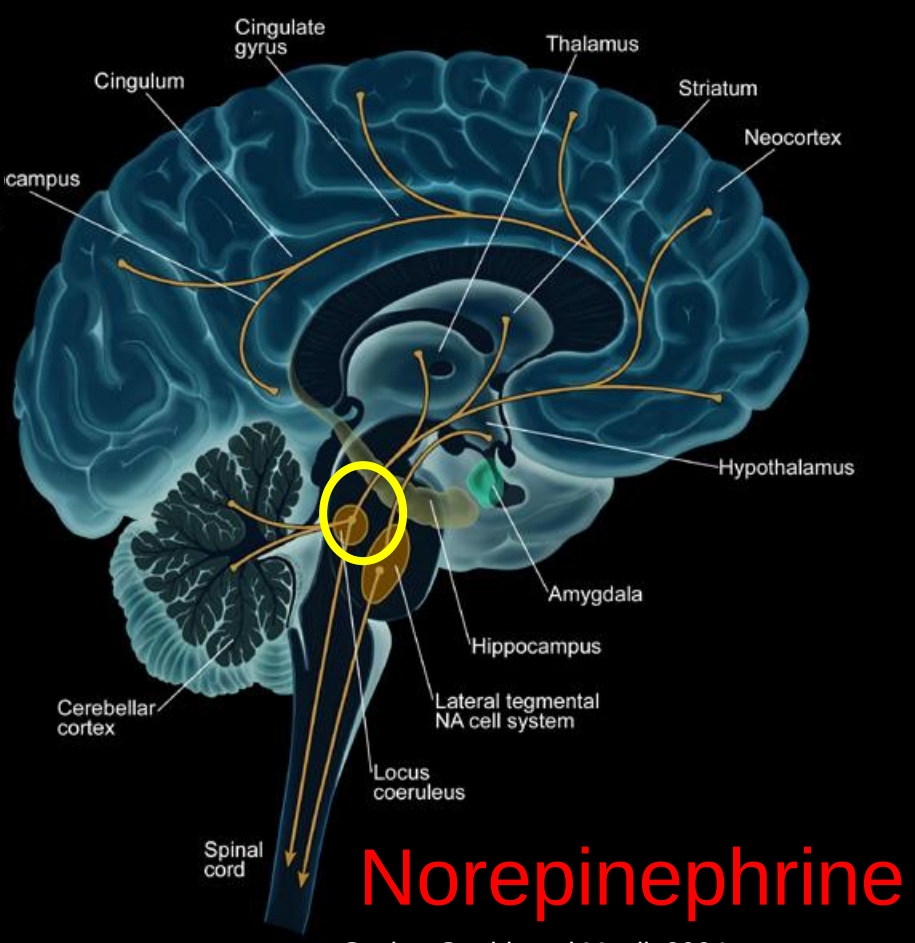
Decreased in patients with BD, increased in patients on lithium, increased CBF/glucose metabolism

Schloesser et al., 2010
Trend in Neuroscience

Monoamines in Treatment of Depression and Anxiety



Serotonin



Norepinephrine

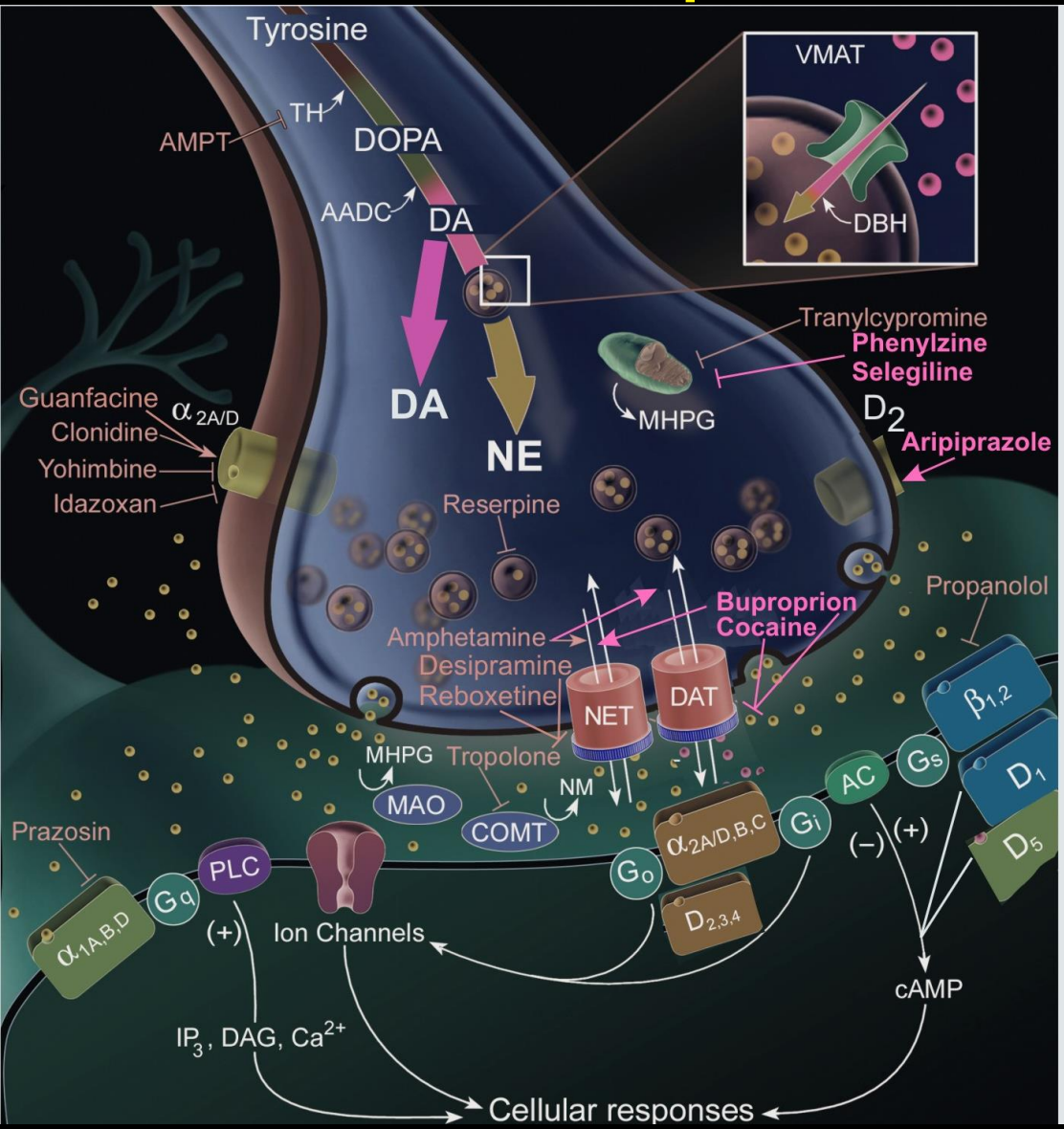
Szabo, Gould, and Manji, 2004
The APA *Textbook of Psychopharmacology*

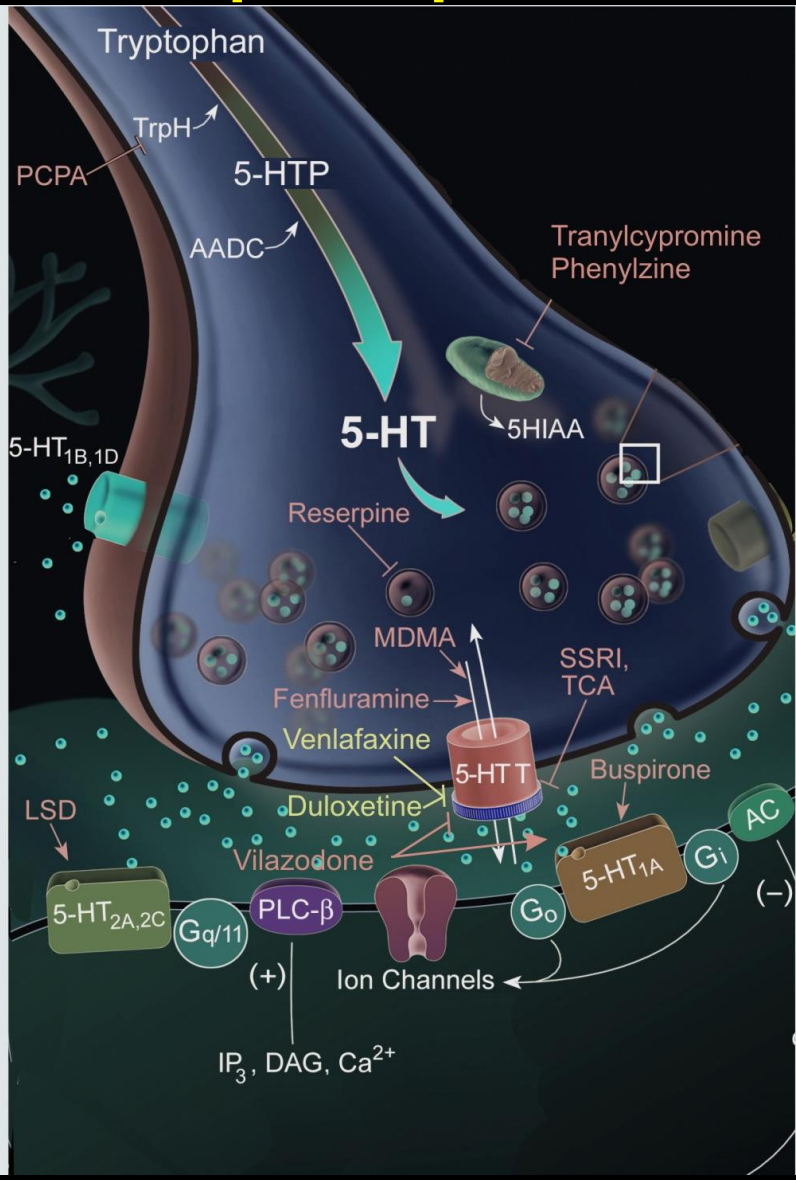
Prior to Esketamine, FDA approved antidepressants target one or both systems

Monoamines are neuromodulatory and antidepressants take weeks to work

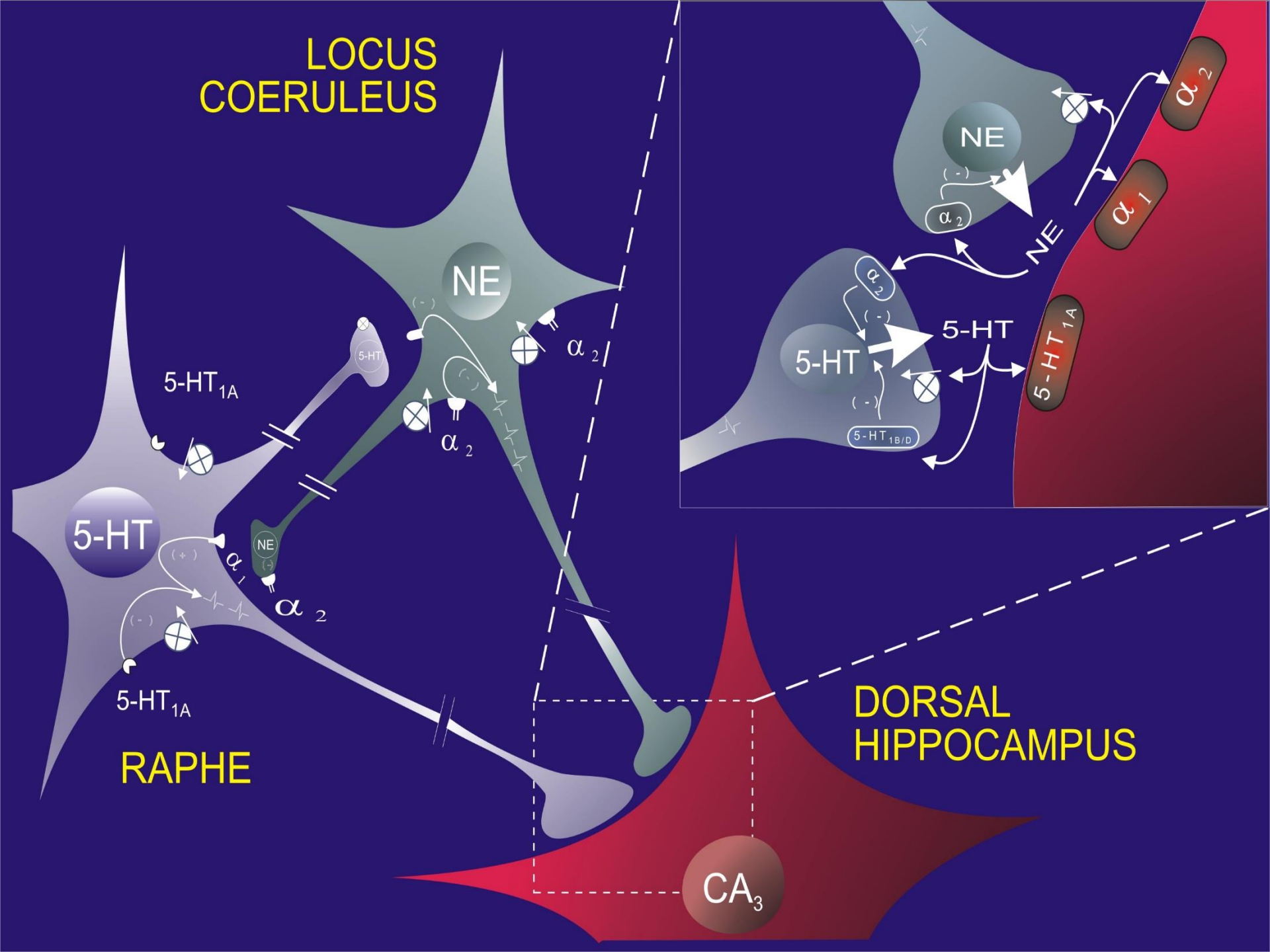
Greater understanding of neural circuits and individual differences are needed

Serotonin, Dopamine, Norepinephrine

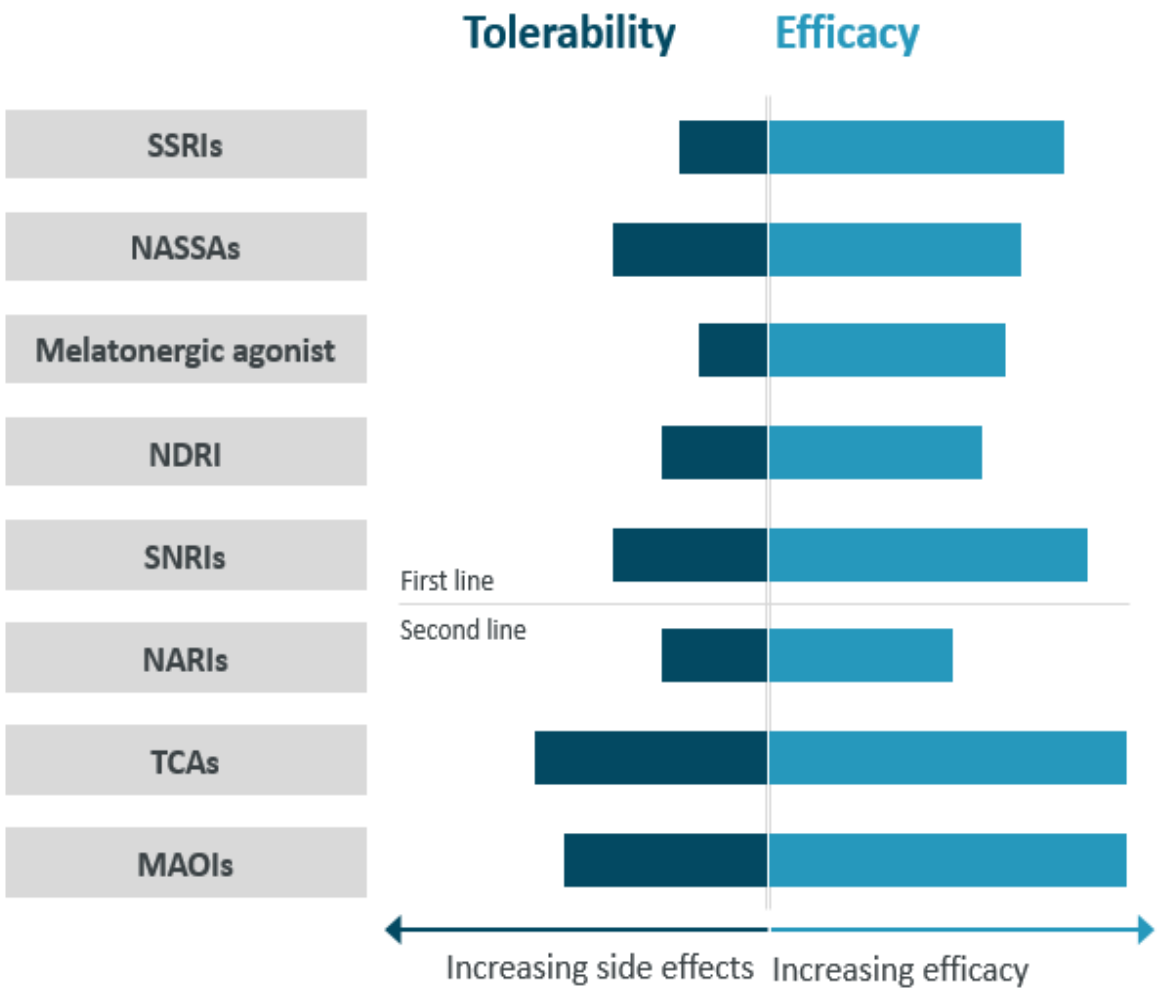




Szabo and Nemeroff, 2014
Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, Fifth Edition

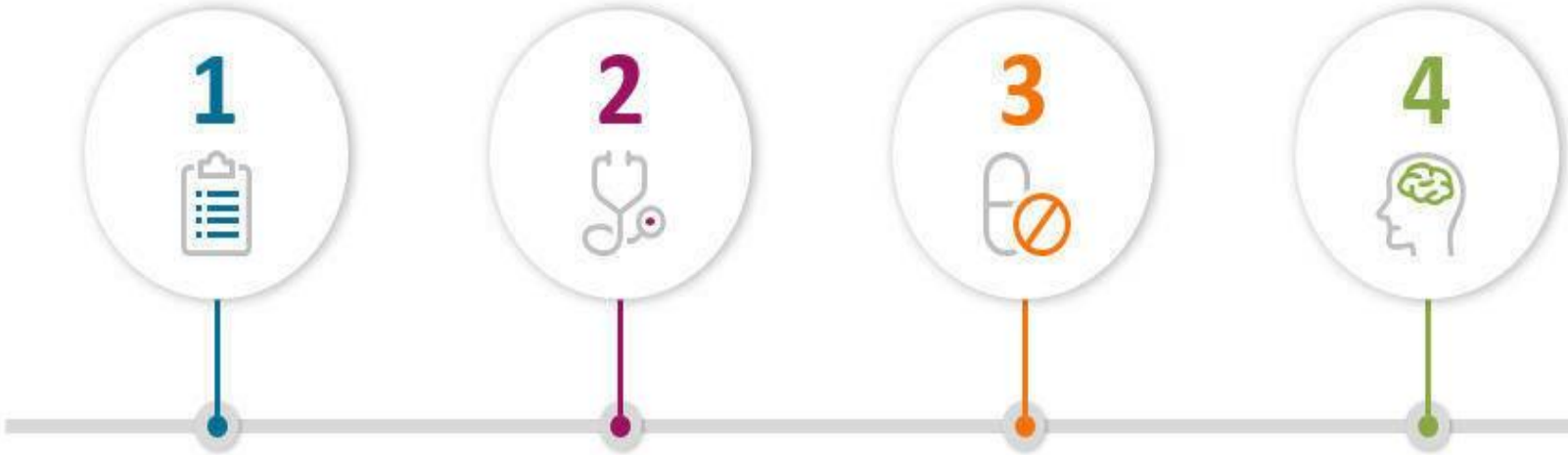

LOCUS
COERULEUS
NE
α 2
α 2
5-HT
5-HT1A
5-HT
α 1
NE
α 2
5-HT1A
RAPHE
DORSAL
HIPPOCAMPUS
CA3
NE
α 2
α 1
α 2
NE
5-HT
5-HT
5-HT1A
5-HT1B/D

CLINICAL UTILITY OF ANTIDEPRESSANTS



Malhi, G. S., et al. (2015). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry, 49*(12), 1087-1206.

STRATEGIES TO ADDRESS MEDICATION NON-RESPONSE



Review diagnosis

1. Review subtype of depression (melancholic, psychotic, atypical)
2. Re-asses for comorbidities
   - Substance misuse
   - Bipolar disorder
   - Medical illness or medications inducing mood disorder
   - Personality dysfunction
3. Seek second opinion
4. Review adherence and dose

Nonresponse to 2 or 3 adequate antidepressant trials

Treatment refractory depression OR treatment resistant depression

Treatment strategies

1. Switch/ substitute
2. Increase dose
3. Augment/ combine
   - Lithium
   - Second generation antipsychotics
   - Thyroid hormone
   - Antidepressant combinations

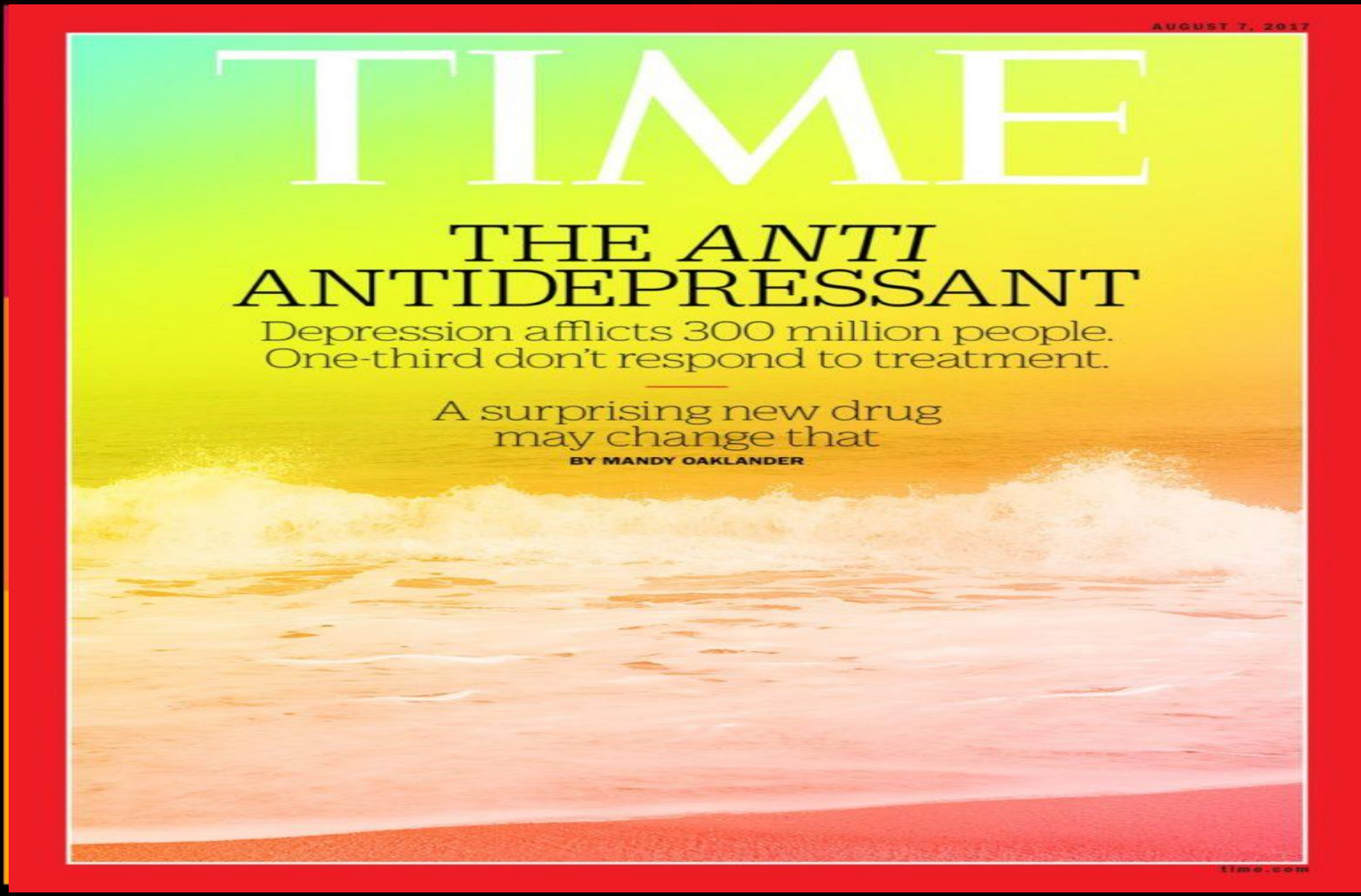
Neurostimulation

1. ECT
2. rTMS

Presynaptic Targets: Antidepressant Action

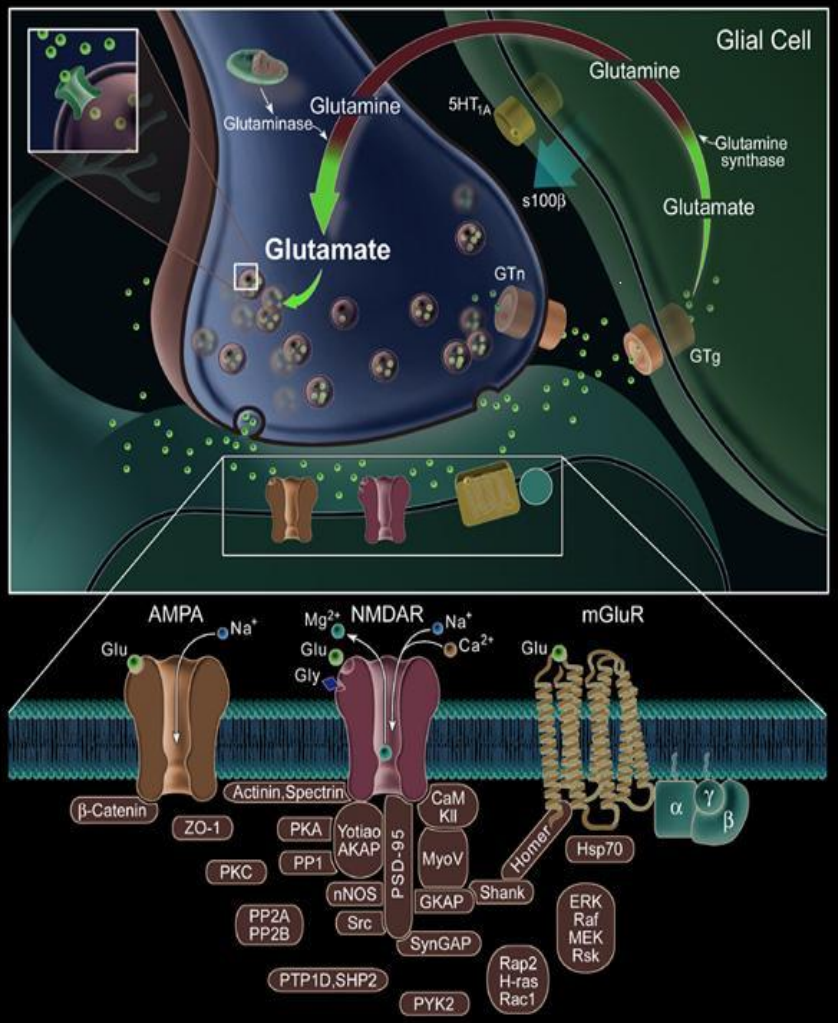
- All antidepressant drugs target and increase 5-HT and/or NE transmission following a long-term administration only
- Drugs that target both neurotransmitter systems appear more effective (TCAs and Venlafaxine), but have more side-effects
- Addition of atypical antipsychotics and lithium to treatment resistant patients on an SSRI is effective (STAR*D Project)
- Modulating 5-HT and NE interactions during a sustained antidepressant treatment are effective treatments/take time
- Insight into neurochemical changes to sustained psychotropic treatments may lead to other therapeutic avenues…make way for GLUTAMATE and postsynaptic targets.

KETAMINE and ESKETAMINE



"We can give you enough medication to alleviate the pain but not enough to make it fun."

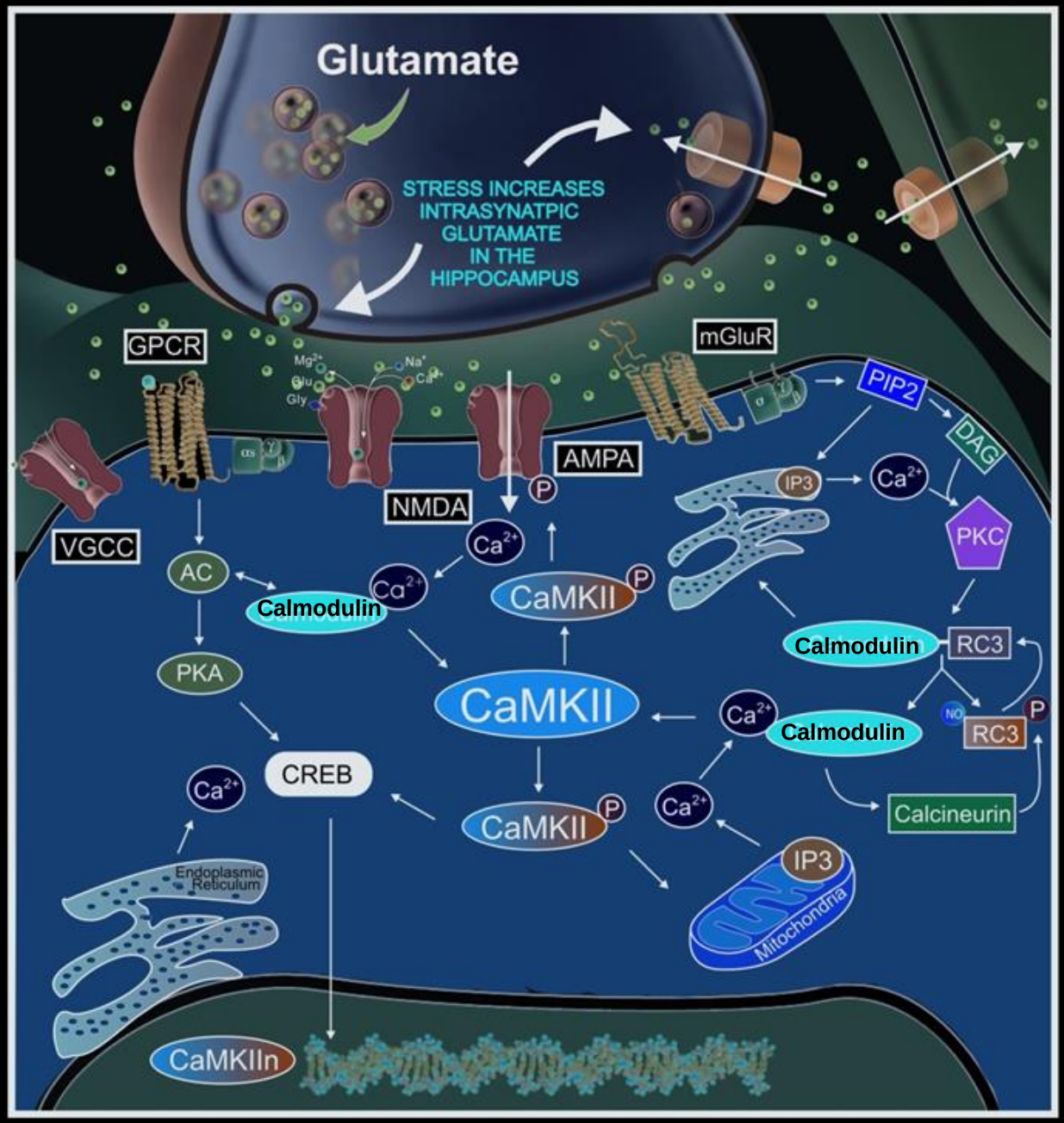
Glutamate System



Receptor Subunit Types

Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
NR1	GluR 1	GluR 5	mGlu 1 a-b-cv	mGlu 2	mGlu 4 a-b
NR 2 A-B-C-D	GluR 2	GluR 6 mGlu 5 a-b	mGlu 3	mGlu 6	
NR3 A-B	GluR 3	GluR 7	mGlu 7 a-b		
	GluR 4	KA 1			mGlu 8 a-b
		KA 2			

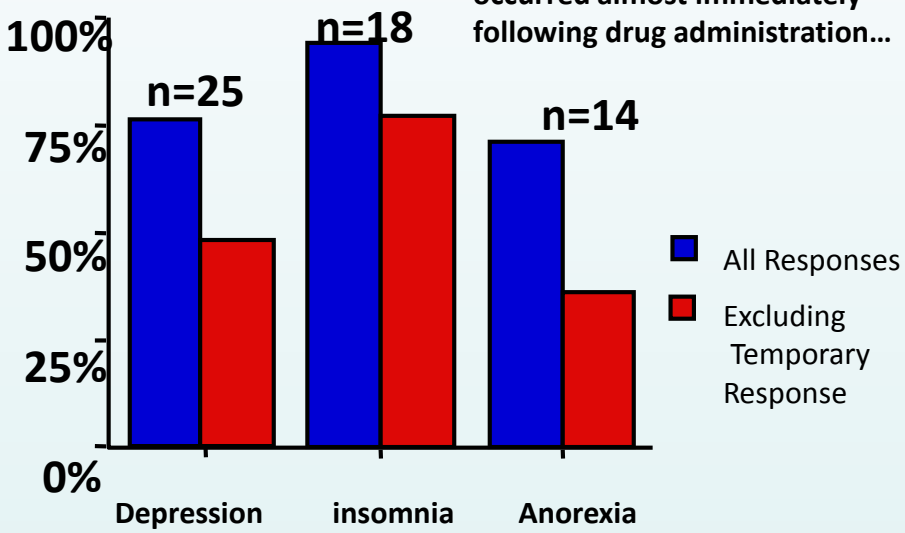
Szabo, Gould, Manji, 2009
APA Textbook of Psychopharmacology



Du, Szabo, Gray, Manji, 2004
Int J Neuropsychopharm

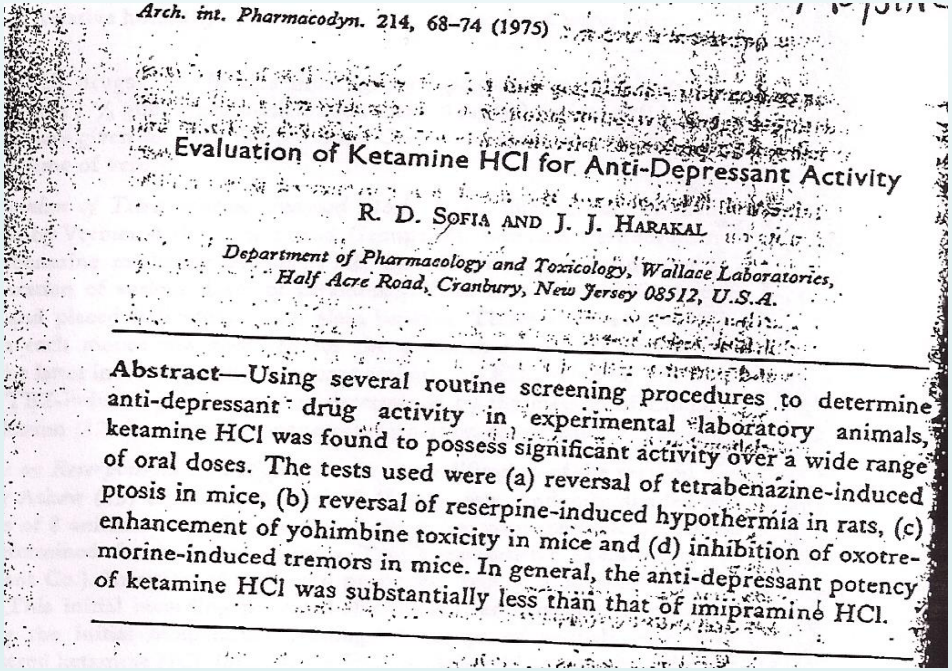
NEVER A TRULY "*NEW* IDEA"

DCS treatment



"It is difficult to explain why psychiatric benefits should have occurred almost immediately following drug administration…

(Crane, Compr Psychiatry 1961)



Arch. int. Pharmacodyn. 214, 68–74 (1975)

Evaluation of Ketamine HCl for Anti-Depressant Activity

R. D. Sofia and J. J. Harakal

Department of Pharmacology and Toxicology, Wallace Laboratories, Half Acre Road, Cranbury, New Jersey 08512, U.S.A.

Abstract—Using several routine screening procedures to determine anti-depressant drug activity in experimental laboratory animals, ketamine HCl was found to possess significant activity over a wide range of oral doses. The tests used were (a) reversal of tetrabenazine-induced ptosis in mice, (b) reversal of reserpine-induced hypothermia in rats, (c) enhancement of yohimbine toxicity in mice and (d) inhibition of oxotremorine-induced tremors in mice. In general, the anti-depressant potency of ketamine HCl was substantially less than that of imipramine HCl.

(Crane, Compr Psychiatry 1961)

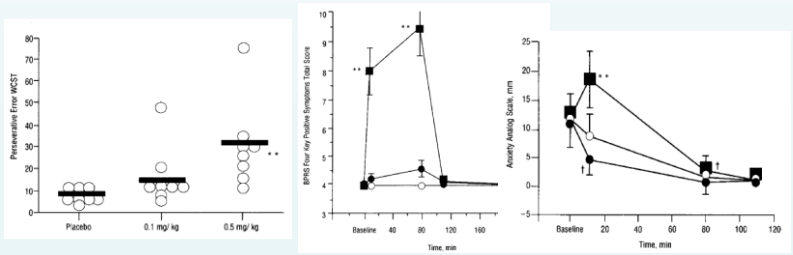
PURSUING KETAMINE AS AN ANTIDEPRESSANT

Subanesthetic Effects of the Noncompetitive NMDA Antagonist, Ketamine, in Humans

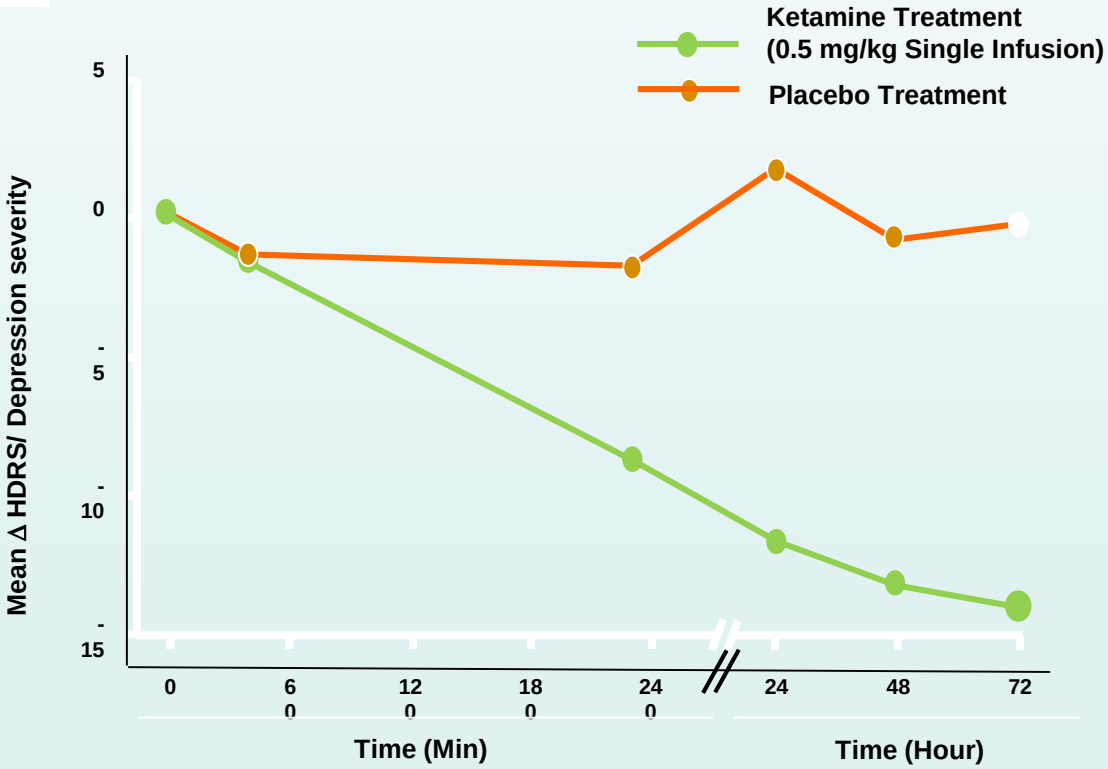
Psychotomimetic, Perceptual, Cognitive, and Neuroendocrine Responses

John H. Krystal, MD; Laurence P. Karper, MD; John P. Seibyl, MD; Glenna K. Freeman; Richard Delaney, PhD; J. Douglas Bremner, MD; George R. Heninger, MD; Malcolm B. Bowers, Jr, MD; Dennis S. Charney, MD

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

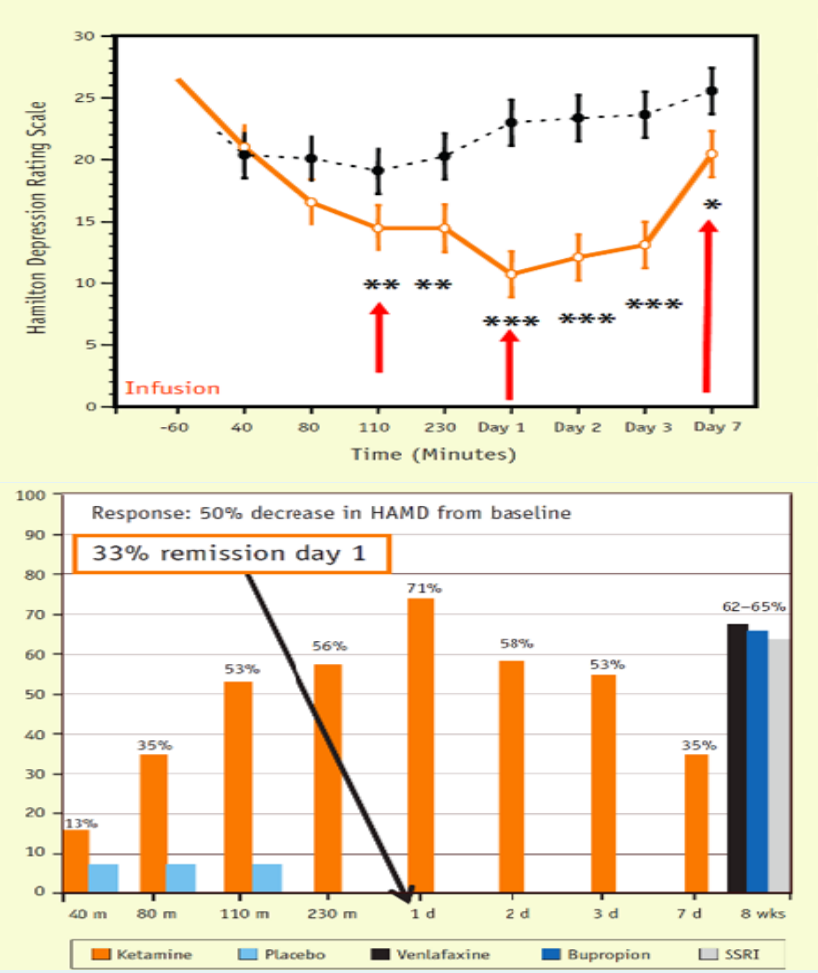


Cognition Perception Anxiety



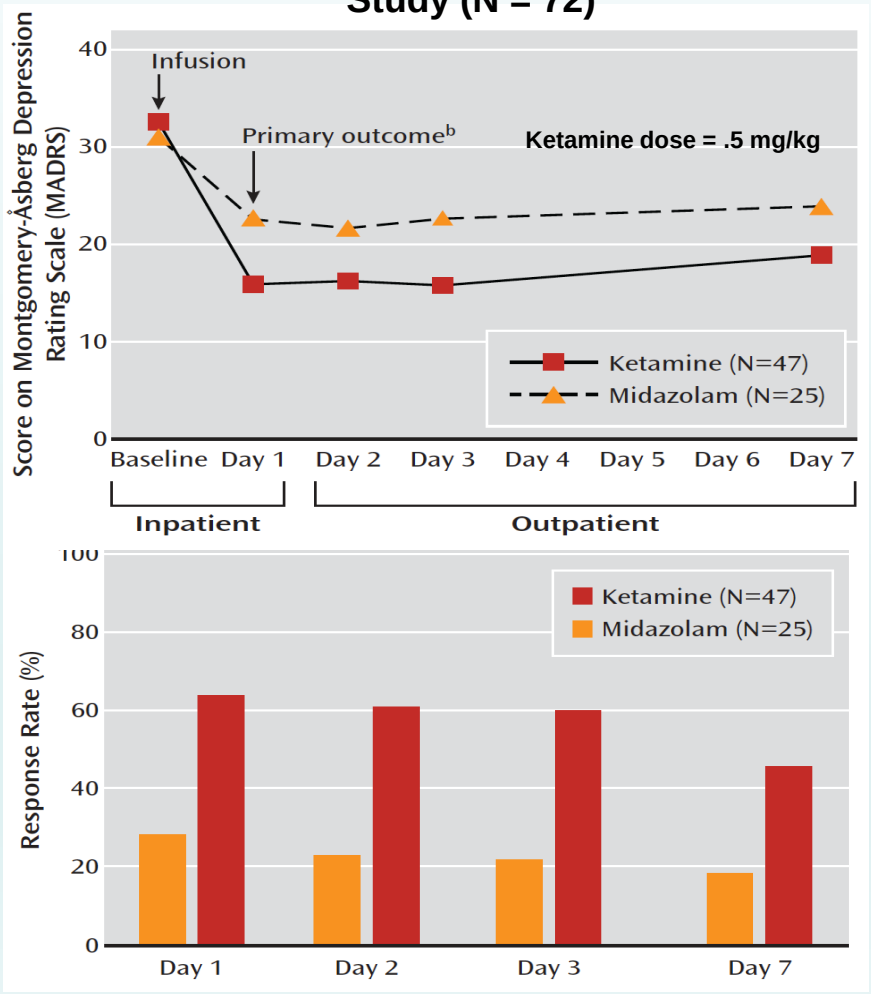
Single Subanesthetic Dose Ketamine Infusion Trials in TRD

Ketamine (0.5 mg/kg over 40 minutes) Rapidly Effective vs Saline Placebo: Replication Study (N = 17)



Zarate CA Jr, et al. *Arch Gen Psychiatry*. 2006;63(8):856-864.

Ketamine Superior to Psychoactive Control: Baylor/Mt Sinai NIMH funded Study (N = 72)

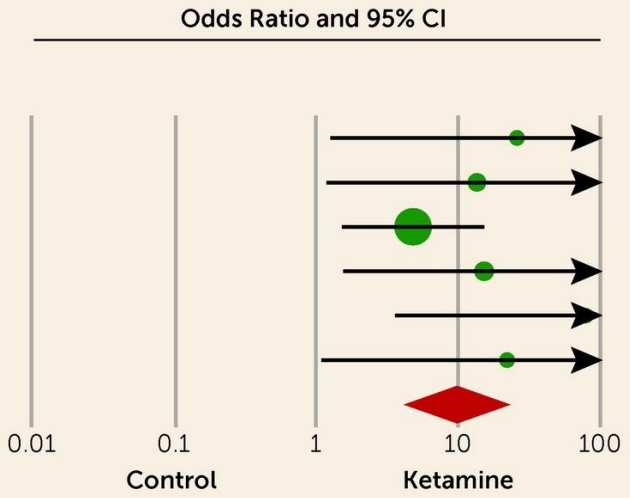


Murrough JW, et al. *Am J Psychiatry*. 2013;170(10):1134-1142.

Single Infusion of Ketamine – Meta-Analytic Efficacy in TRD (N = 147)

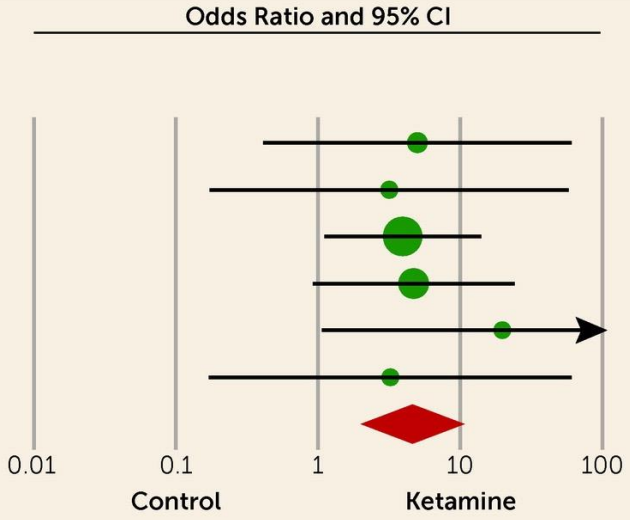
A **At 1 day**

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



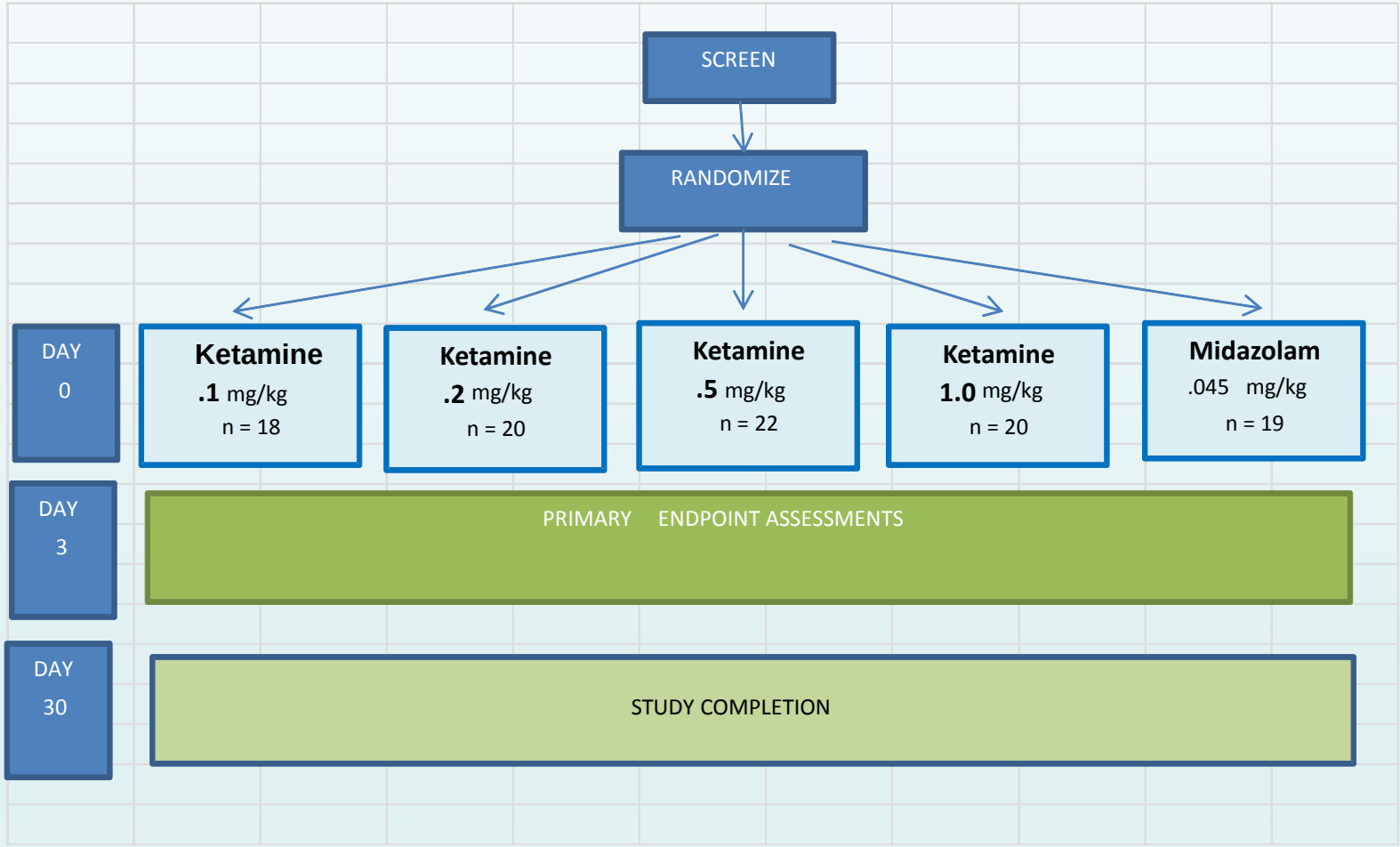
B **At 1 week**

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



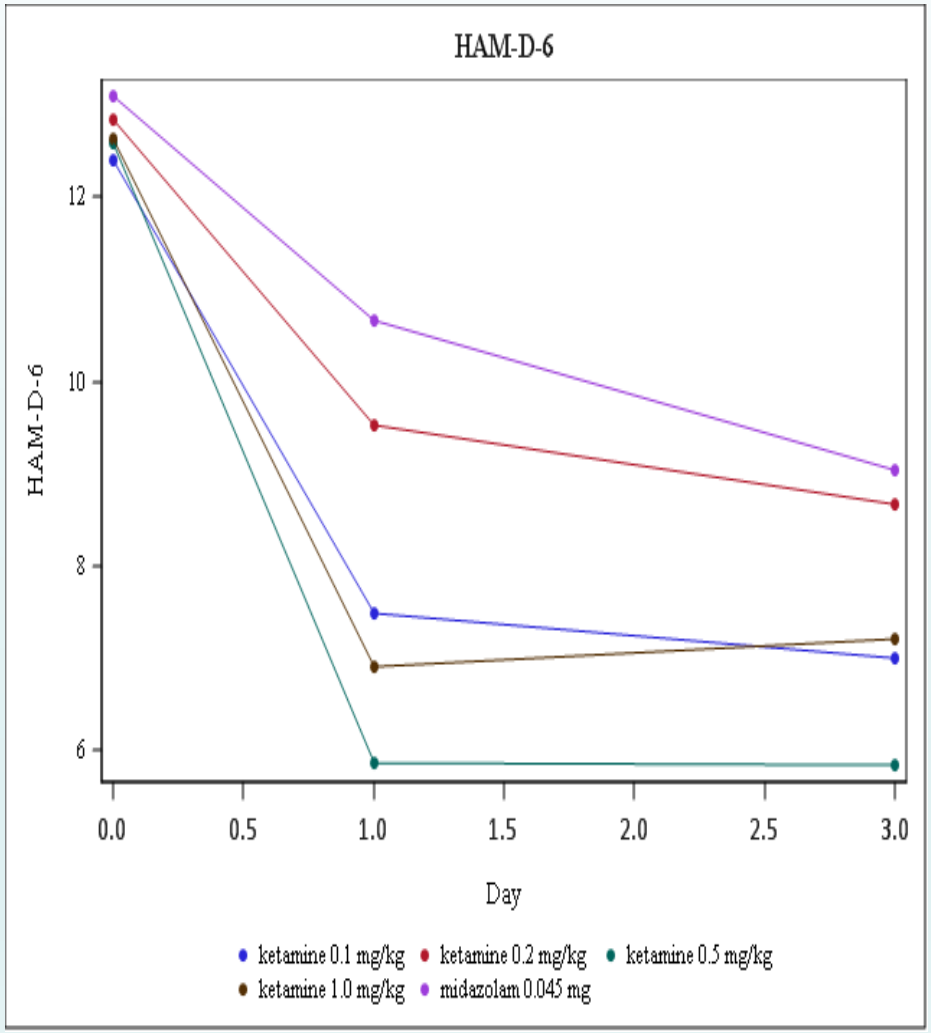
Newport DJ, et al. *Am J Psychiatry*. 2015;172(10):950-966.

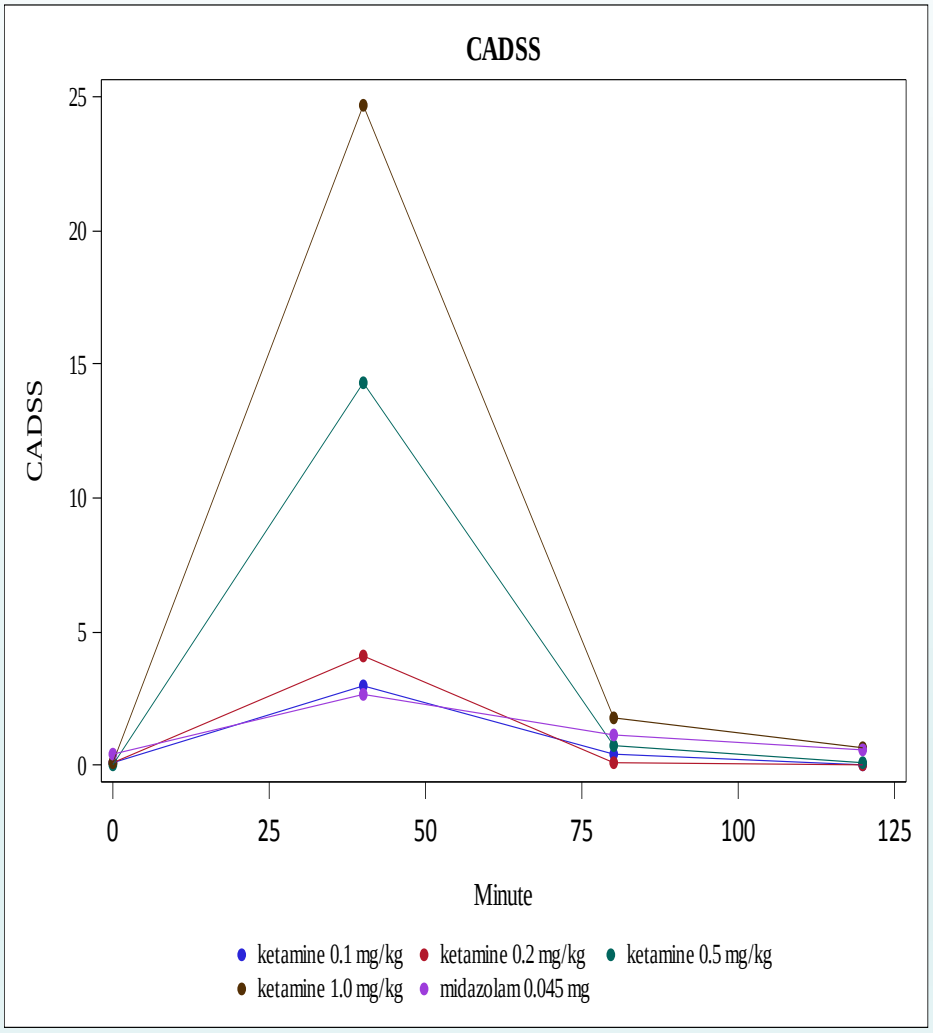
Double-Blind, Placebo-Controlled, Dose-Ranging Trial of IV Ketamine as Adjunctive Therapy in TRD (NIMH RAPID Trial, N=99)



Fava M, Molecular Psychiatry, 2018

IV Ketamine Dose-Response: NIMH RAPID Trial

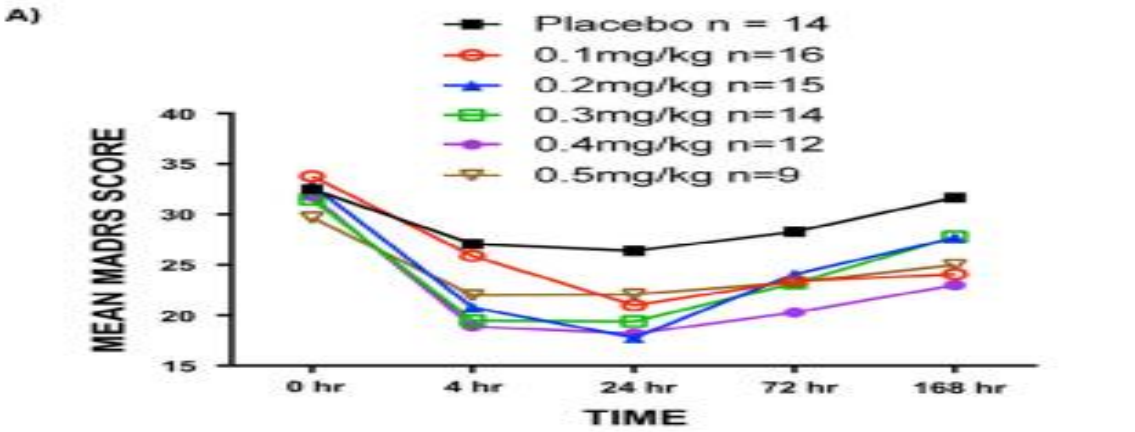


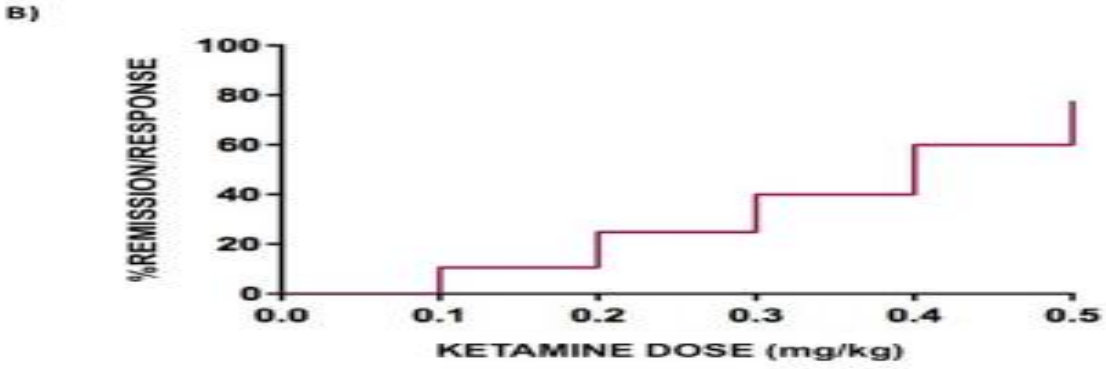


Fava M, Molecular Psychiatry, 2018

Dose-Dependent Efficacy of Ketamine in Late-Life Depression

FIGURE 2. [A] MADRS scores for midazolam and all ketamine dose levels in the RCT phase. [B] Percentage of remitters and responders at any time point across ketamine dose levels in the RCT phase. Note data are identical for remission and response rates because all responders were also remitters.

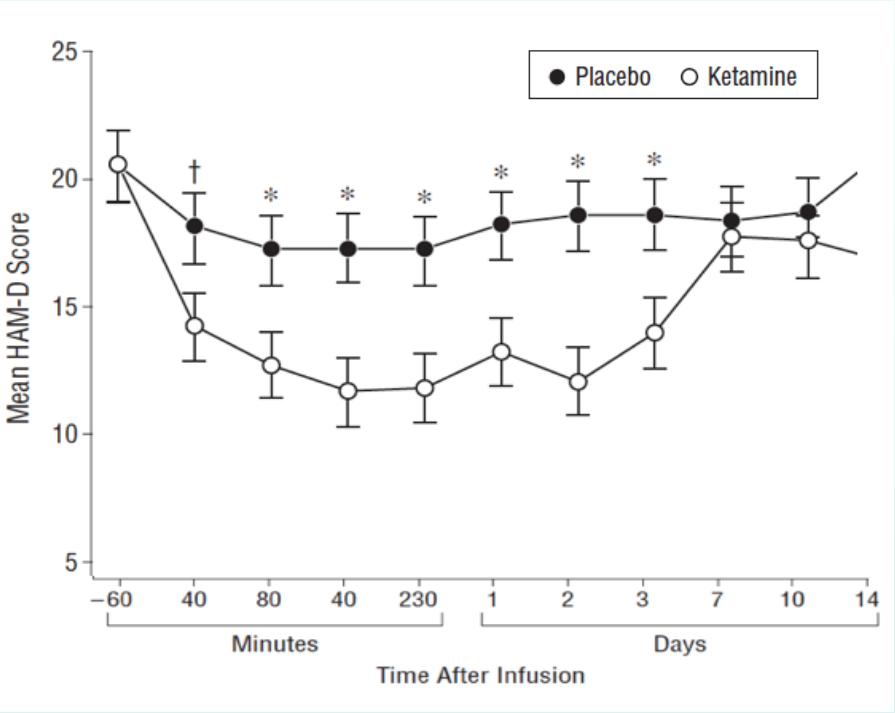


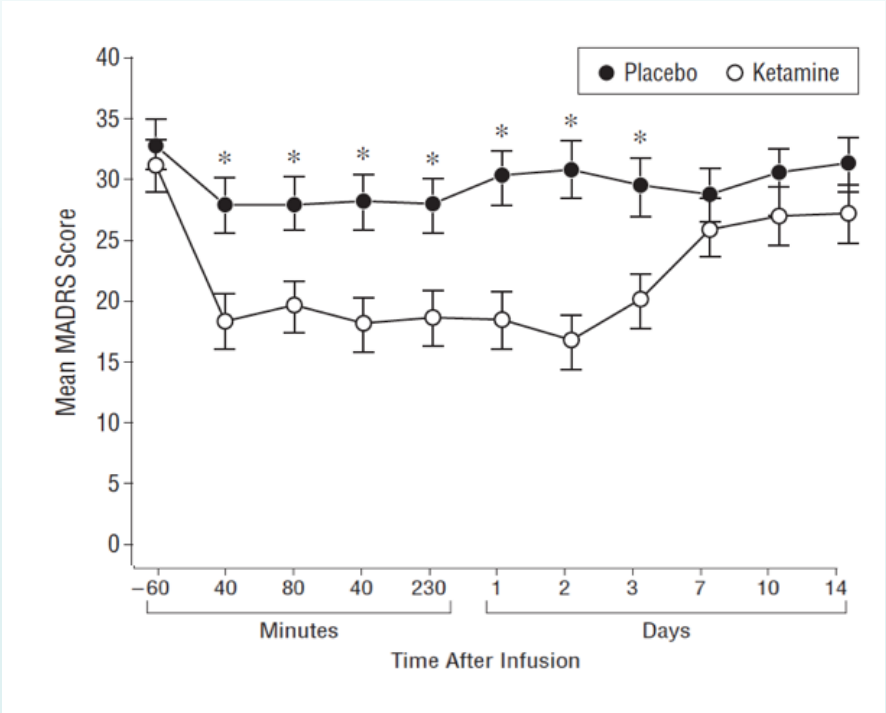


George, et al. The American Journal of Geriatric Psychiatry , 25(11),1199-1209

Ketamine in Treatment-Resistant Bipolar Depression

Dose: 0.5 mg/kg ketamine

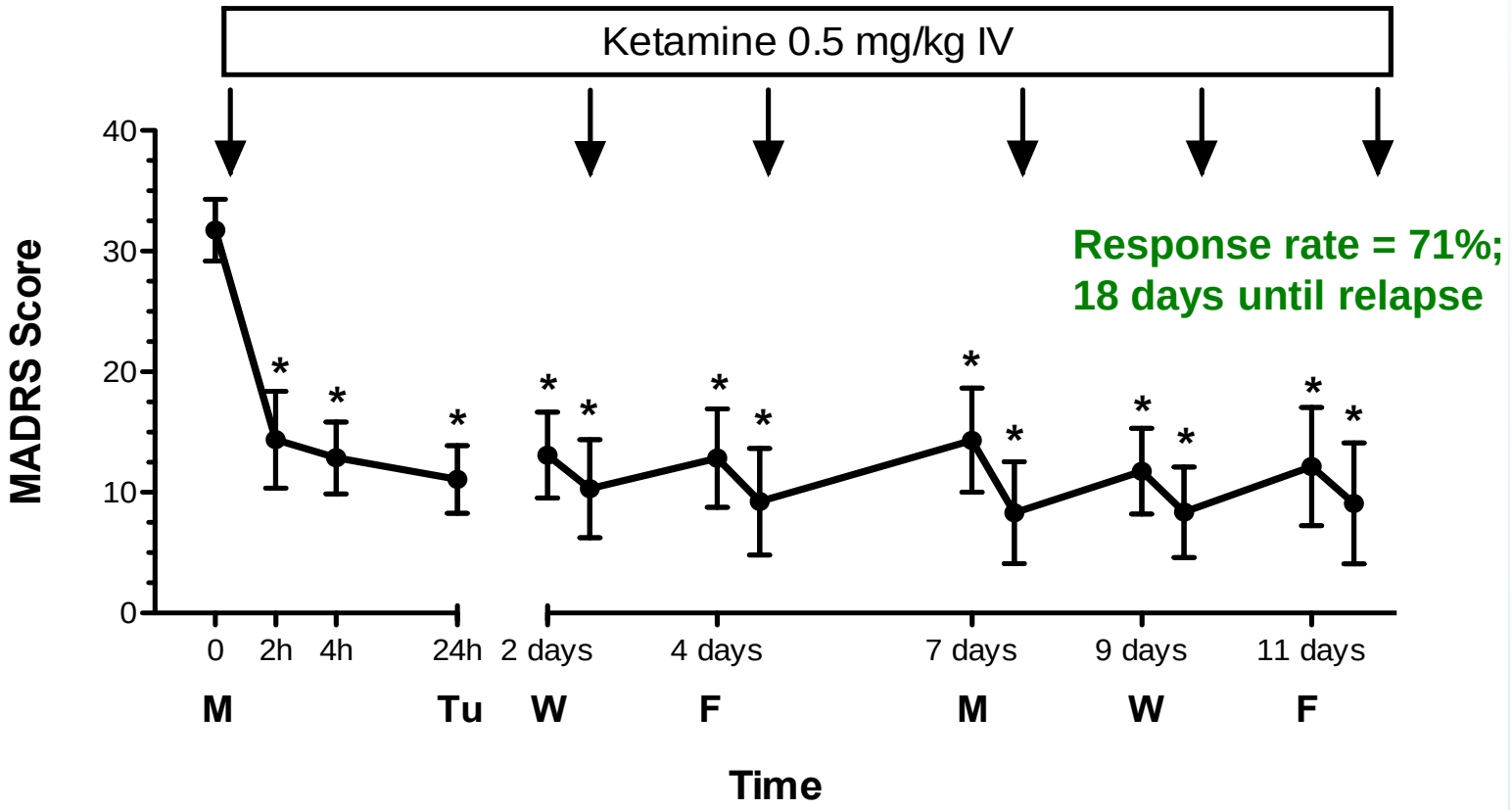




Depressive symptoms significantly improved in participants receiving ketamine compared with placebo

Diazgranados N, et al. *Arch Gen Psychiatry*. 2010;67(8):793-802.

Thrice-Weekly Ketamine Infusions in TRD: Mt Sinai Sample (N = 24)



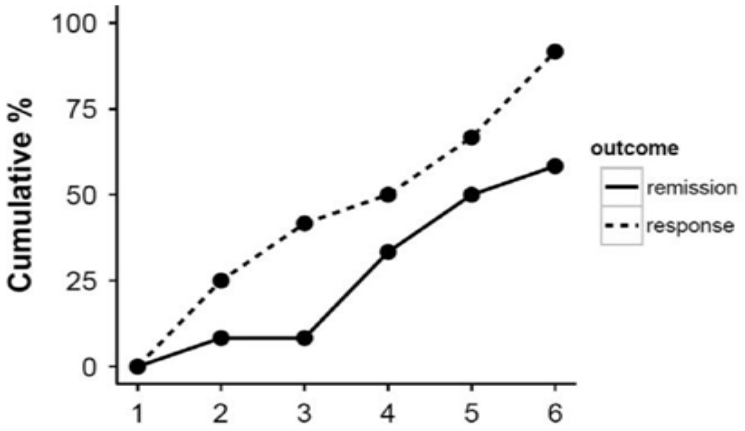
24 patients with TRD enrolled in a course of 6 ketamine infusions on a Monday-Wednesday-Friday schedule over two weeks. P values based on the Related-Samples Wilcoxon Signed Rank Test. Error bars reflect 95% CI. Asterisk indicates time-point significantly different from baseline ($p<0.001$)

Murrough JW, et al. *Biol Psychiatry*. 2013;74(4):250-256.

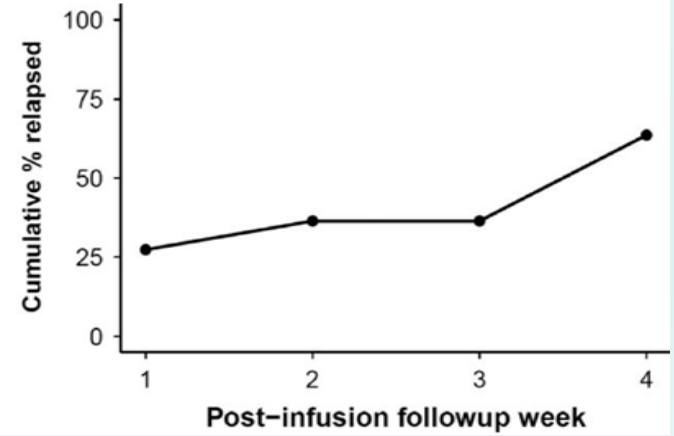
Multi-Infusion Ketamine Trials in TRD

Thrice-Weekly Ketamine Infusions in TRD: Minneapolis VA Sample (N = 14)

92% responded; 67% remitted

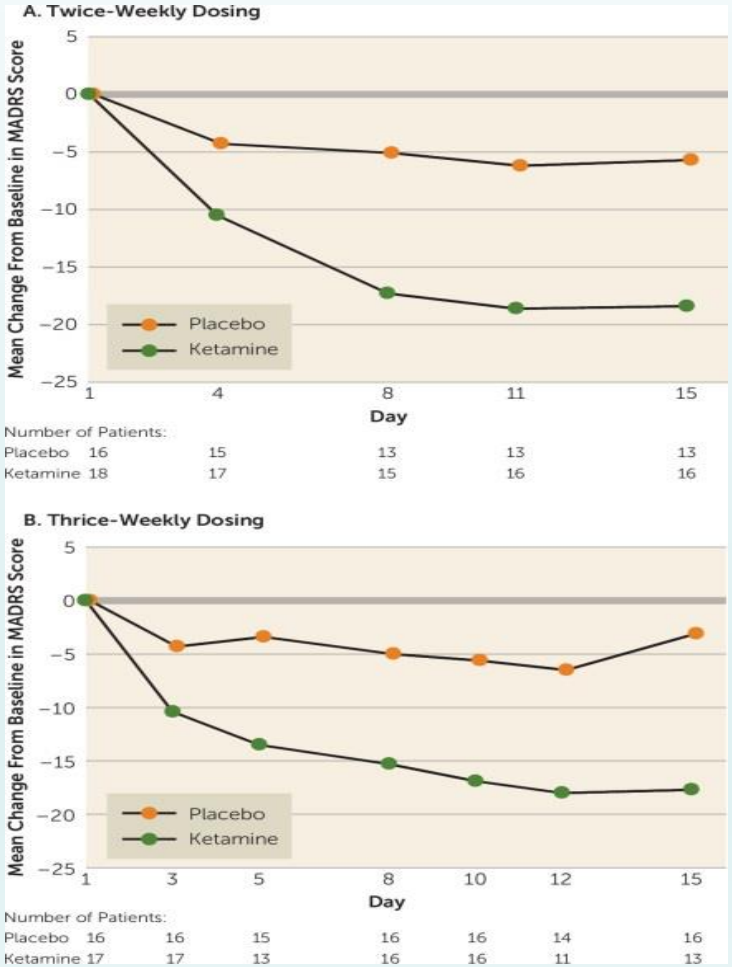


Mean time to relapse = 16 days



Shiroma PR, et al. *J Affect Disord*. 2014;155:123-129.

Twice-Weekly Dosing as Effective as Thrice-Weekly Dosing in TRD (N=67)

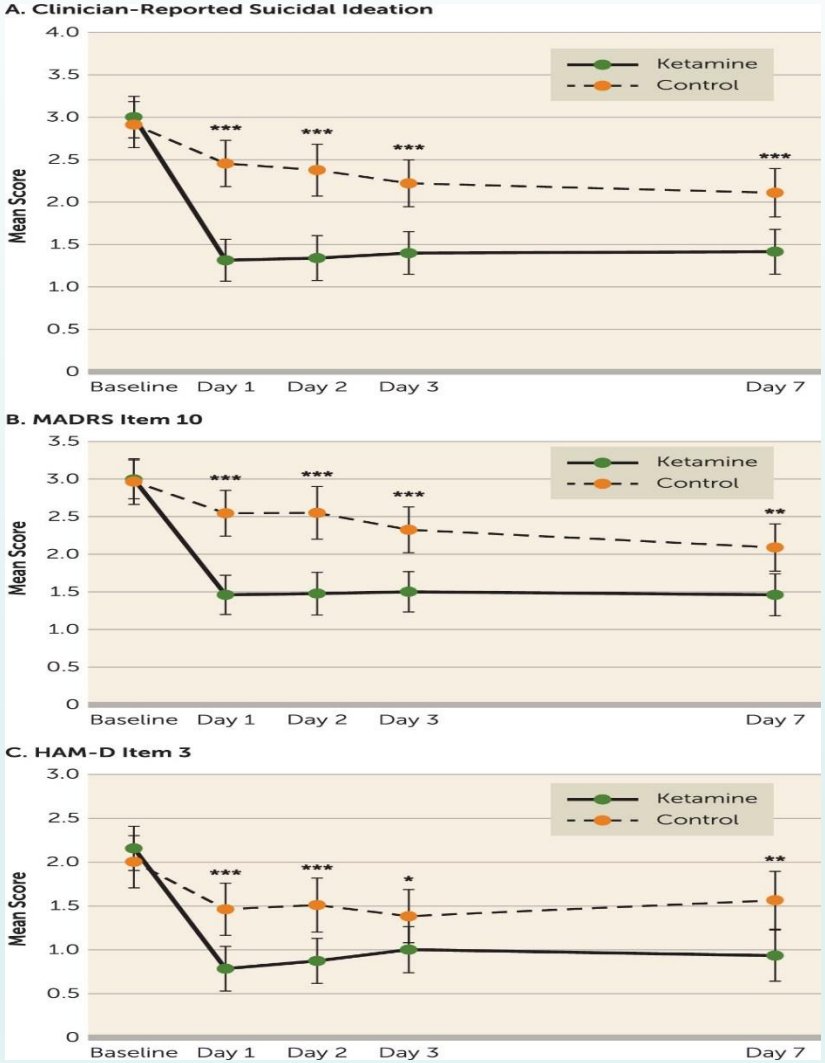


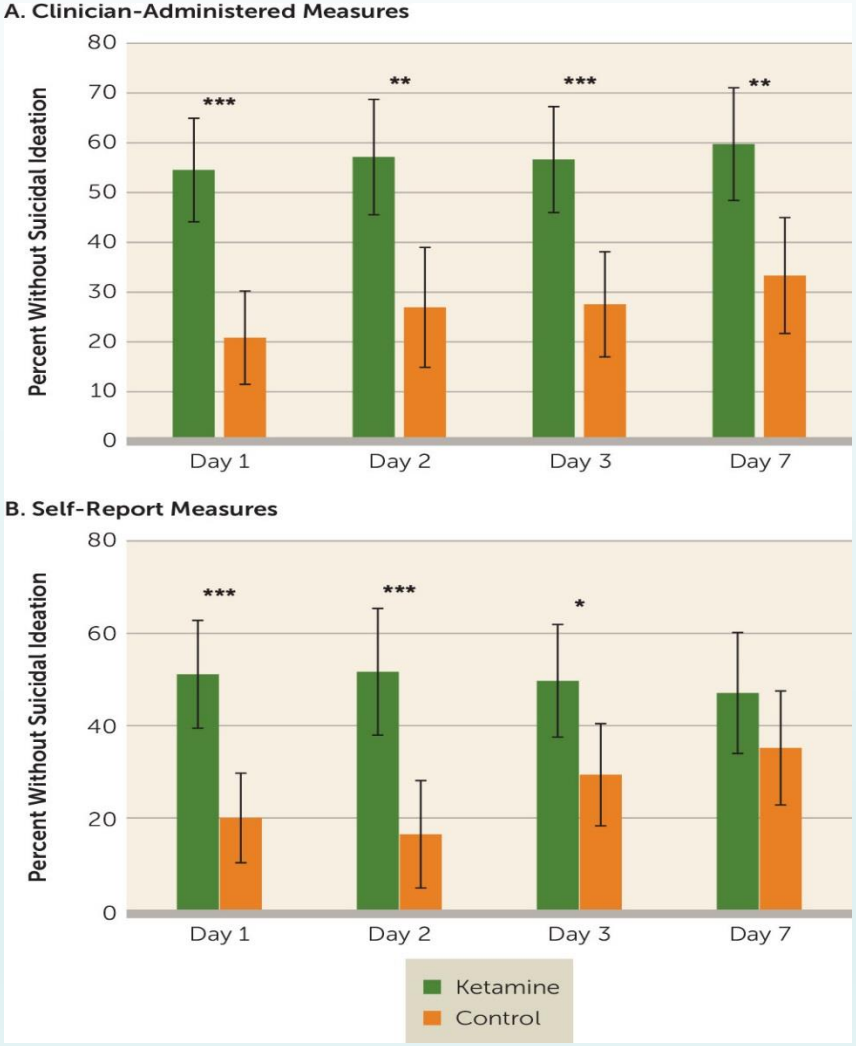
Ket: 69% responded, 38% remitted
PBO: 15% responded; 7.7% remitted

Ket: 54% responded; 23% remitted
PBO: 6% responded; 0% remitted

Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Effect of Ketamine on Suicidal Ideation: Individual Patient Meta-Analysis

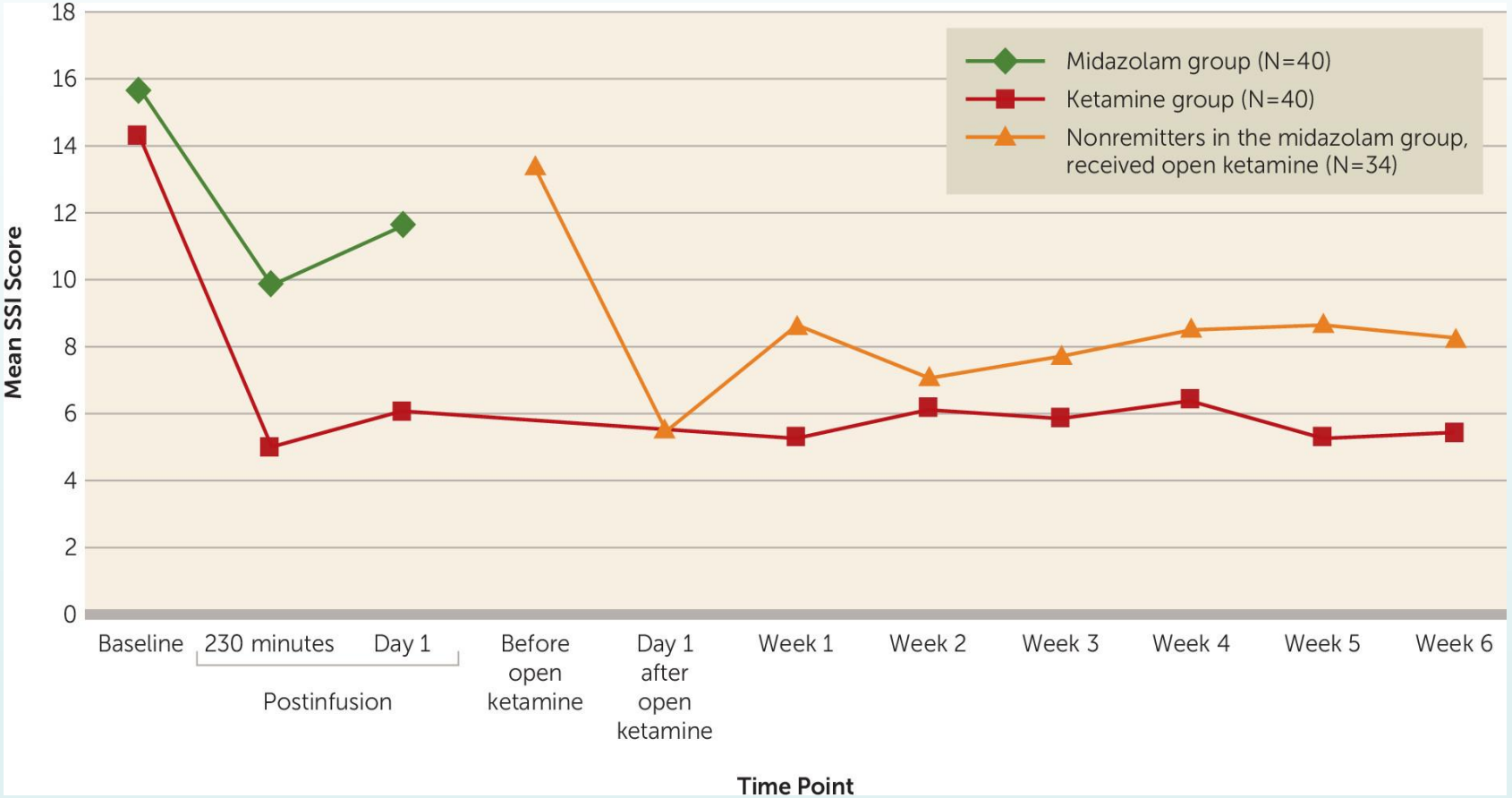




*p<0.05. **p<0.01. ***p<0.001.

Wilkinson S, et al *Am J Psychiatry* 2018; 175 (2): 150-158.

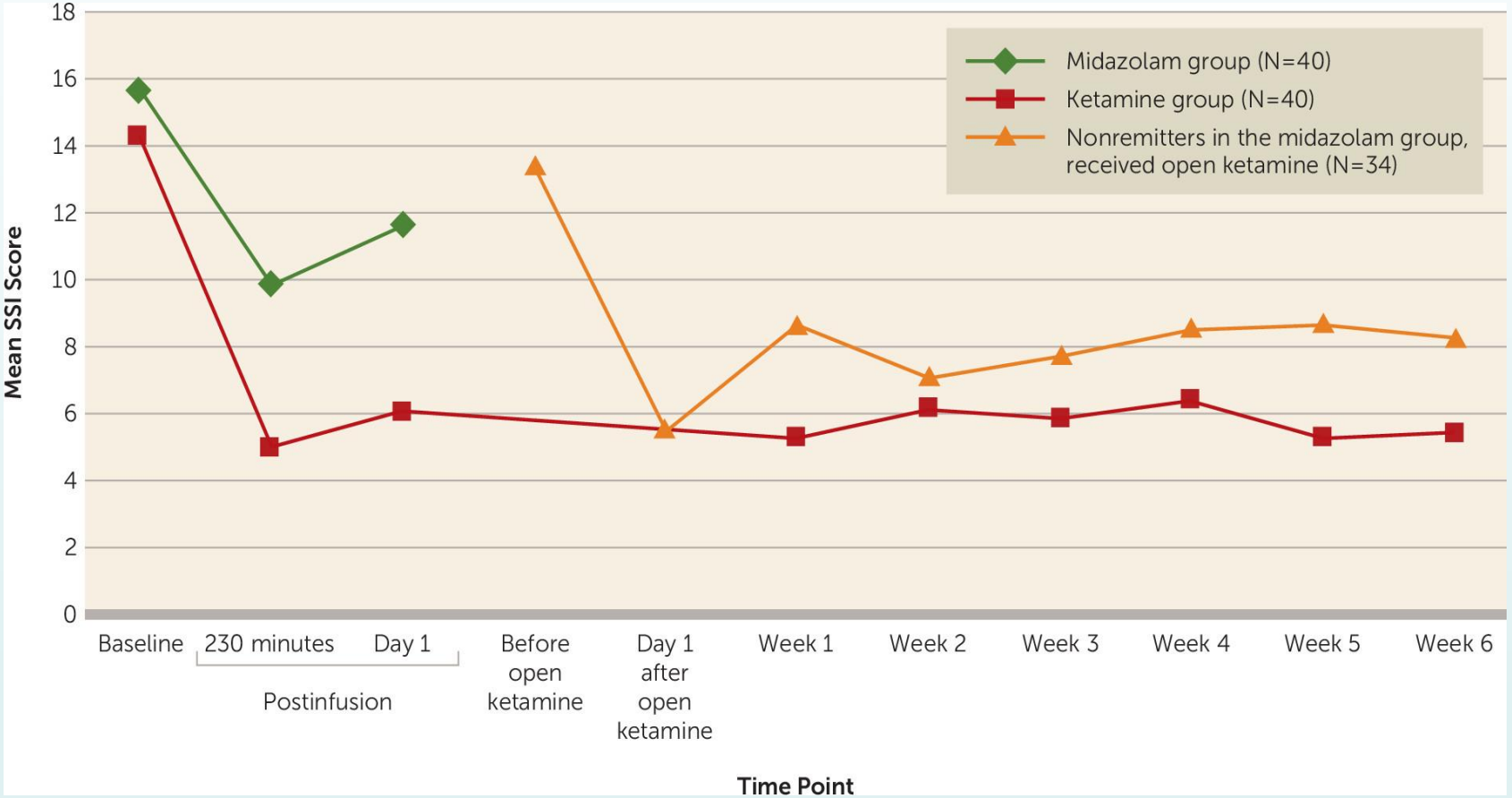
IV Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression



Day 1 (24 hr post infusion): Ketamine: 55% response; Midazolam: 30% response

Grunebaum MF, et al. *Am J Psychiatry*, published online 12/5/17

IV Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression



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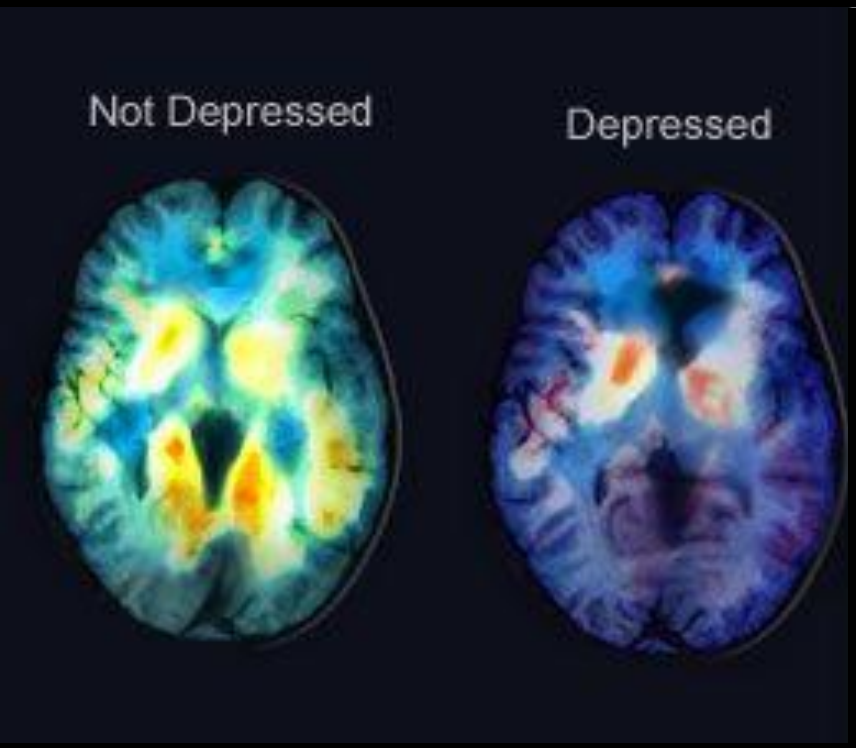
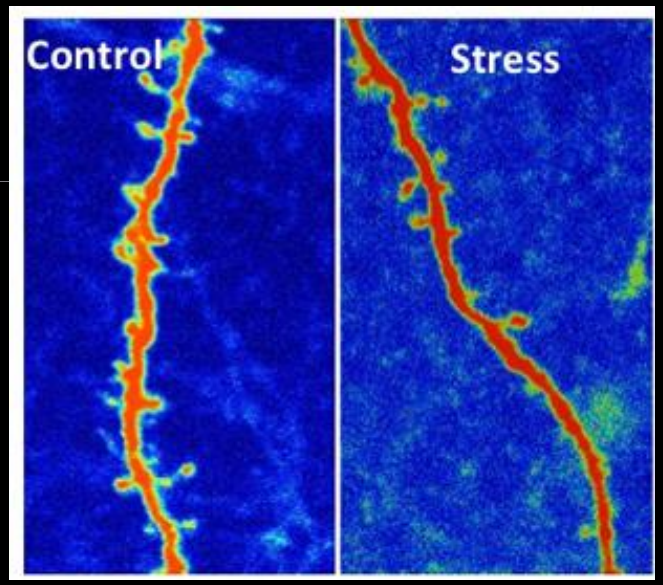
Grunebaum MF, et al. *Am J Psychiatry*, published online 12/5/17

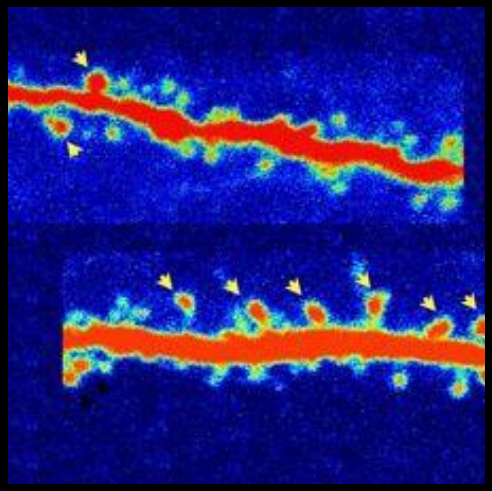
Ketamine - Stress - Depression



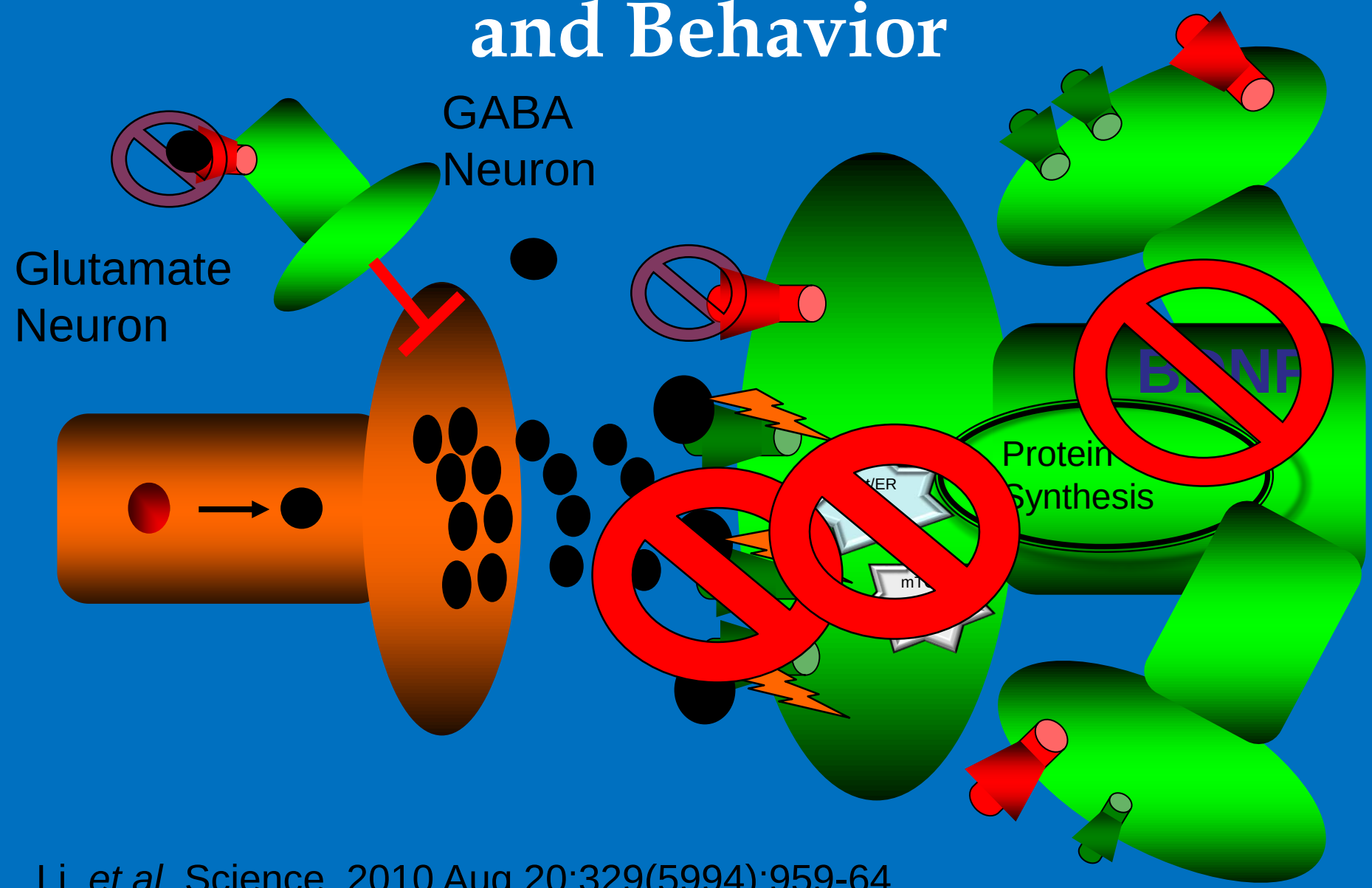


Control

Ketamine



Ketamine's Effects on Plasticity and Behavior



Li, *et al.* Science. 2010 Aug 20;329(5994):959-64.

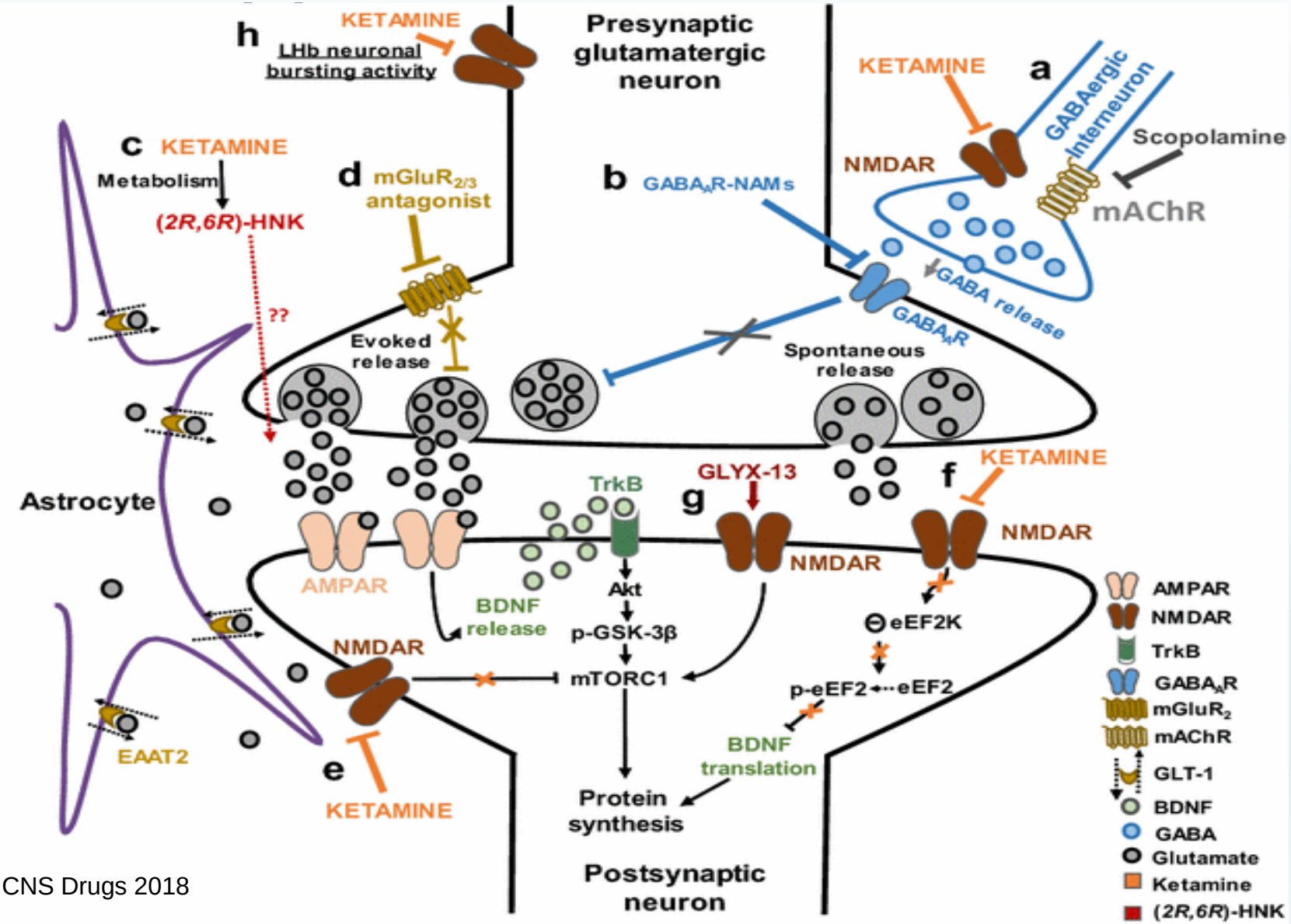
ARTICLE Nature. 2016 May 26;533(7604):481-6
doi:10.1038/nature17998

NMDAR inhibition–independent antidepressant actions of ketamine metabolites

Panos Zanos[1], Ruin Moaddel[2], Patrick J. Morris[3], Polymnia Georgiou[1], Jonathan Fischell[4], Greg I. Elmer[1,5,6], Manickavasagom Alkondon[7], Peixiong Yuan[8], Heather J. Pribut[1], Nagendra S. Singh[2], Katina S. S. Dossou[2], Yuhong Fang[3], Xi-Ping Huang[9], Cheryl L. Mayo[6], Irving W. Wainer[2]†, Edson X. Albuquerque[5,7,10], Scott M. Thompson[1,4], Craig J. Thomas[3], Carlos A. Zarate Jr[8] & Todd D. Gould[1,5,11]

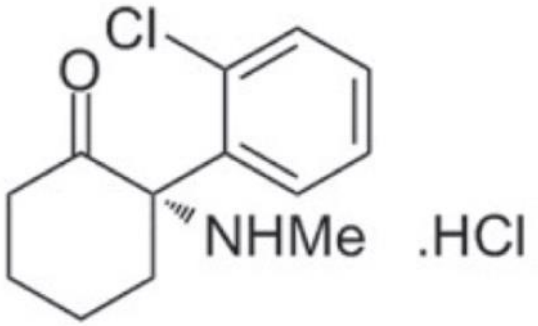
Major depressive disorder affects around 16 per cent of the world population at some point in their lives. Despite the availability of numerous monoaminergic-based antidepressants, most patients require several weeks, if not months, to respond to these treatments, and many patients never attain sustained remission of their symptoms. The non-competitive, glutamatergic NMDAR (*N*-methyl-D-aspartate receptor) antagonist (*R*,*S*)-ketamine exerts rapid and sustained antidepressant effects after a single dose in patients with depression, but its use is associated with undesirable side effects. Here we show that the metabolism of (*R*,*S*)-ketamine to (2*S*,6*S*;2*R*,6*R*)-hydroxynorketamine (HNK) is essential for its antidepressant effects, and that the (2*R*,6*R*)-HNK enantiomer exerts behavioural, electroencephalographic, electrophysiological and cellular antidepressant-related actions in mice. These antidepressant actions are independent of NMDAR inhibition but involve early and sustained activation of AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors). We also establish that (2*R*,6*R*)-HNK lacks ketamine-related side effects. Our data implicate a novel mechanism underlying the antidepressant properties of (*R*,*S*)-ketamine and have relevance for the development of next-generation, rapid-acting antidepressants.

Proposed Mechanisms of Action of Ketamine and other Rapid Acting Antidepressants



Zanos et al CNS Drugs 2018

Esketamine (Spravato)



SPRAVATO™

(esketamine) nasal spray, CIII

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO™ safely and effectively. See full prescribing information for SPRAVATO™.

SPRAVATO™ (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)**
- **Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)**
- **SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)**

Contraindications

SPRAVATO™ is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or to any of the excipients

Drug Interactions with SPRAVATO™

- **CNS Depressants**: Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRAVATO™ with CNS depressants.
- **Psychostimulants**: Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO™ with psychostimulants.
- **Monoamine Oxidase Inhibitors (MAOIs)**: Concomitant use with MAOIs may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO™ with MAOIs.

Most Common Adverse Reactions

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO™ (incidence ≥5% and at least twice that of placebo nasal spray + oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Adverse Reactions Leading to Discontinuation of Treatment

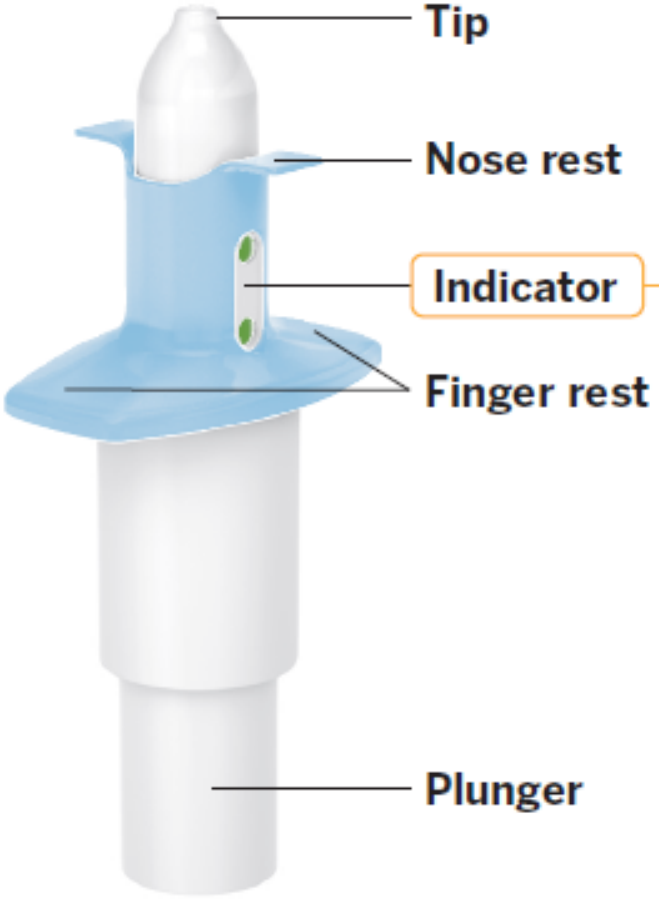
	SPRAVATO™ + oral AD	Placebo Nasal Spray + oral AD
Short-Term Studies*		
Adults <65 yrs	4.6%	1.4%
Adults ≥65 yrs	5.6%	3.1%
Long-Term Maintenance Study	2.6%	2.1%

Across all phase 3 studies, adverse reactions leading to SPRAVATO™ discontinuation in more than 2 patients were (in order of frequency): anxiety (1.2%), depression (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

**Study 1 pooled with another 4-week study

Esketamine (Spravato)

Nasal Spray Device

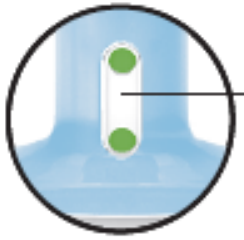


Each device delivers two sprays containing a total of 28 mg of esketamine.

Indicator

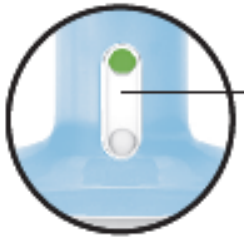
One device contains 2 sprays. (1 spray for each nostril)

2 green dots (0 mg delivered)



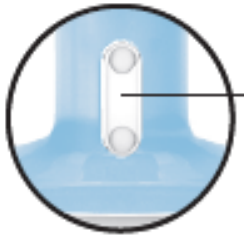
Device full

1 green dot



One spray delivered

No green dots
Two sprays (28 mg) delivered



Device empty

Esketamine (Spravato)

Recommended Dosage For Esketamine in Adults[1]

		Adults
Induction Phase	**Weeks 1-4:**	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	**Weeks 5-8:**	56 mg or 84 mg
	Administer once weekly	
	Week 9 and after:	56 mg or 84 mg
	Administer every 2 weeks or once weekly[a]	

[a]Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Esketamine (Spravato)

Step 1 **Get ready**

Before first device only:

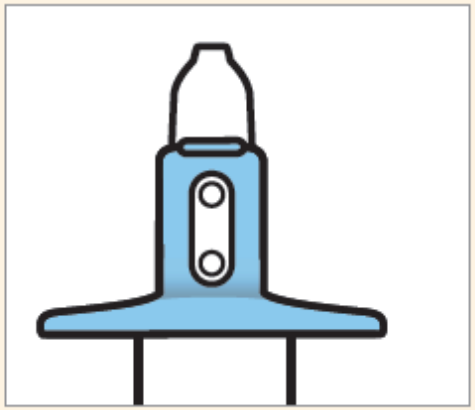
Instruct patient to blow nose **before first device only**.

Confirm required number of devices.

56 mg = 2 devices
84 mg = 3 devices

Esketamine (Spravato)

Step 5 Confirm delivery and rest



Healthcare professional:

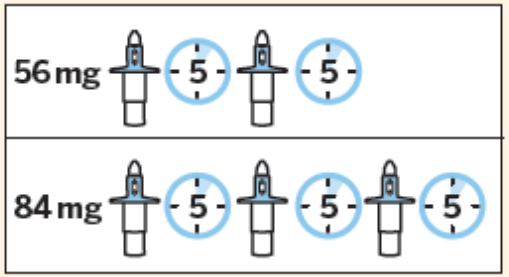
- Take device from patient.
- **Check that indicator shows no green dots**. If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm device is empty.

Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device.**
- If liquid drips out, dab nose with a tissue.

⚠ **Do not** blow nose.

Next device



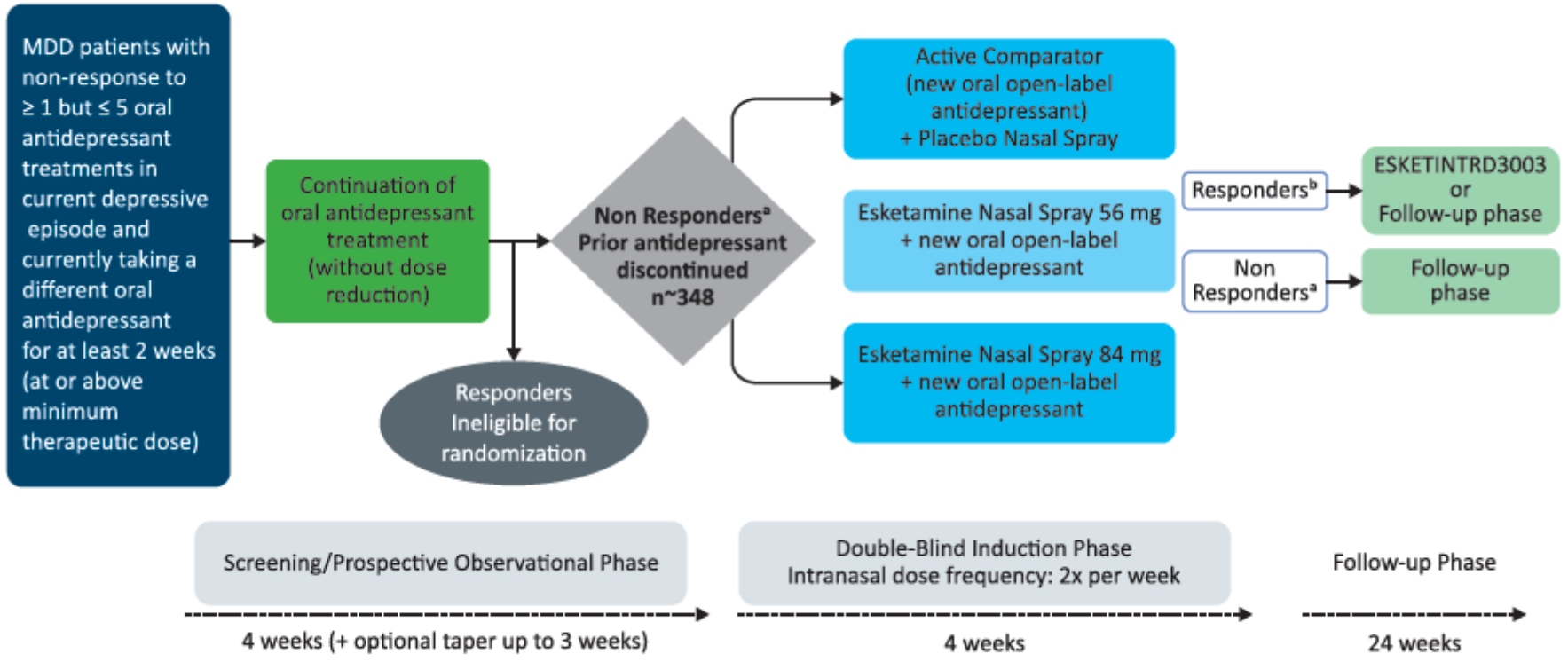
Healthcare professional:

- **Repeat Steps 2-5** for the next device.

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.

Esketamine (Spravato)

Figure 1. Study Design



a. Non-response at end of screening = ≤ 25% improvement in MADRS total score from week 1 to week 4 and a MADRS total score ≥ 28 at weeks 2 and 4.
b. Responder = ≥ 50% reduction in the MADRS total score from baseline (Day 1 pre-randomization) to the end of the double-blind phase.

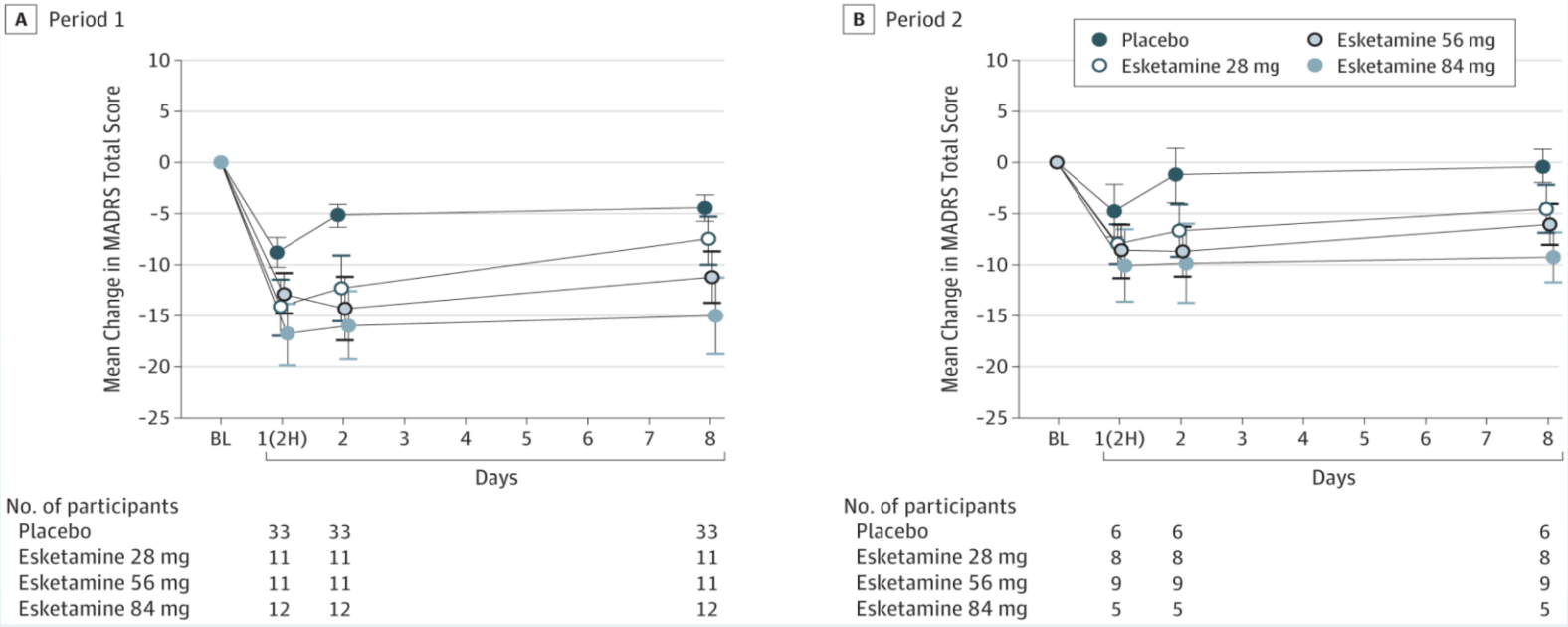
Esketamine (Spravato)

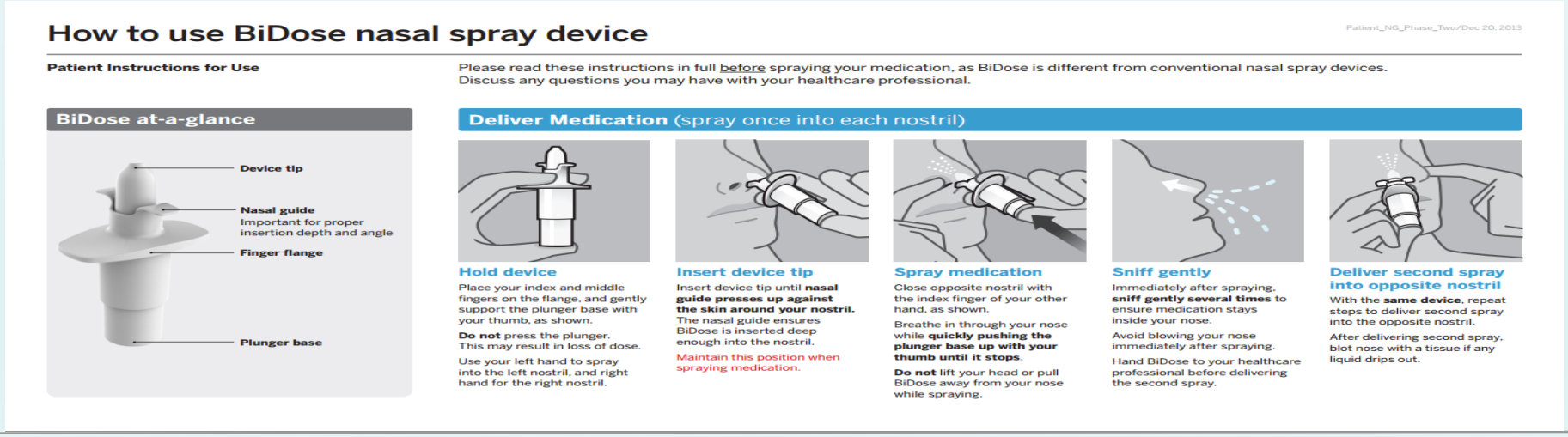
Incidence of Specific AE in Week 1 and Incidence/Frequency of Same AE in Weeks 2-4

Specific AE	4-Week Incidence	Week 1 Incidence (number of monitoring periods [0-2] AE observed)	Number of Subjects with AEs in Weeks 2-4	Number of Sessions (0-6) in which an AE was experienced in Weeks 2-4
Nausea	28.30%	None - 79.7% (n=275)	5.5% (n=15)	1.07
		Once - 20.3% (n=70)	44.3% (n=31)	2.37
		Twice - 5.2% (n=18)	66.7% (n=12)	3.62
Dissociation	26.6%	None – 77.7% (n=268)	5.6% (n=15)	1.95
		Once – 22.3% (n=77)	71.4% (n=55)	4.14
		Twice – 11.3% (n=39)	94.9% (n=37)	4.57
Dizziness	23.7%	None – 76.5% (n=264)	6.4% (n=17)	1.54
		Once – 23.5% (n=81)	70.4% (n=57)	3.22
		Twice – 9.3% (n=32)	90.6% (n=29)	3.70
Vertigo	22.5%	None – 82.9% (n=286)	6.3% (n=18)	2.54
		Once – 17.1% (n=59)	71.2% (n=42)	4.48
		Twice – 9.9% (n=34)	85.3% (n=29)	5.24
Somnolence	17.3%	None – 88.7% (n=306)	6.2% (n=19)	2.53
		Once – 11.3% (n=39)	71.8% (n=28)	3.07
		Twice – 2.9% (n=10)	100% (n=10)	4.13

Data sample was a combination of data from the 3 intranasal ESK groups from the fixed-dose and flexible-dose studies (n=345). The first-week incidence groups are not mutually exclusive – the "Twice" group is a subset of the "Once" group.

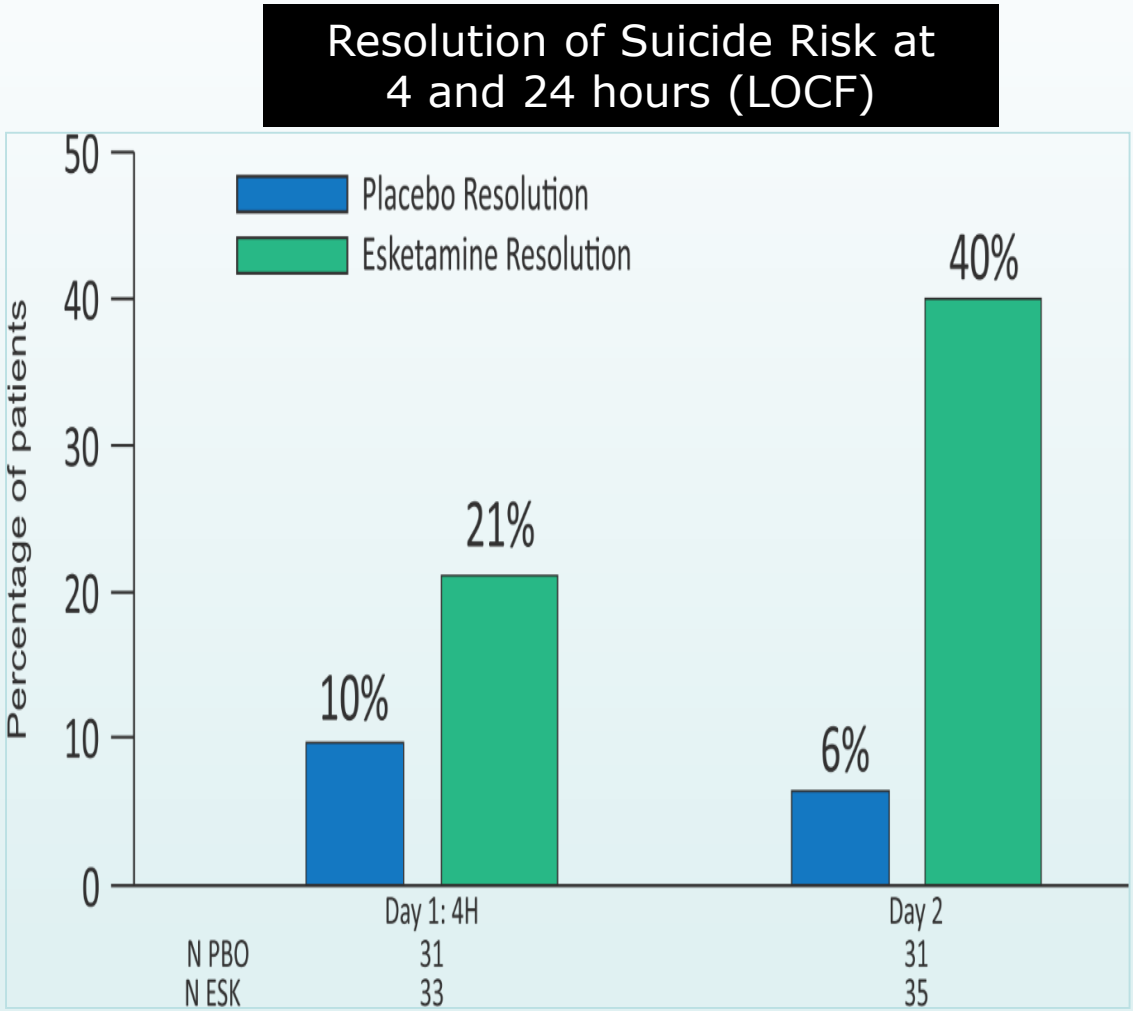
Adjunctive Intranasal Esketamine in TRD (N=67*)





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

Effect of Intranasal Esketamine on Suicide Risk



Proportion of patients achieving resolution of suicide risk (CGJ-SR Score 0 or 1) at day 1 (4 hour postdose) and day 2 (~24 hours postdose) LOCF

Janssen Research & Development, data on file

Safety: Ketamine and Opiate Receptors

- Shatzberg et al., Attenuation of Antidepressant Effects of **Ketamine** by Opioid Receptor Antagonism. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, Hawkins J, Birnbaum J, Lyons DM, Rodriguez CI, Schatzberg AF. Am J Psychiatry. 2018 Dec 1;175(12):1205-1215.

- Interpreting **Ketamine**'s Opioid Receptor Dependent Effect: Response to Sanacora. Heifets BD, Williams NR, Blasey C, Sudheimer K, Rodriguez CI, Schatzberg AF. Am J Psychiatry. 2019 Mar 1;176(3):249-250.

- "We broadly agree with Dr. Sanacora that an opioid receptor antagonist's effect can be explained either by direct interaction at the opioid receptor, an indirect interaction at the cellular level, perhaps mediated by cross-talk between *N*-methyl-D-aspartate and opioid receptors, or by an indirect effect wherein the action of endogenous opioids, presumably stimulated by ketamine infusion, is blocked"

- Could endogenous opioid mechanisms explain antidepressant responses to many active agents, including ketamine, as well as to placebo? We cannot discount this possibility.

COPE Supported Centers Provide Innovative, Evidence-Based Psychiatric Treatment.

COPE is proud to provide administrative and advisory support to highly specialized psychiatric clinics that provide expert consultations and innovative, evidence-based psychiatric treatment for the most difficult to treat cases of major depression, anxiety, bipolar depression, chronic pain and opioid addiction among others. Patients who come to these clinics have tried other treatments, to no avail, and are looking for something more revolutionary than the standard protocol. If you or someone you love is suffering from one of these treatment-resistant mental illnesses, we encourage you to reach out to a COPE supported center near you to learn more about these innovative, effective, evidence-based treatments.

COPE Supported Centers Provide Effective Treatments for

Major Depression

Bipolar Depression

Generalized Anxiety Disorder

Post-traumatic Stress Disorder (PTSD)

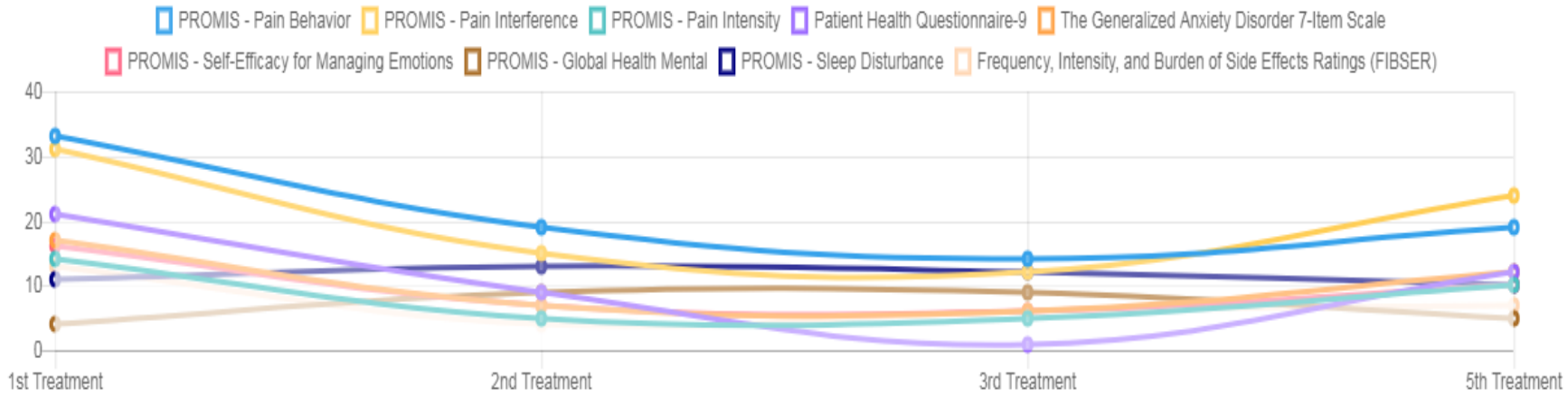
Obsessive Compulsive Disorder (OCD)

Chronic Pain

Patient Self-Rating of Symptoms to Ketamine

Patient Administered Scales

Acute Phase(6 Treatments over 2 Weeks)



1st Treatment **Progress:** 100% **Completed:** 2018-02-06 View Results

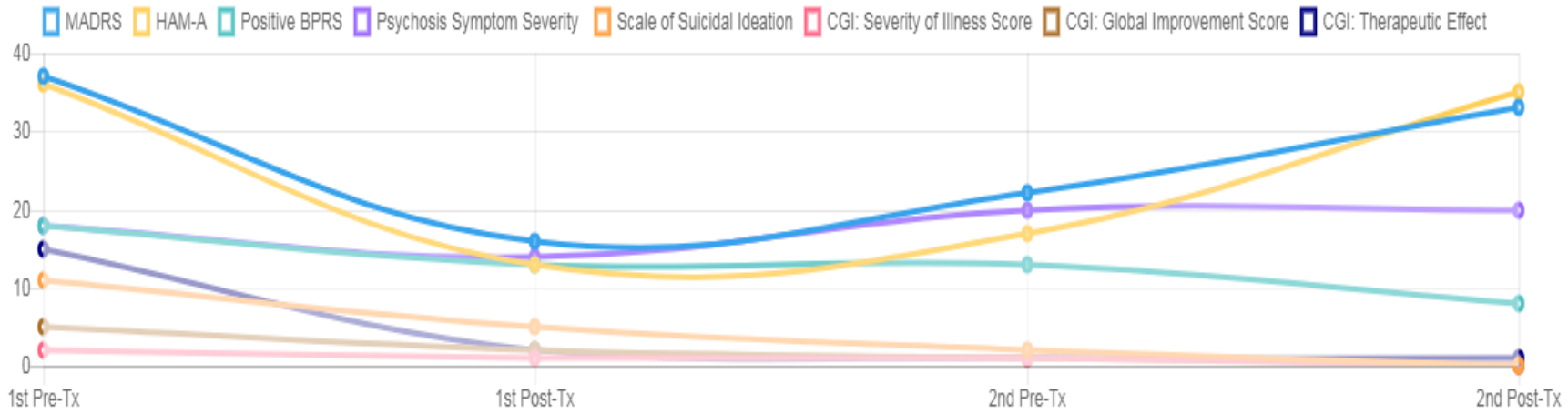
- PROMIS Pain Behavior = 33 out of 42
- PROMIS Pain Interference = 31 out of 40
- PROMIS Pain Intensity = 14 out of 15
- PHQ-9 = 21 out of 27
- GAD-7 = 17 out of 21
- PROMIS Emotions = 16 out of 20
- PROMIS Global Health Mental = 4 out of 10
- PROMIS Sleep Disturbance = 11 out of 20
- FIBSER = 13 out of 18

Provider Ratings to Optimize/Stop Ketamine Tx

Provider Administered Scales

These scales are to be done on the day of treatment by a COPE provider. The questions are in reference to baseline symptom evaluation by the provider or since the last treatment at COPE.
Please complete the scales prior to each treatment in each of the stages below. Once completed an option to complete the Post-Treatment assessment will appear and should be done after the infusion.

Acute Phase(6 Treatments over 2 Weeks)



1st Pre-Treatment Assessment **Progress:** 100% **Completed:** 2018-02-06 View Results

- MADRS = 37 out of 60
- HAM-A (Severe Severity) = 36 out of 56
- BPRS - Positive Symptom Rating = 18 out of 28
- Clinician-Rated Dimensions of Psychosis Symptom Severity = 18 out of 32
- Scale of Suicidal Ideation = 11 out of 16
- CGI: Severity of Illness = 2 out of 7
- CGI: Global Improvement = 5 out of 7

Report Generated On: **Monday 2nd of April, 2018**

Patient #: **FullTest2**

PATIENT 1ST PRETREATMENT ASSESSMENT - OCD

Dimensional Obsessive-Compulsive Scale (DOCS): 39 out of 80

Time spent thinking about contamination and engaging in washing or cleaning behaviors	**less than 1 hour each day 1**
Extent avoiding situations to prevent contamination concern, washing, cleaning, or showing	**a little annoyance 1**
How distressed or anxious about contamination thoughts	**moderately distressed/anxious 2**
Daily routine disrupted by contamination concersn and excessive cleaning	**my life is disrupted in many ways and i have trouble managing 3**
Difficulty disregarding thoughts about contamination and refraining from washing behaviors	**a little difficult 1**
Time spent thinking about harm or disasters	**8 hours or more each day 4**
Extent avoiding situations that you would check for harm	**a great deal of avoidance 3**
Distress level when cannot check for harm	**mildly distressed/anxious 1**
Extent daily route disruption thoughts of harm	**a little disruption 1** **but i mostly function well 1**
Difficulty disregarding thoughts of harm	**moderately difficult 2**
Time spent with unpleasant thoughts	**less than 1 hour each day 1**
Extent avoiding things that trigger unwanted thoughts	**none at all 0**
Distress level with unwanted thoughts	**severely distressed/anxious 3**
Extent of daily routine interruption by unwanted thoughts	**many things are disrupted 2**

COPE Real-World Registry: IV Ketamine in Depression

Demographics (n =119)
72 (61%) female
45 (38%) male
1 (0.8%) transgender female-male
1 (0.8%) transgender male-female

Baseline/Prior to Tx 1:
PHQ-9 = 20.2
MADRS = 36.6
GAD-7 = 12.2

Acute Phase – 3 Tx/wk X 2 weeks
PHQ-9 = 9.4
MADRS = 13.1
GAD-7 = 6.9

A significant reduction of 54.9% in PHQ-9, 35.6% in MADRS, and 29.9% in GAD-7 occurred after the first infusion (p<.0001).

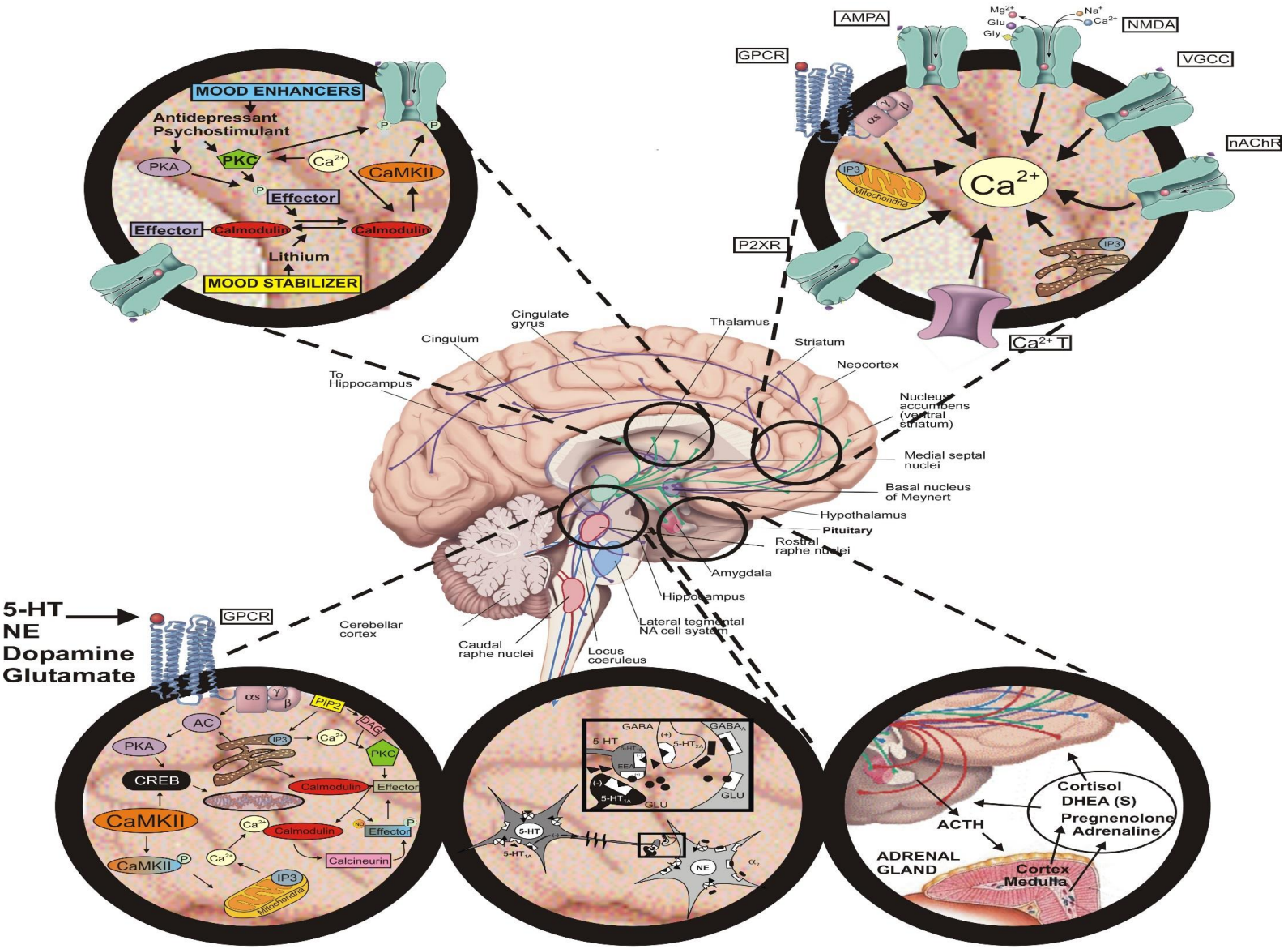
Sustained Phase – 1 Tx/wk X 4 weeks
PHQ-9 = 8.5
MADRS = 10.7
GAD-7 = 5.9

A *sustained* 50% reduction in depressive and anxiety symptoms occurred after 6 treatments.

Maintenance Phase – 1 Tx/month X 6 months
PHQ-9 = 7.5
MADRS = 12.1
GAD-7 = 6.9

Remission of symptoms were *maintained* using the COPE ketamine treatment algorithm at 7 months.

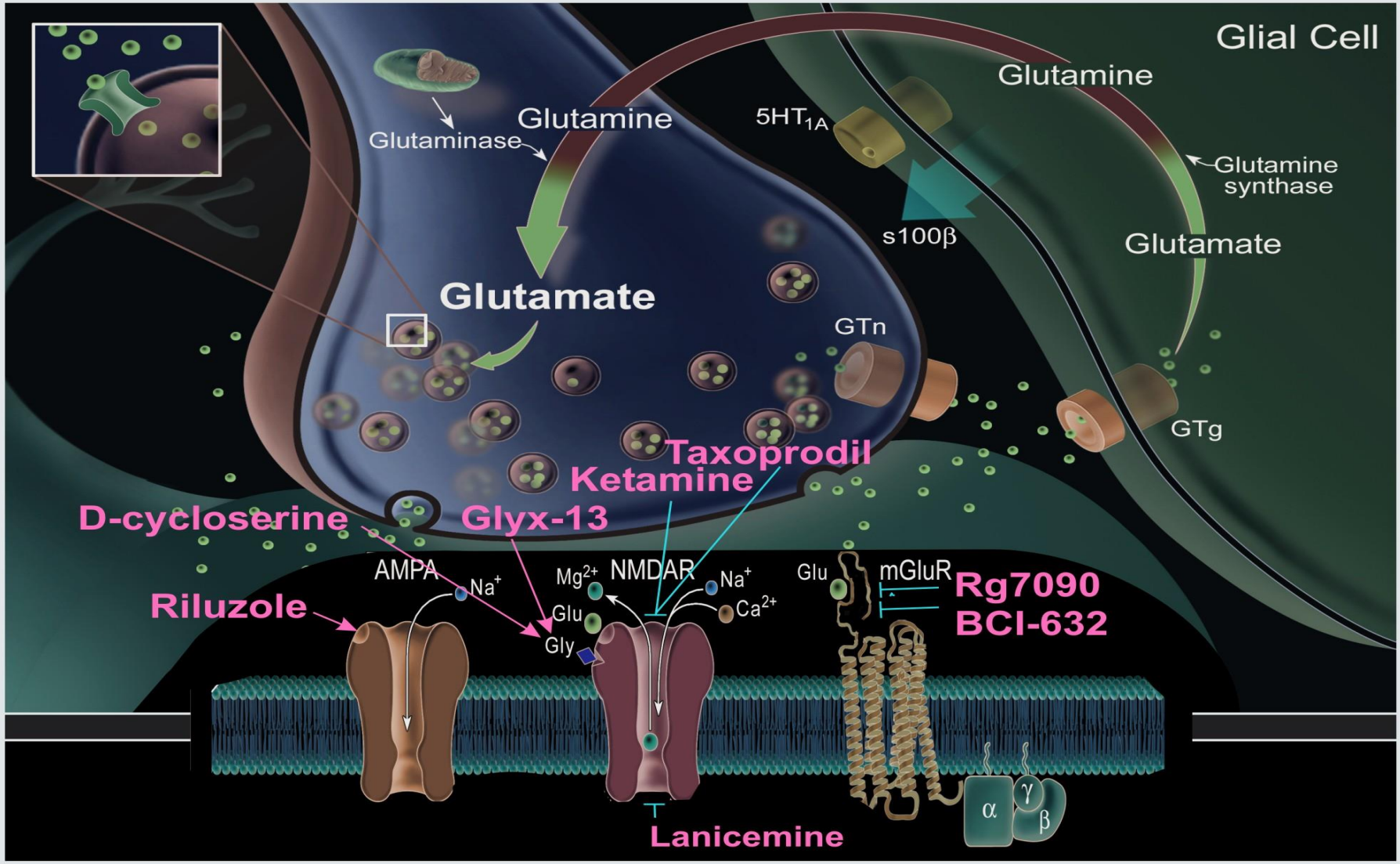
Drug Targets and Brain Circuit Regulation



Adapted from Szabo et al., 2014

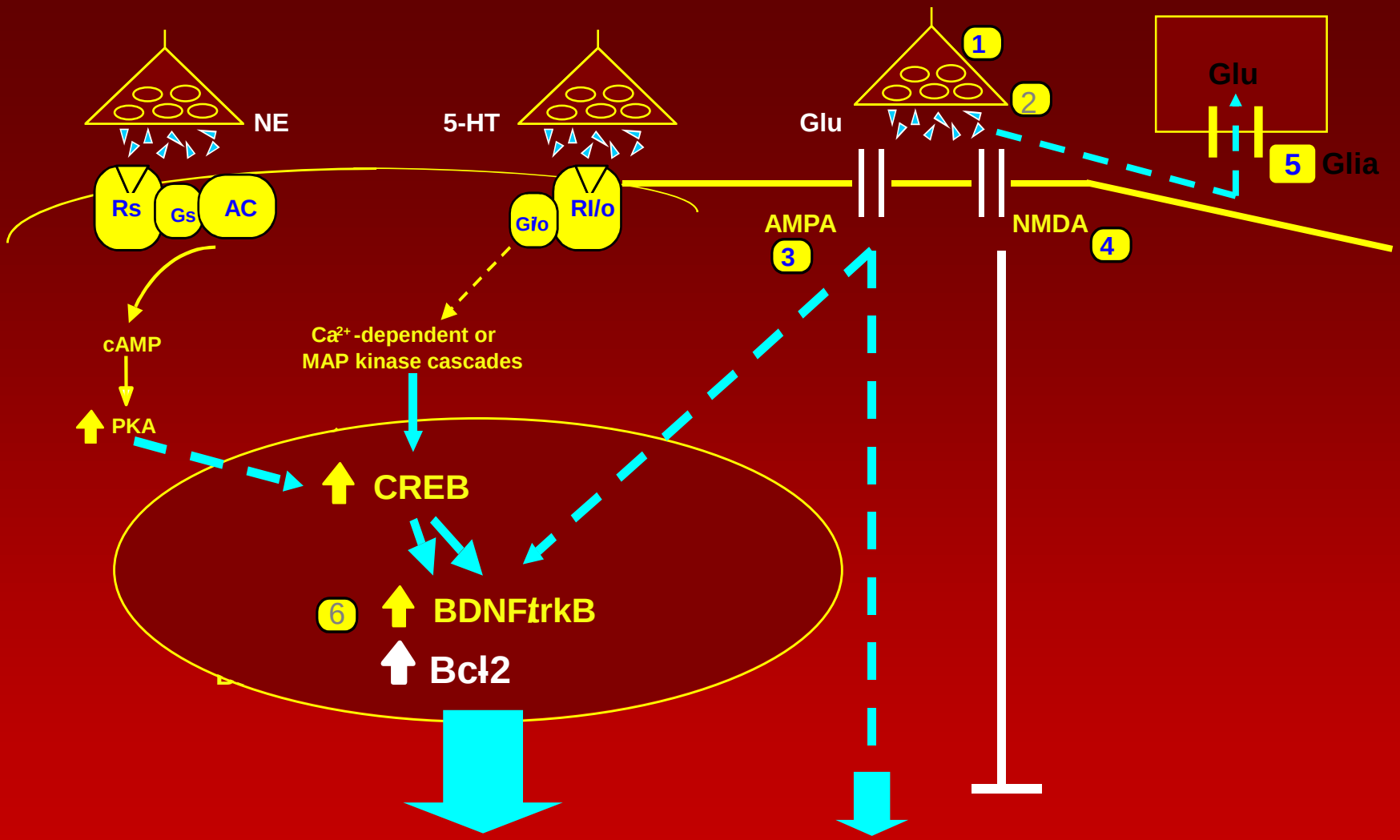
APA Textbook of Psychopharmacology

Novel Glutamate Treatments for Depression



Szabo and Nemeroff, 2014
Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, Fifth Edition

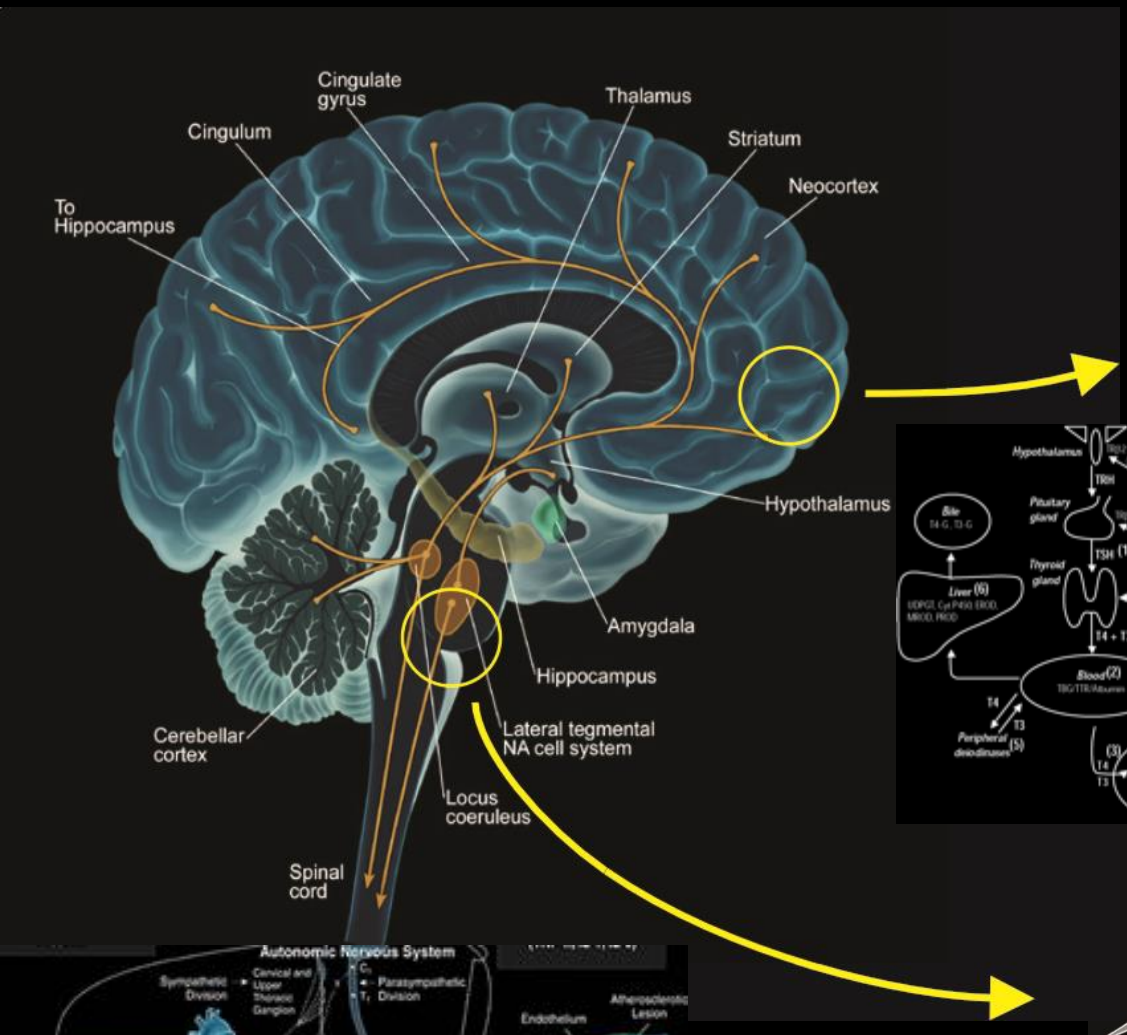
Conserved Underlying Mechanism of Antidepressants

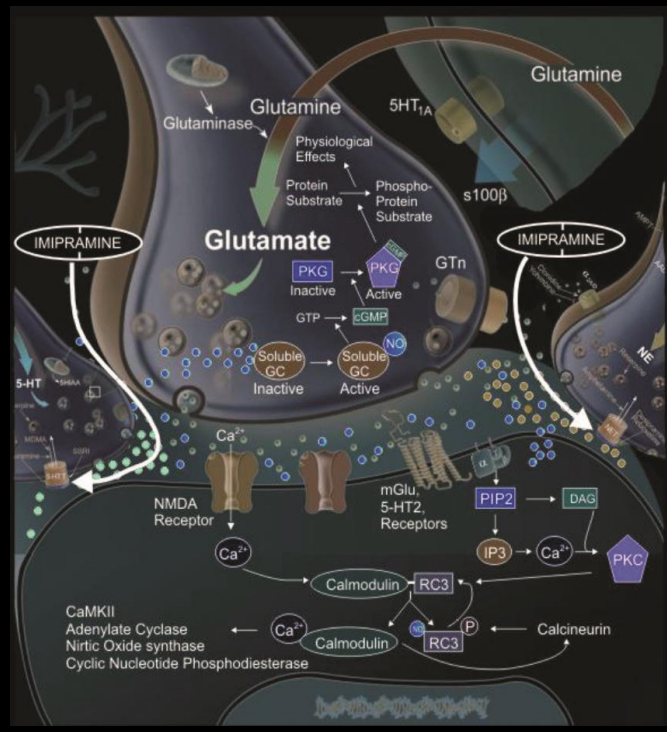


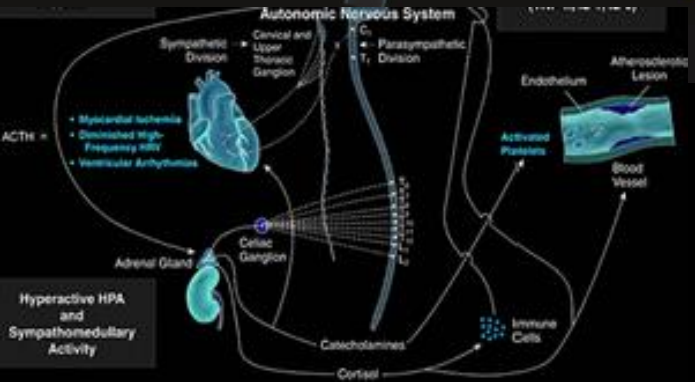
Enhancement of synaptic plasticity and cellular resilience

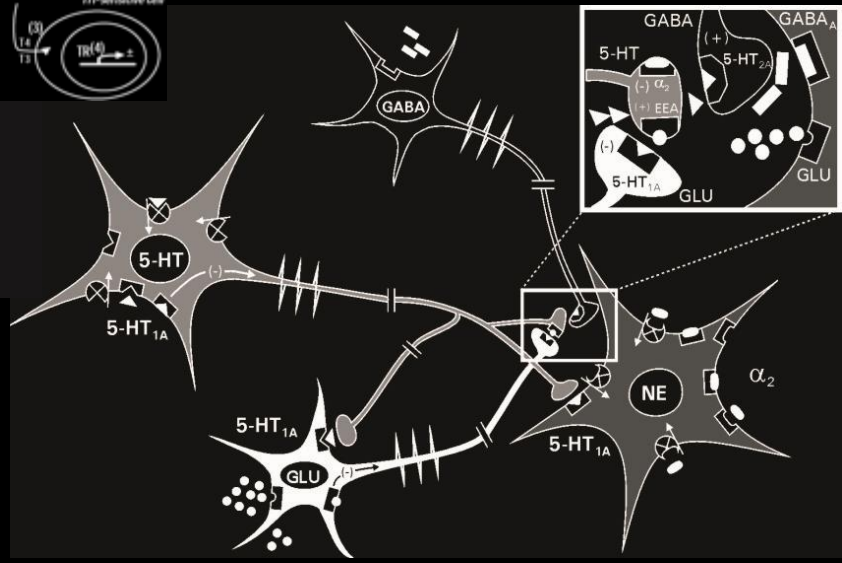
Restoration, enhancement & maintenance of neural connectivity mechanisms essential for healthy affective functioning and buffering against deterioration of neural functioning

Multimodal Treatment Approaches Needed









Going Forward with Neuroscience Endpoints

Antidepressant Effect on the Firing Activity of Locus Coeruleus Norepinephrine Neurons in Rats

Antidepressant Class	Drug	Acute	Long-Term
MAOI	Phenelzine	↓	↓
TCA	Clorgyline	↓	↓
	Desipramine	↓	↓
	Imipramine	↓	↓
NE reuptake inhibitor	Reboxetine	↓	↓
α_2-adrenergic antagonist	Mirtazapine	↑	↓
Dual NE/5-HT reuptake inhibitors	Venlafaxine	↓	↓
	Milnacipran	↓	↓
	Duloxetine	↓	↓
SSRI	Paroxetine	Ø	↓
	Citalopram	Ø	↓
NE releaser	Bupropion	↓	Ø

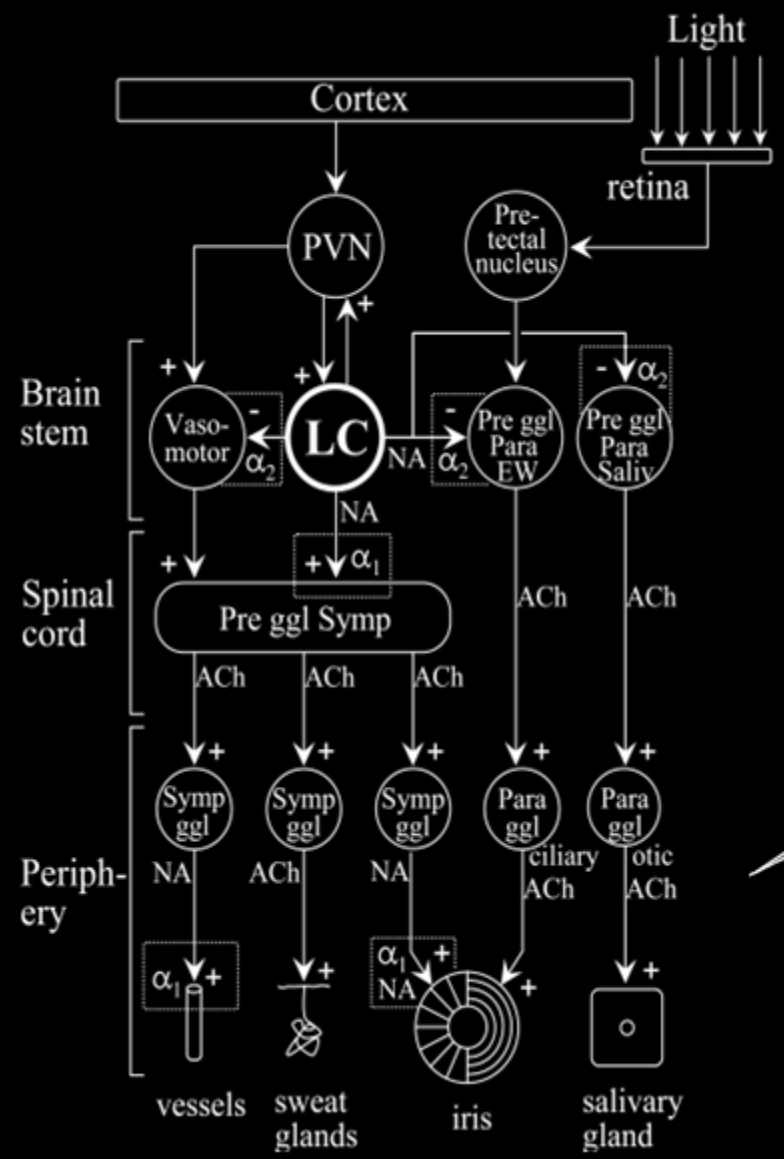
Adapted from Szabo and Blier, 2001 (CNS Spectrums)

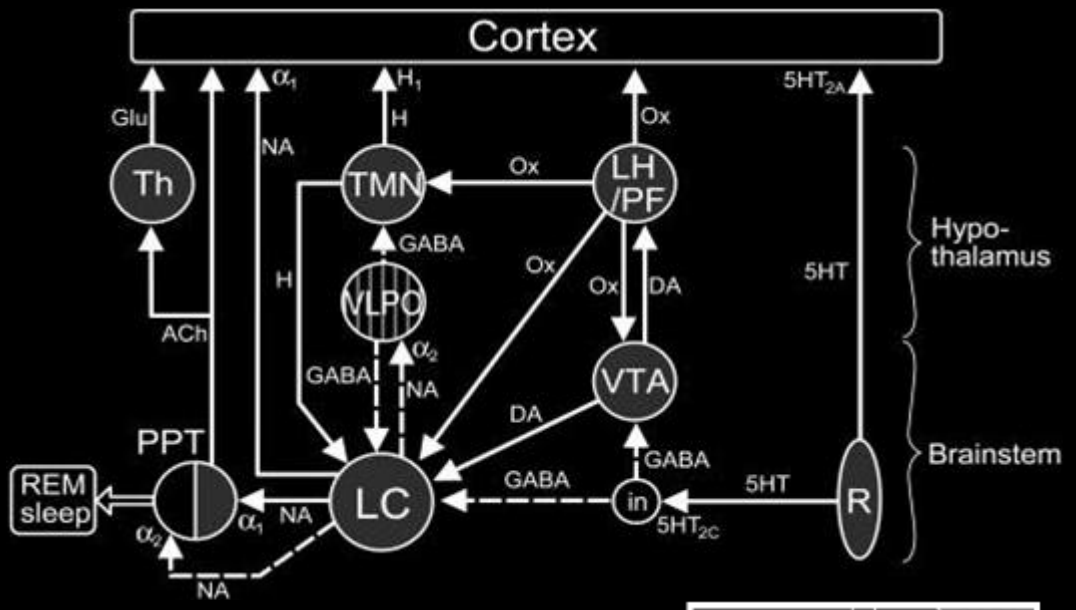
Illicit Drug Effect on the Firing Activity of Locus Coeruleus Norepinephrine Neurons in Rats

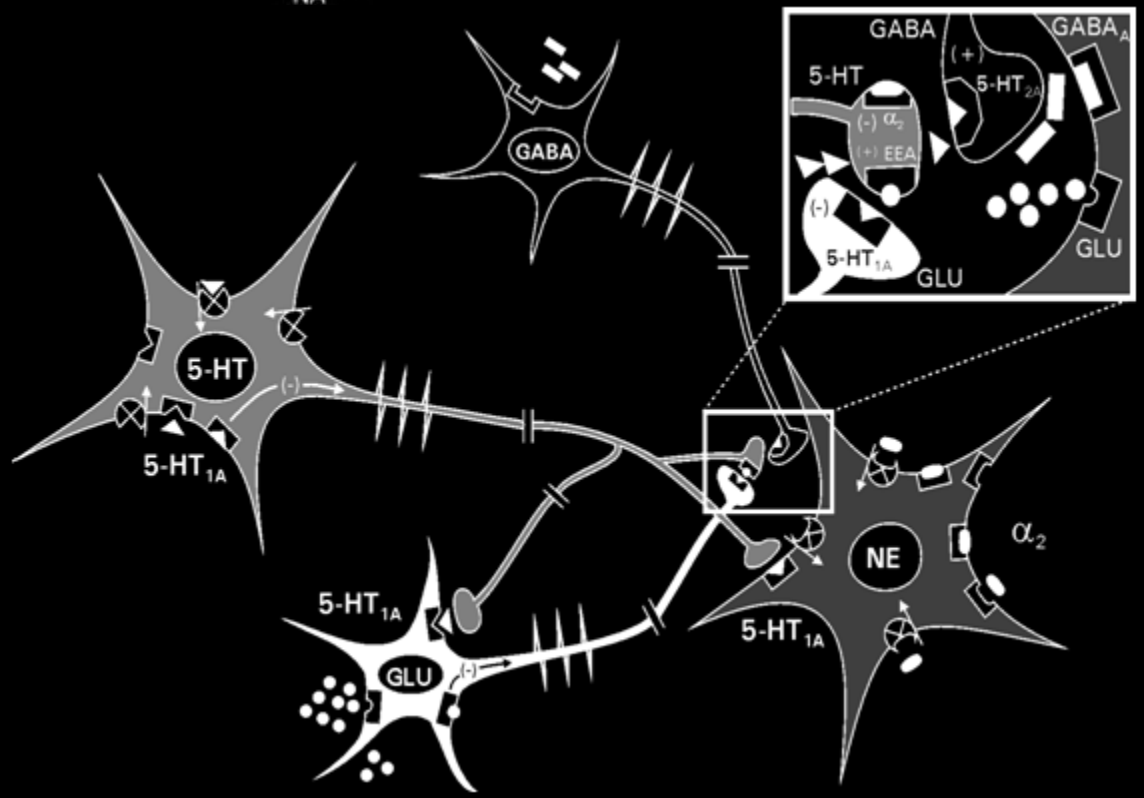
Drug Class	Drug	Acute	Withdrawal
Sedatives	Alcohol	↓	↑
	Alprozolam	↓	↑
	Heroin	↓	↑
	GHB	↓	↑
Entactogen	Ecstacy	↓	↑
Dissociative	Ketamine	?	?
Hallucinogen	PCP	↓	?
	LSD	↓	?
	Mescaline	↓	?
Canabinoid	Marijuanna	↑	?

Szabo (Unpublished)

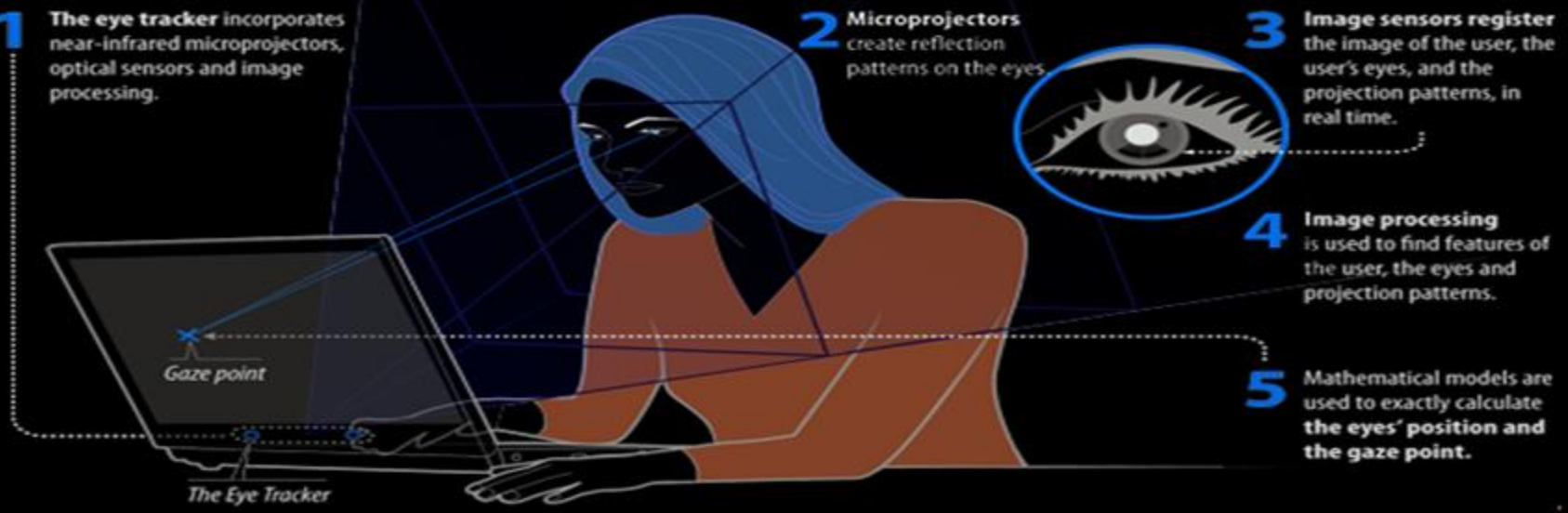
Keeping Eye on the Locus Coeruleus

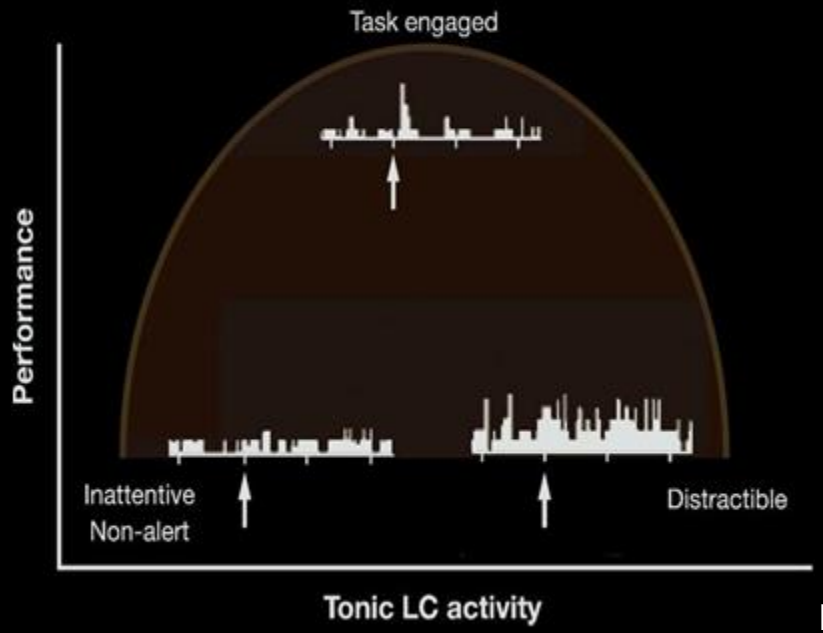


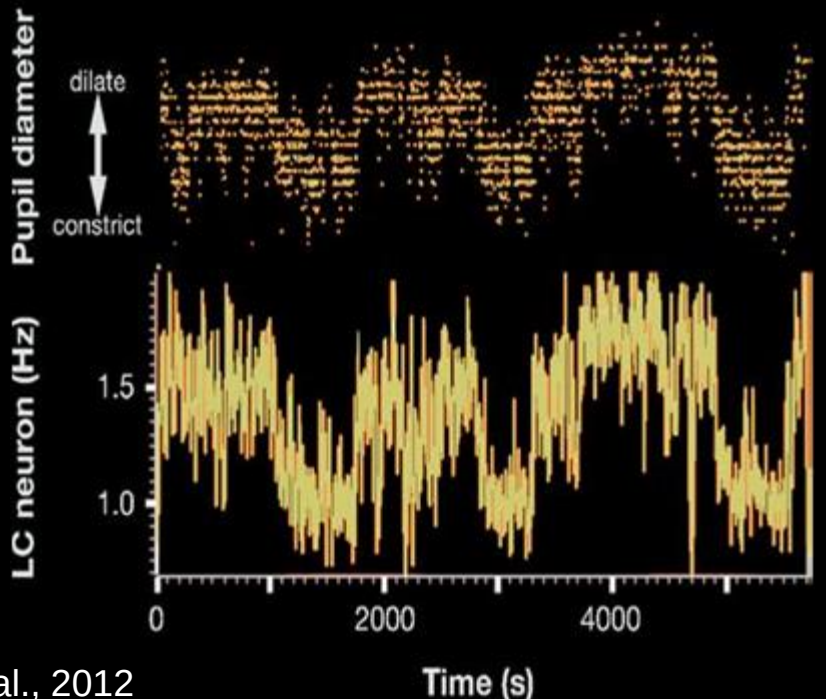




Pupilometry and LC Activity

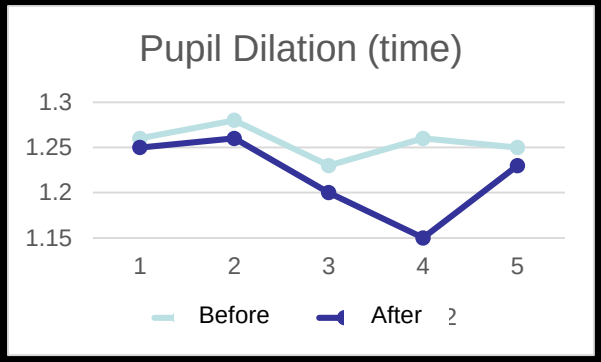




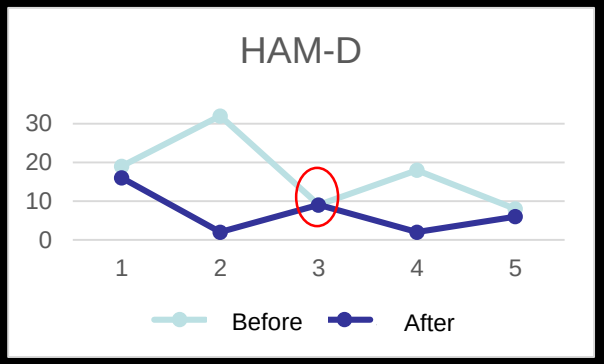


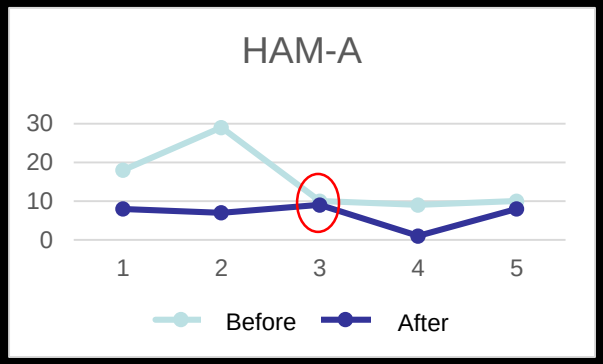
Naylor et al., 2012

Pupillometery and Target Engagement: Personalizing Ketamine Treatment

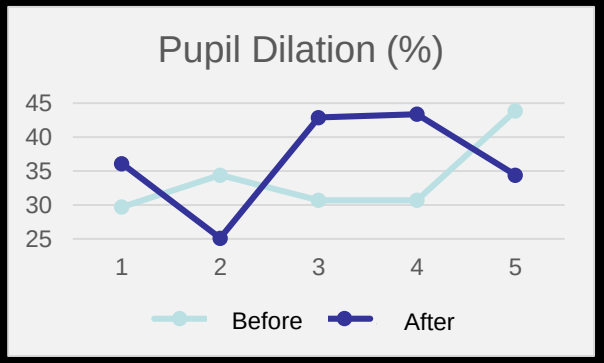


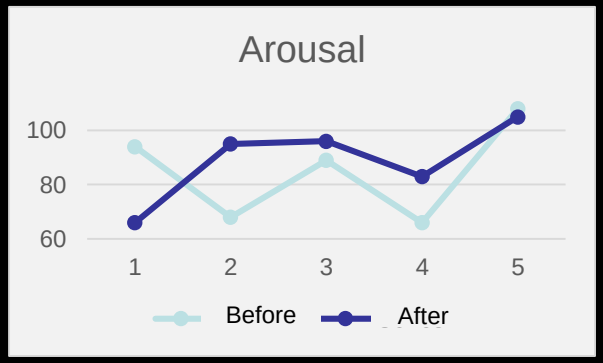
Shorter time to *peak pupil dilation to dark* following ketamine infusion (1.23s vs 1.26s)





Depression and anxiety scores before infusion (17.2 and 15.2) and after (7.0 and 6.6)





The change in pupil dilation and arousal did not correspond to these effects

Acknowledgments

FUNDAMENTAL NEUROSCIENCE

- Electrophysiology
  Pierre Blier, MD, PhD (McGill University)
  Claude de Montigny, MD, PhD (McGill University)

- Cellular and Molecular Biology
  Jing Du, MD (NIH)
  Husseini Manji, MD (NIH)

- Behavior
  Jean Harry, MD (NIEHS-NTP)
  Christopher McPherson, PhD (NIEHS)

BIOMARKER DEVELOPMENT

- Pupilometry
  John Pearson, PhD (Duke University)
  Micheal Platt, PhD (Duke University)

- Metabolomics and Microbiome
  Susan Sumner (RTI)

HUMAN CLINICAL STUDIES

- Experimental Therapeutics
  Bruce Burnett, PhD (Duke University)
  Corey Fowler, PhD (Duke University)
  Andrew Krystal, MD, MSc (Duke University)
  Holly Lisanby, MD (Duke University)
  Barry Mangum, PhD (Duke University)
  Christine Marx, MD, MSc (VA Hospital/Duke)
  Jennifer Naylor, PhD (Va Hospital/Duke)
  Angel Peterchev, PhD (Duke University)

- Addictions
  Brett Froeliger , PhD (MUSC)
  Corey Fowler, PhD (Duke University)
  Mark Gold, MD (University of Florida)
  Tong Lee, MD, PhD (Duke University)
  Joseph McClernon (Duke University)
  Ashwin Partkar, MD (Duke University)

- Cognitive Disorders
  Joseph McEvoy, MD (Duke University/CRH)

- Toxicology
  Bruce Goldberger, PhD (University of Florida)
  David T Szabo, PhD (FDA)

- Environmental Health
  Linda Birnbaum, PhD (NIEHS)
  K. Welsh-Bohmer, PhD (Duke University)
  John Ervin, MSc (Duke University)
  Kate Hayden, PhD (Duke University)