Esketamine for Treatment Resistant Depression

How Special is Special K: Evolution, Revolution or Fashion?

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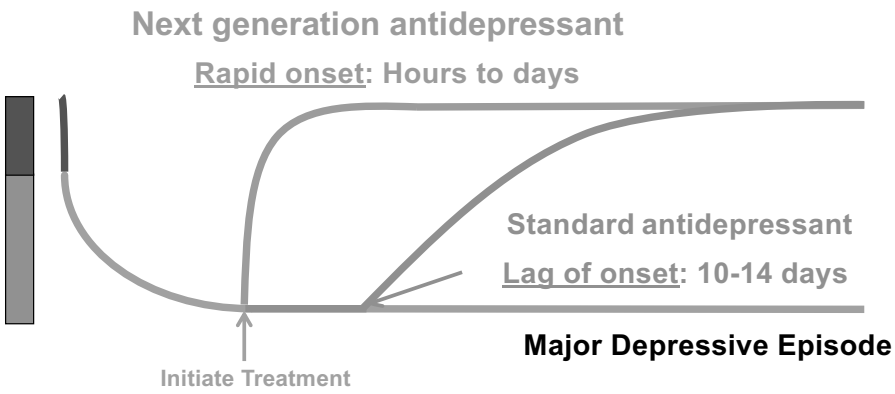
Psychopharmacology Update: 2019

Presented by The Maryland Psychiatric Society

Depression: The Need for Improved Treatments

Problems with Current Antidepressants:

- Low remission rates
- Lag of onset of antidepressant effects



Courtesy of Carlos Zarate Jr, MD

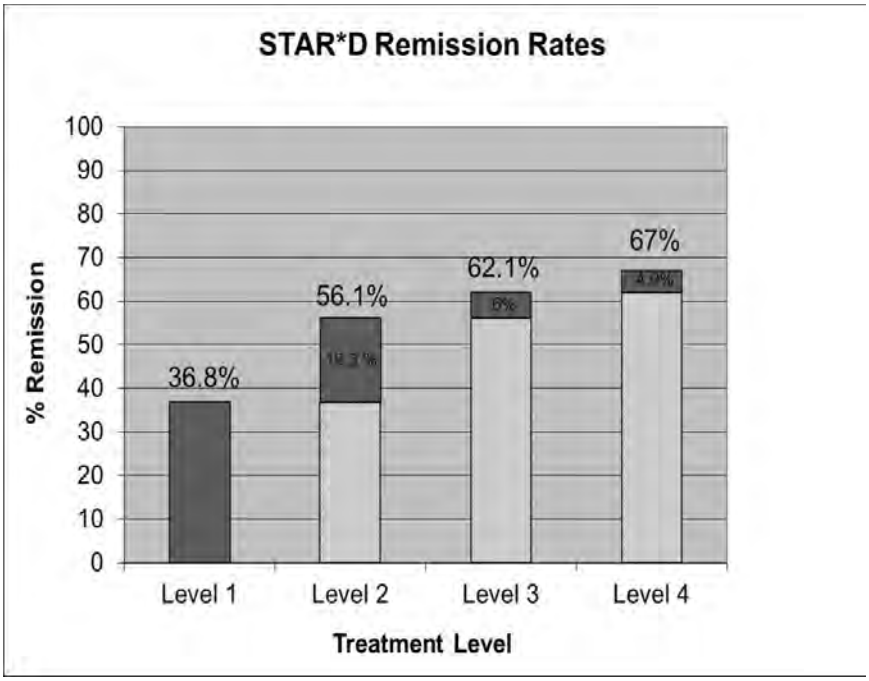
Augmentation Strategies for MDD

Augmentation	Evidence Rating*	Added $ Monthly
lithium 900 mg (to TCA)	A	2
T3 25 ug (to TCA)	A	3
mirtazapine 15 mg	A/B	18
buspirone 40 mg	B	4
bupropion SR 300 mg	B	42
olanzapine 10 mg	B	172
modafinil 200 mg	B/C	110
nortriptyline 100 mg	C	2
pindolol 10 mg	C	2
lithium 900 mg (to SSRI)	C	2
T3 25 ug (to SSRI)	C	3
venlafaxine XR 150 mg	C	54
other atypicals	C	70-158

*Thase ME. CNS Spectrums 2004;9(11):808-821.(updated)

A= >1 RCTs
B= 1 RCT, plus c
C= Case series, anecdotal report, expert opinion
D= Anecdotal reports but experts have not endorsed

Treatment Resistant Depression

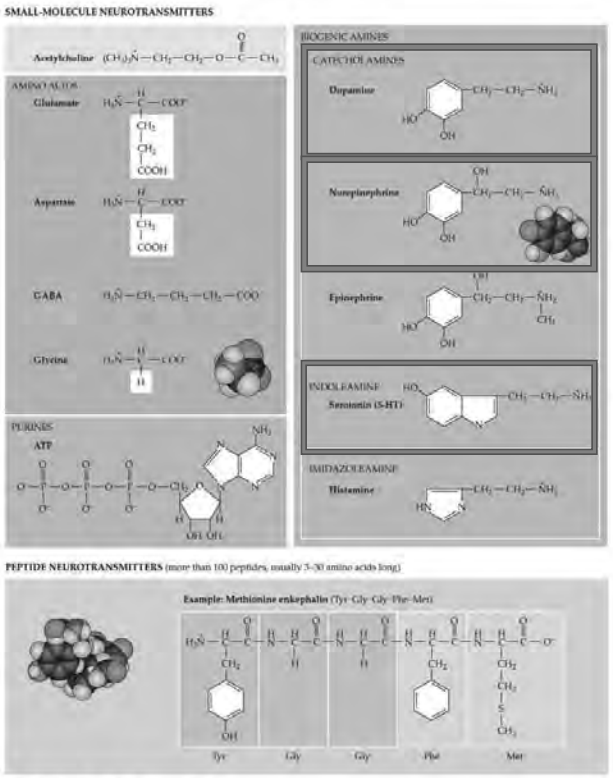


Trivedi et al. (Am J Psychiatry, 2006); Rush et al. (NEJM, 2006)

Table 1: Summary of FDA-Approved Products for Treatment of TRD

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Authority
FDA Approved Treatments Combine by Pharmacologic Class, if relevant						
Symbyax (Fluoxetine plus Olanzapine)	TRD	2003	Oral daily	MADRS Total Score Change from Baseline of -16 vs. olanzapine -12 and placebo -10 for Study 1, -18 vs. -14 and -9 for Study 2	Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and extrapyramidal symptoms/ akathisia	CDER
ECT	TRD (associated with either MDD or Bipolar Disorder)	1976 (most recent update 2018)	Bitemporal or unilateral temporal; up to 3 times a week for 6 to 10 treatments initially	Not available; approval based on various studies from research literature.	Memory concerns, use of general anesthesia	CDRH
TMS	TRD (patients who failed only 1 anti-depressant)	2008	Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)	MADRS Total Score Change from Baseline of -6 at Week 4 and Week 6 active TMS vs. -4 at Week 4 and Week 6 sham TMS. Approval based on post-hoc analysis and responder/remission rates.	No major safety issues, limited long-term safety data	CDRH
VNS	TRD	2005	Once (surgical implant)	12-week sham placebo-controlled study not statistically significant. Approval was based on long-term open-label HAM-D responder data (30% response in 1 year versus 13% treatment as usual). 12-week open-label pilot study showed 34% MADRS responders.	Surgical intervention risks (allergies, infection, etc.)	CDRH

Survey of the major neurotransmitters

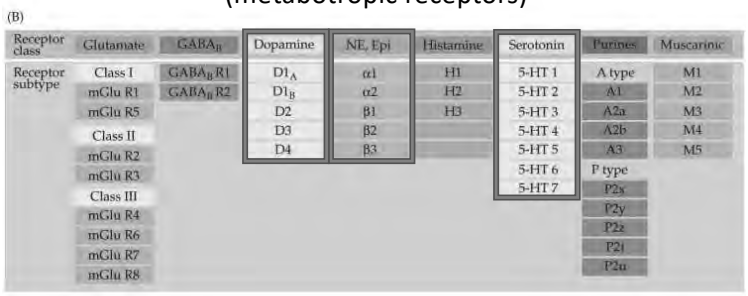


NEUROSCIENCE, Fourth Edition, Figure 6.1

A word about classifying neurotransmitters

Some neurotransmitters have fast (ion channel) and neuromodulatory modes (GPCR) of function

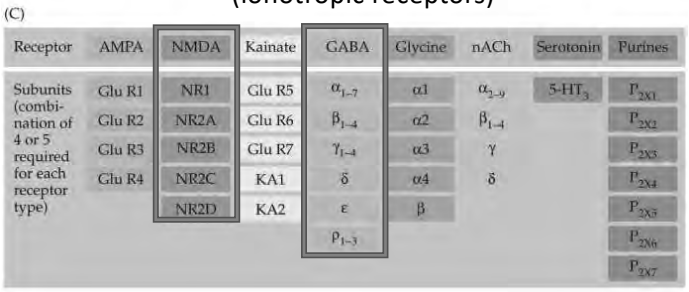
Modulatory mode: G-protein coupled receptors (metabotropic receptors)



Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_BR1$	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_BR2$	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2i	
	mGlu R8						P2u	

NEUROSCIENCE, Fourth Edition, Figure 6.5 (Part 2)

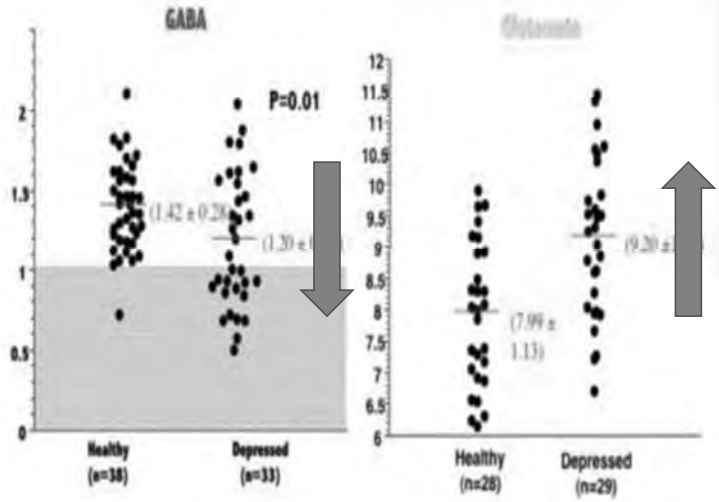
Fast mode: ion channel receptors (ionotropic receptors)



Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	α1	α_{2-9}	$5\text{-}HT_3$	P_{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α2	β_{1-4}		P_{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α3	γ		P_{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P_{2X4}
		NR2D	KA2	ε	β			P_{2X5}
				ρ_{1-3}				P_{2X6}
								P_{2X7}

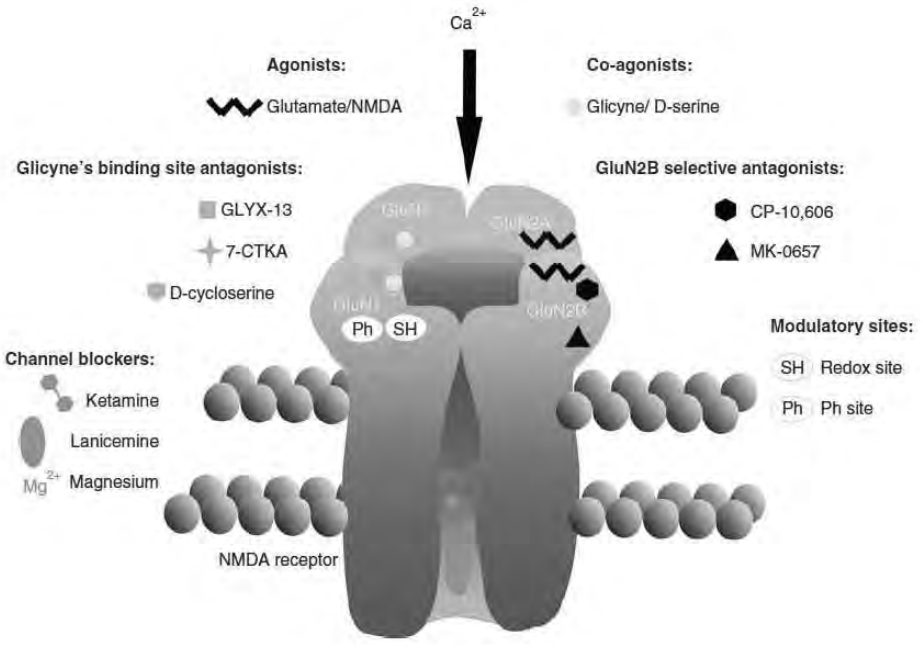
NEUROSCIENCE, Fourth Edition, Figure 6.4 (Part 3)

GABA and Glutamate Levels in Patients with MDD



Sanacora G, et al. *Arch Gen Psychiatry*. 2004;61(7):705-713.

The **NMDA receptor** channels play an important role in synaptic plasticity and synapse formation underlying memory, learning and formation of neural networks during development in the central nervous system(CNS). Overactivation of the receptor, causing excessive influx of Ca^{2+} can lead to excitotoxicity which is implied to be involved in some neurodegenerative disorders.



Pochwat, et al, Expert Opin. Investig. Drugs (2014) 23(9)

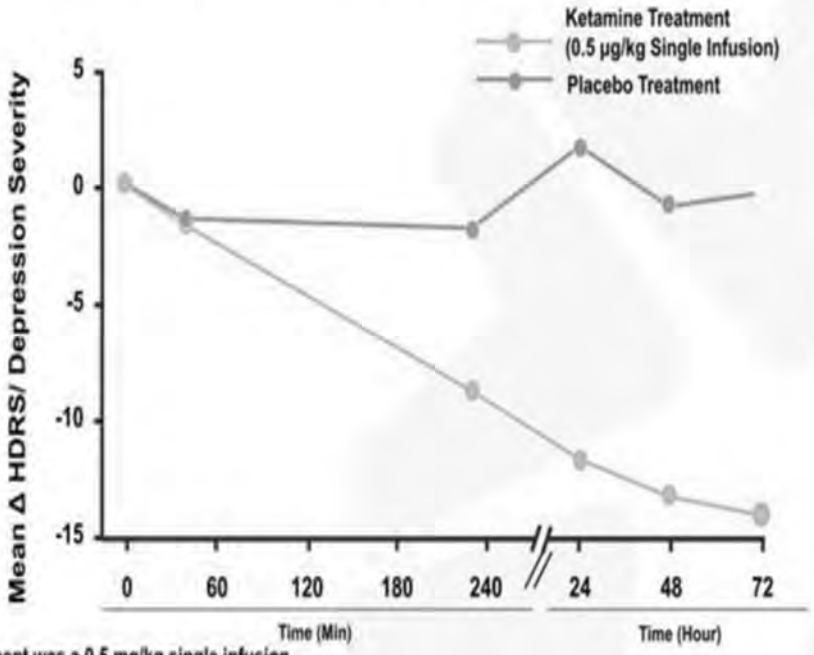
Ketamine Introduction

- Ketamine is a **structural analog** of the **dissociative anesthetic** and **recreational drug phencyclidine** (PCP)
- Chemist **Calvin Stevens first synthesized** ketamine in **1962**
- Ketamine was tested in **clinical trials** performed in **pediatric** and **adult surgical patients**, and the **FDA approved it for human use in 1970**
- Ketamine classifies as a **Class-III controlled substance** since 1999.
- Ketamine was involved in **0.12% of the United States Emergency Department visits in 2011.**
- Intramuscular and intravenous forms of ketamine are commonly used to provide **pediatric anesthesia**, especially for high-risk children or patients in **limited-resource settings**.
- **In surgical settings**, ketamine is **typically combined with benzodiazepines**, which can reduce the adverse psychological symptoms that occur during emergence.

Ketamine's Benefits

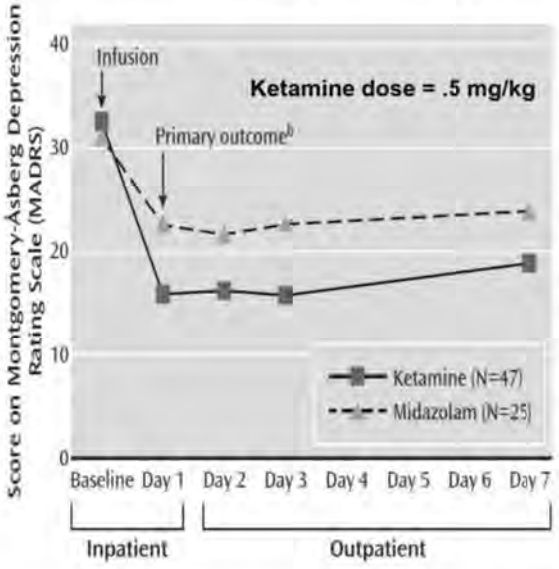
- Ketamine is an **essential medicine** used for **anaesthesia and analgesia (pain relief) in adults and children**, having been **listed on the WHO Essential Medicines** List since 1985.
- Ketamine is **safer to administer than other types of anaesthetic agents** and pain relief as it **does not depress breathing or lower blood pressure** and **does not require expensive patient-monitoring equipment.**
- **Its high level of safety makes it indispensable** for surgery **in low- and middle-income countries**, disaster situations and conflict zones.
- The **illicit use of ketamine has been reported on a relatively small global scale for several decades. Ketamine dependence or overdose is rare**, however chronic abuse can cause side effects including urinary tract problems.
- The **WHO Expert Committee on Drug Dependence has recommended that ketamine should not be controlled under the international drug control conventions** due to its essential role in surgery in low-resource countries and in emergencies.
- **Fact file on ketamine, WHO, 2016**

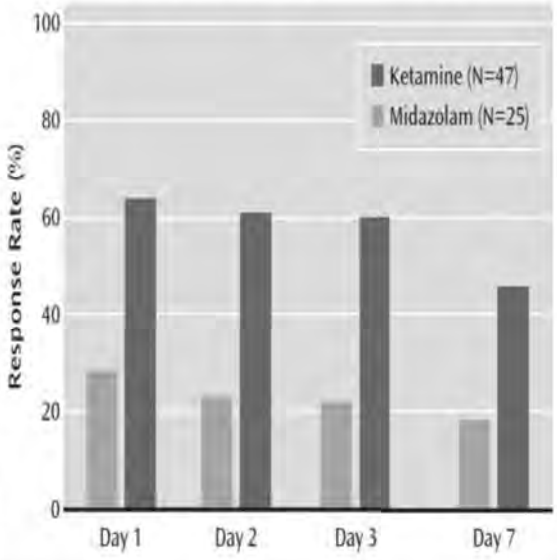
Antidepressant Actions of Ketamine



Ketamine treatment was a 0.5 mg/kg single infusion.
HDRS = Hamilton Rating Scale for Depression.
Berman RM, et al. *Biol Psychiatry*. 2000;47(4):351-354.

Single Ketamine Infusion is Superior to Psychoactive Control in TRD: Baylor/Mt Sinai Study (N = 72)





Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($P \leq .002$).

MADRS = Montgomery-Åsberg Depression Rating Scale.
Murrough JW, et al. *Am J Psychiatry*. 2013;170(10):1134-1142.

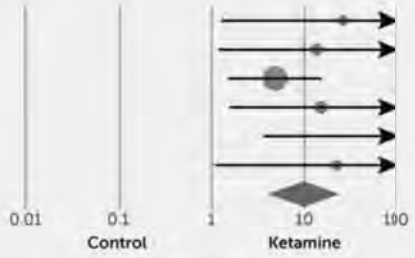
Single Infusion of Ketamine – Efficacy in TRD (N = 147)

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

Statistics for Each Study

Odds Ratio and 95% CI

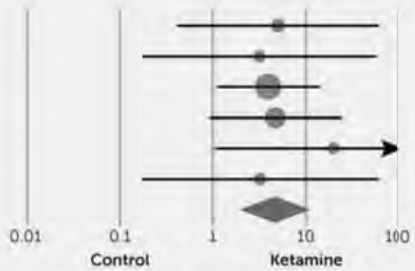


B **At 1 week**

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

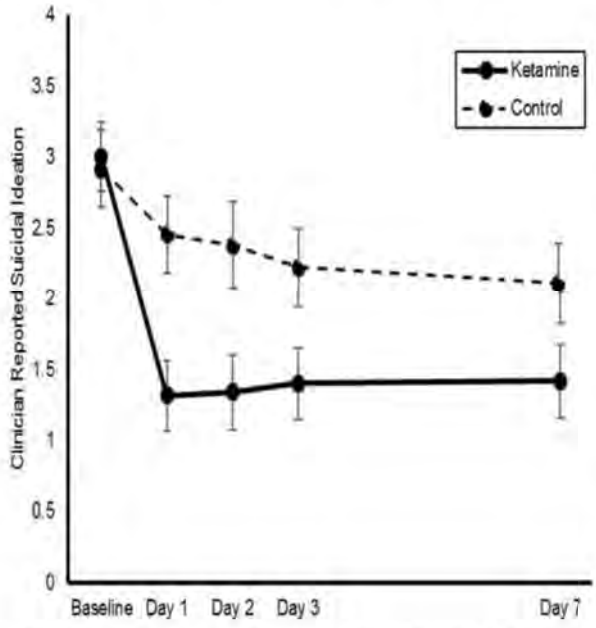
Statistics for Each Study

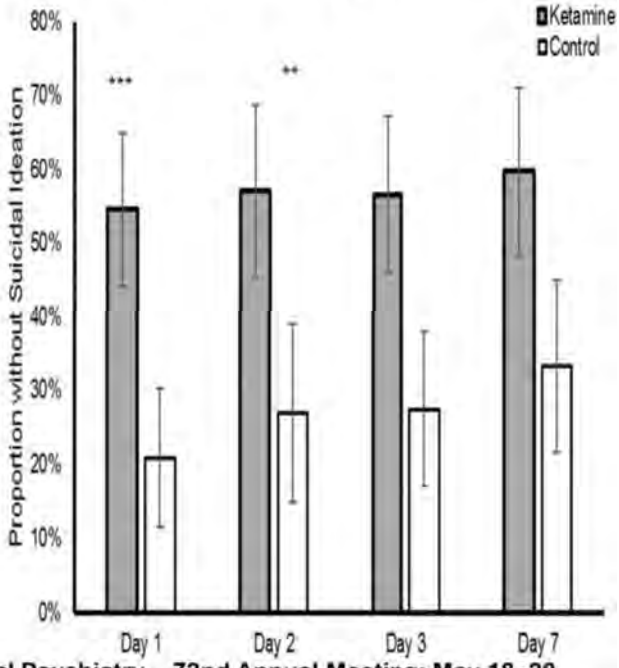
Odds Ratio and 95% CI



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

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

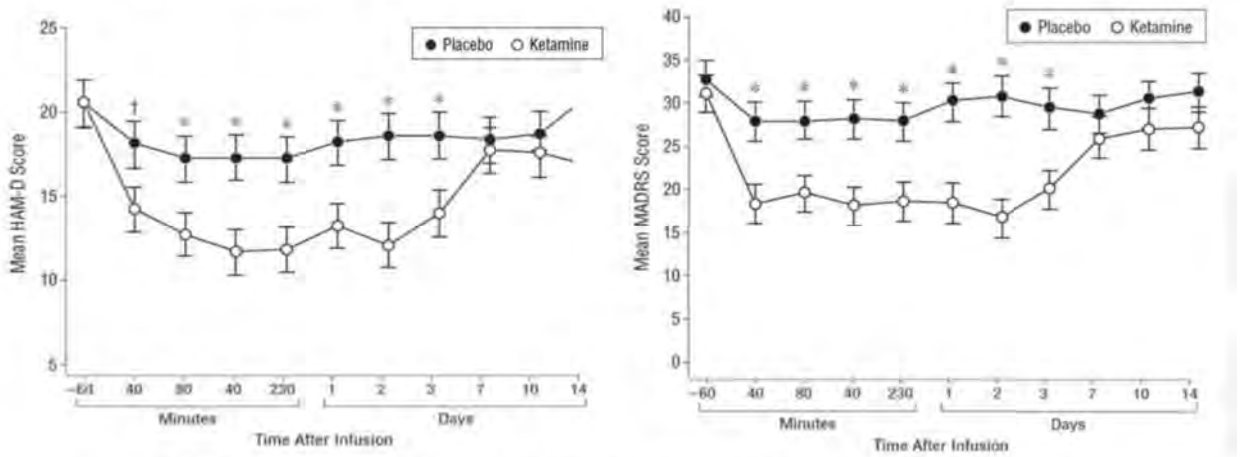




Wilkinson S, et al. Presented at: Society of Biological Psychiatry – 72nd Annual Meeting; May 18–20, 2017; San Diego, CA.

Add-on Trial of Ketamine in Treatment-Resistant Bipolar Depression

Dose: 0.5 mg/kg ketamine

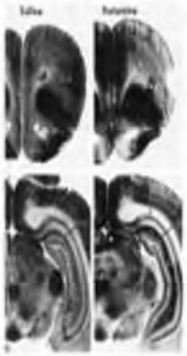


Depressive symptoms significantly improved in participants receiving ketamine compared with placebo

*$P < .001$; †$P < .01$.

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

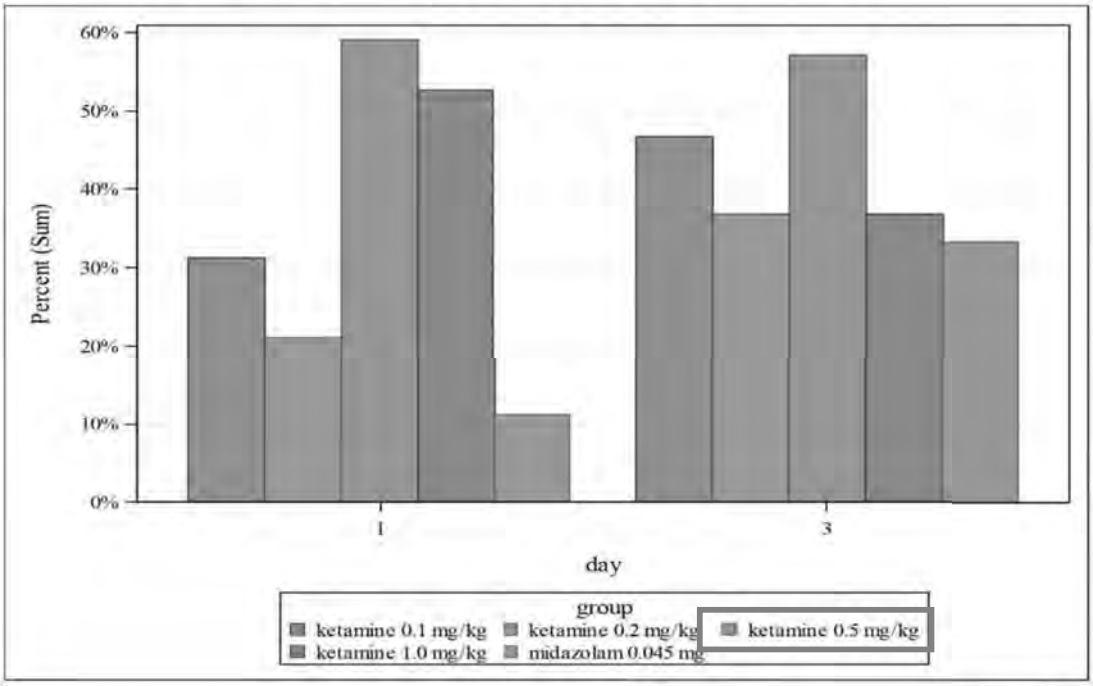
Dose-Response Effects of Ketamine on 2-DG Uptake in Rodents



Brain regions	Saline	Ketamine (35 mg/kg)	Ketamine (100 mg/kg)
Medial prefrontal cortex	497 ± 27	769 ± 36*	330 ± 42
Ventrolateral orbital cortex	513 ± 13	800 ± 38*	306 ± 35
Claustrum	503 ± 53	836 ± 45*	304 ± 32
Piriform cortex	576 ± 32	977 ± 58*	333 ± 36
Cingulate cortex	509 ± 36	739 ± 58*	295 ± 39
Somatosensory cortex, layers 2,3	544 ± 23	573 ± 41	293 ± 47
Somatosensory cortex, layer 4	594 ± 43	644 ± 47	302 ± 44
Somatosensory cortex, layer 6	475 ± 42	533 ± 43	293 ± 43
Retrosplenial cortex	585 ± 67	766 ± 23*	324 ± 38
Lateral septum	365 ± 33	411 ± 39	227 ± 36
Medial septum	463 ± 46	618 ± 61*	265 ± 44
Anteroventral thalamic n.	615 ± 43	815 ± 34*	361 ± 41
Ventroposterior medial thalamic n.	540 ± 25	677 ± 40*	301 ± 30
Paraventricular thalamic n.	328 ± 29	431 ± 22*	216 ± 28
Medial geniculate	583 ± 33	709 ± 26	305 ± 30
Hypothalamic paraventricular n.	374 ± 32	434 ± 23	227 ± 16
Corpus callosum	308 ± 26	346 ± 26	211 ± 30
Dentate gyrus	439 ± 52	576 ± 16*	281 ± 44
Hippocampus, CA1 stratum radiatum	393 ± 33	443 ± 15	252 ± 29
Hippocampus, CA3 stratum radiatum	405 ± 34	507 ± 21*	258 ± 26
Hippocampus, stratum lacunosum moleculare	513 ± 54	792 ± 39*	373 ± 39
Amygdala, basolateral n.	471 ± 47	652 ± 20*	296 ± 36
Amygdala, central n.	354 ± 52	431 ± 25	231 ± 33

Duncan GE, et al. *Brain Res.* 1998;787(2):181-190.

HAM-D-6 Response Rates

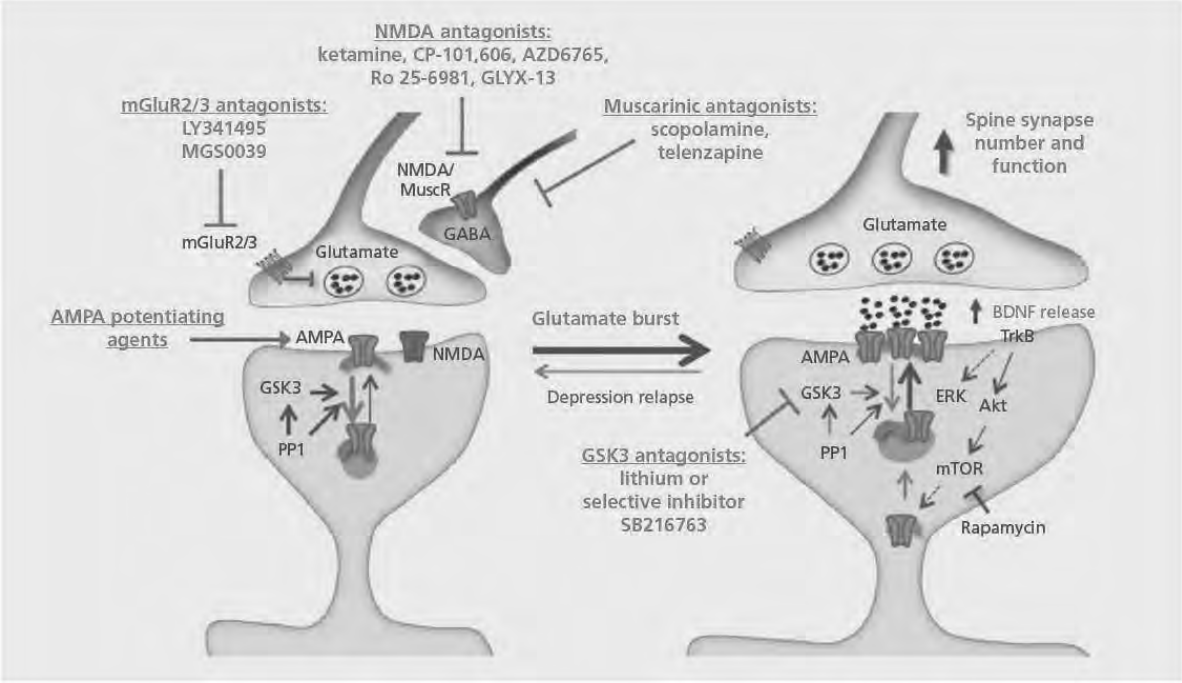


Fava M, et al. Presented at: American Society of Clinical Psychopharmacology Annual Meeting; May 29–June 2, 2017; Miami, FL.

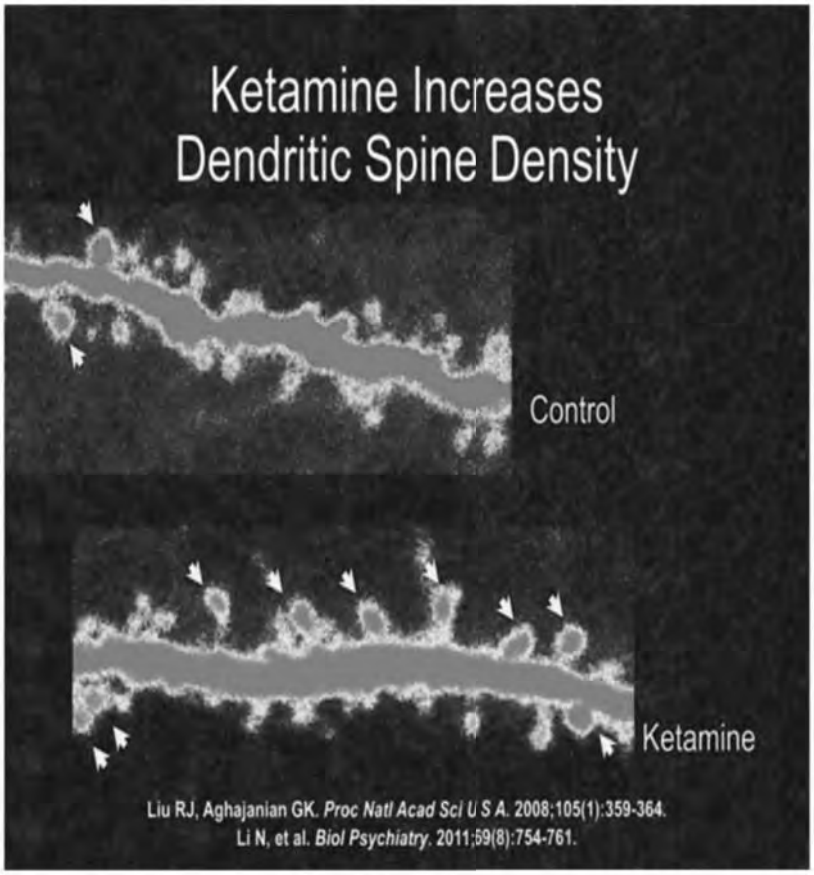
Randomized-Controlled Trial of Low-Dose Ketamine Adjunctive to ECT in TRD

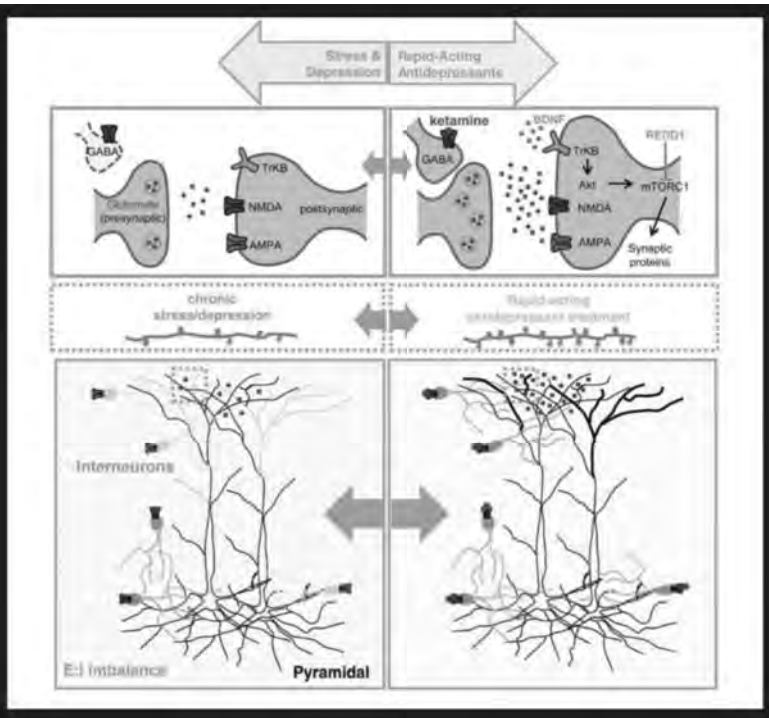
- **No benefit** of 0.5 mg/kg ketamine bolus (n = 40) in conjunction with standard anesthetic agent during a course of bitemporal ECT compared with placebo (n = 39)
- Primary Outcome: Hopkins Verbal Learning Test, Delayed Verbal Recall
- No benefit vs placebo on any efficacy outcome, including time-to-response and response at endpoint

Anderson IM, et al. *Lancet Psychiatry*. 2017;4(5):365-377.



Antidepressant remodeling of synaptic connections - Duman
Dialogues in Clinical Neuroscience - Vol 16 · No. 1 · 2014


Ketamine Increases
Dendritic Spine Density
Control
Ketamine
Liu RJ, Aghajanian GK. Proc Natl Acad Sci U S A. 2008;105(1):359-364.
Li N, et al. Biol Psychiatry. 2011;69(8):754-761.

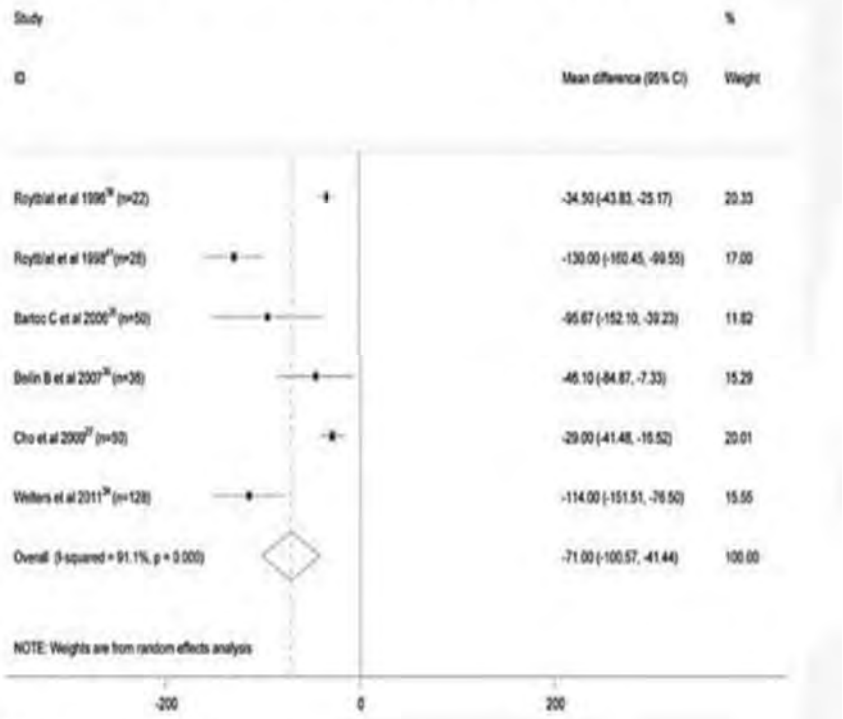


Gerhard and Duman, 2018

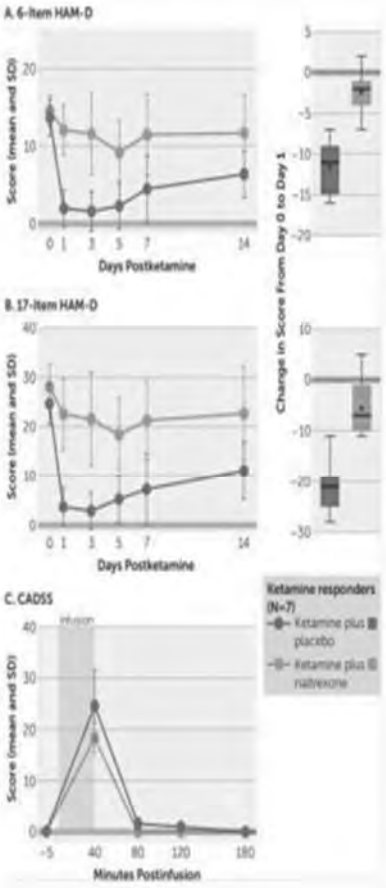
Rapid Antidepressant Effect Associated with Ketamine

Madhukar Trivedi

Anti-inflammatory Effects ?



Dale O, et al. *Anesth Analg*. 2012;115(4):934-943.



Opioid Effects?

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Nolan R. Williams, M.D., Boris D. Heifets, M.D., Ph.D., Christine Blasey, Ph.D., Keith Sudheimer, Ph.D., Jaspreet Sahnu, B.S., Heather Pankow, B.S., Jessica Hawkins, B.S., Justin Birnbaum, M.D., David M. Lyons, Ph.D., Carolyn I. Rodriguez, M.D., Ph.D., Alan F. Schatzberg, M.D. **Show Fewer Authors**

Journal of Neurochemistry JNC

ORIGINAL ARTICLE

Potentiation of μ-opioid receptor-mediated signaling by ketamine

Achla Gupta, Lakshmi A. Devi and Ivone Gomes

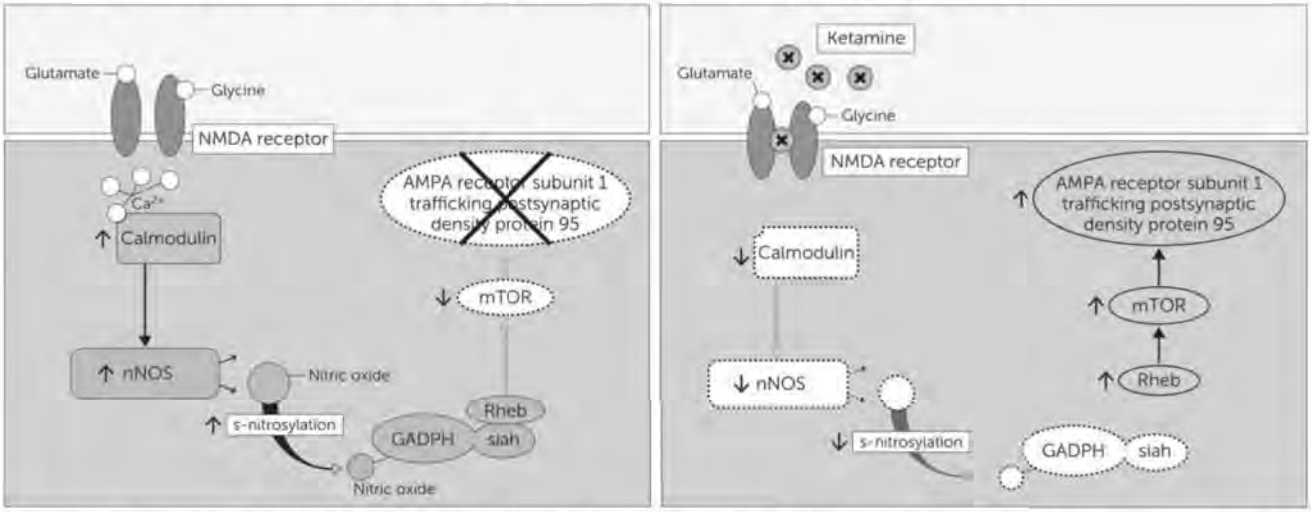
Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, New York, USA

Williams NR, et al. *Am J Psychiatry*. 2018 Aug 29;[Epub ahead of print].
Gupta A, et al. *J Neurochem*. 2011;119(2):294-302.

Explaining Naltrexone's Interference With Ketamine's Antidepressant Effect

Wang & Kaplin, Am J Psych 176:5, May 2019

FIGURE 2. Ketamine-induced antidepressant effects mediated by mammalian target of rapamycin (mTOR)[a]

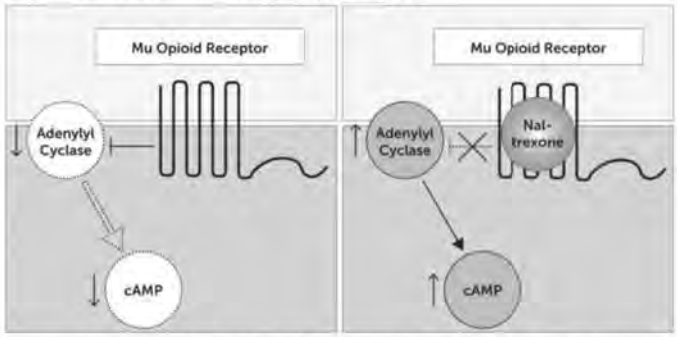


[a] Harraz et al. (4) established that inhibition of nitrergic RAS homolog enriched in brain (Rheb) degradation mediated ketamine's antidepressant effect. Under normal conditions, Ca^{2+} influx activates calmodulin and neuronal nitric oxide synthase (nNOS), resulting in s-nitrosylation ternary complex formation of GADPH-Siah1, which reduces mTOR activation. Blockade of Ca^{2+} influx by ketamine at the *N*-methyl-D-aspartate (NMDA) receptor inhibits nitrergic degradation of Rheb, allowing it to stimulate mTOR.

Explaining Naltrexone's Interference With Ketamine's Antidepressant Effect

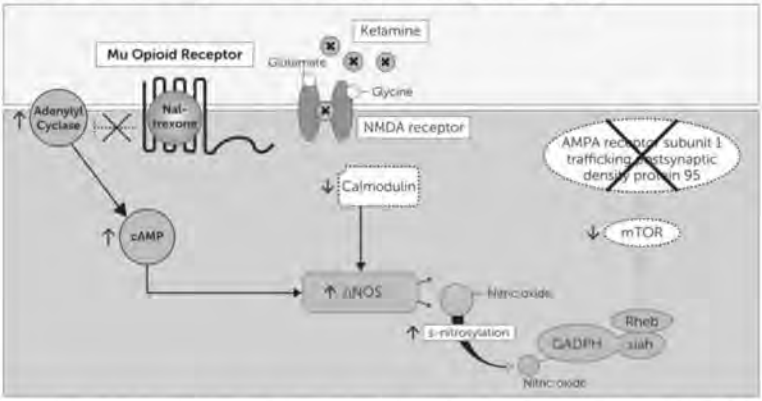
Wang & Kaplin, Am J Psych 176:5, May 2019

FIGURE 1. Naltrexone blocks the constitutive inhibition of mu opioid receptors[a]



[a] The mu opioid receptor constitutively inhibits cAMP signaling, which is reversed under withdrawal conditions or administration of an antagonist like naltrexone.

FIGURE 3. Naltrexone attenuates the antidepressant effects of ketamine through cAMP signaling[a]



[a] Antagonism of mu opioid receptors by naltrexone reduces the constitutive inhibition of cAMP. Subsequent elevation of cAMP activates neuronal nitric oxide synthase (nNOS), thus reactivating the nitrergic degradation of RAS homolog enriched in brain (Rheb).

Rigorous Translational Models Are Key to Studying Ketamine's Antidepressant Mechanism: Response to Wang and Kaplin

TO THE EDITOR: We thank Mr. Wang and Dr. Kaplin for elaborating in detail an interesting signaling mechanism that we briefly referenced in our article, one that could account for the involvement of both opioid and *N*-methyl-D-aspartate (NMDA) receptors in mediating ketamine's antidepressant effect. We fully agree that our data do not distinguish whether ketamine acts directly at opioid receptors, or indirectly, perhaps via enhanced release of endogenous opioids or by intracellular signaling crosstalk between opioid and NMDA receptors in the manner described by Mr. Wang and Dr. Kaplin.

Boris D. Heifets, M.D., Ph.D.
Nolan R. Williams, M.D.
Christine Blasey, Ph.D.
Keith Sudheimer, Ph.D.
Carolyn I. Rodriguez, M.D., Ph.D.
Alan F. Schatzberg, M.D.

Esketamine Studies We Did at JHH

- **TRD3003; Phase 3, 2017:** A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression. Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity **(SUSTAIN-1)**

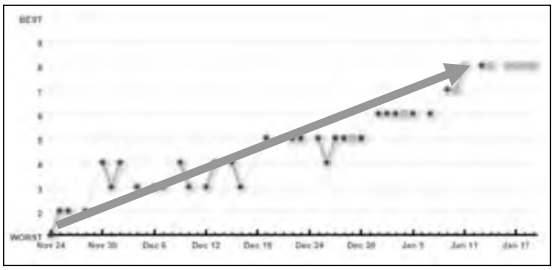
- **TRD3008; Phase 3, 2018:** An Open-label Long-term Extension Safety Study of Intranasal Esketamine in Treatment-resistant Depression. Safety and Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity **(SUSTAIN-3)**

- **SUI3001, Phase 2, 2016:** A double-blind, randomized, placebo controlled study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidality, in subjects assessed to be at imminent risk for suicide

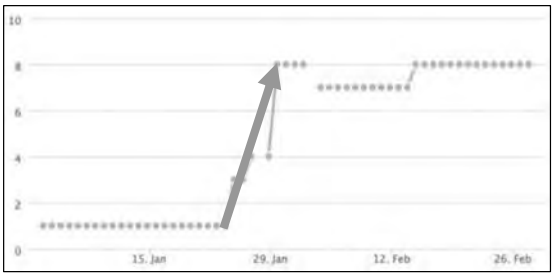
- **SUI3002; Phase 3, 2017:** A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide

Esketamine: FDA Approved March 2019 for TRD

Pros: Novel, Rapid, Treatment Resistant Depression, Suicidality



SSRI



Esketamine

Cons: New, Dissociation, Long-Term SE? Abuse Potential? Maintenance?

FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

February 12, 2019

Four phase 3 randomized controlled trials conducted and submitted under NDA 211243.

- **Trial Design**:
  - **Three trials** (3001, 3002, 3005) were of similar **short-term parallel group design**, and
  - **One** (3003) was a **randomized withdrawal maintenance-of-effect design.**
- **Outcome**:
  - In **two studies** (one parallel-group study and the other randomized withdrawal study), **esketamine was statistically superior to placebo** on study's primary efficacy endpoint;
  - In the other **two short-term parallel group studies, esketamine was not**.
- **Patient Populations**:
  - All studies were **international**, with about **a third of patients in the United Stat**es.
  - The **majority of subjects in all the studies were women in their 40s and 50s, white, with higher body mass index (BMI >24).**
  - **TRD**
    - 33 to 40% of enrolled subjects had failed three or more antidepressant (AD) treatments by the start of screening, and
    - 12 to 17% had failed at least four

Table 2: Esketamine Phase 3 Randomized Double-Blind Active-Controlled Studies

Study	Design	Arms	Dosing	Duration	Primary Endpoint	Patients Enrolled	Population
TRD3002 (TRANSFORM-2)	Parallel-Group	Flexible-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD both arms	Twice Weekly IN (Oral AD Daily)	4-week treatment phase, 24-week follow-up or TRD3003	Change from Baseline (CFB) in MADRS Total Score at Week 4	224 total (114 on ESK + oral AD; 110 on placebo + oral AD)	Adults (18 to 64 years) with TRD
TRD3003 (SUSTAIN-1)	Randomized Withdrawal	Flexible or Fixed-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD all arms	Twice Weekly IN during 4-week phase, then weekly for next 4 weeks, then weekly or every other week per response (Oral AD Daily)	4-week treatment initiated during open-label direct-entry phase or during 3001 or 3002. Then 12-week open-label optimization phase. Then ongoing maintenance phase post- randomization.	Time to relapse during maintenance phase for stable remitters	705 total (437 direct entry + 268 from 3001 or 3002); 176 during maintenance phase (90 on ESK + oral AD; 86 on placebo +oral AD).	Adults (18 to 64 years) with TRD
TRD3001 (TRANSFORM-1)	Parallel-Group	Fixed-Dose Esketamine (56 or 84 mg) vs. Placebo, + Oral AD all arms	Twice Weekly IN (Oral AD Daily)	4-week treatment phase, 24-week follow-up or TRD3003	Change from Baseline (CFB) in MADRS Total Score at Week 4	344 total (115 on ESK 56 mg + oral AD; 116 on ESK 84 mg + oral AD; 113 on placebo + oral AD)	Adults (18 to 64 years) with TRD
TRD3005 (TRANSFORM-3)	Parallel-Group	Flexible-Dose Esketamine (28 or 56 or 84 mg) vs. Placebo, + Oral AD both arms	Twice Weekly IN (Oral AD Daily)	4-week treatment phase, 24-week follow-up or TRD3004 (long-term safety study)	Change from Baseline (CFB) in MADRS Total Score at Week 4	137 total (72 on ESK + oral AD; 65 on placebo + oral AD)	Geriatric (65 years and older) with TRD

Table 3: Study 3002 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

Treatment Arm	N	Baseline MADRS Total Score (SD)	LS Mean Change from Baseline (SE) at Week 4	LS Mean Difference from Placebo (SE) at Week 4	1-Sided *p*-value <0.025
Placebo + Oral AD	109	37.3 (5.7)	-15.8 (1.2)	--	--
Esketamine + Oral AD	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (1.7)	**0.010**

Source: Study 3002 Clinical Study Report (CSR)

Figure 2: Study 3002 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

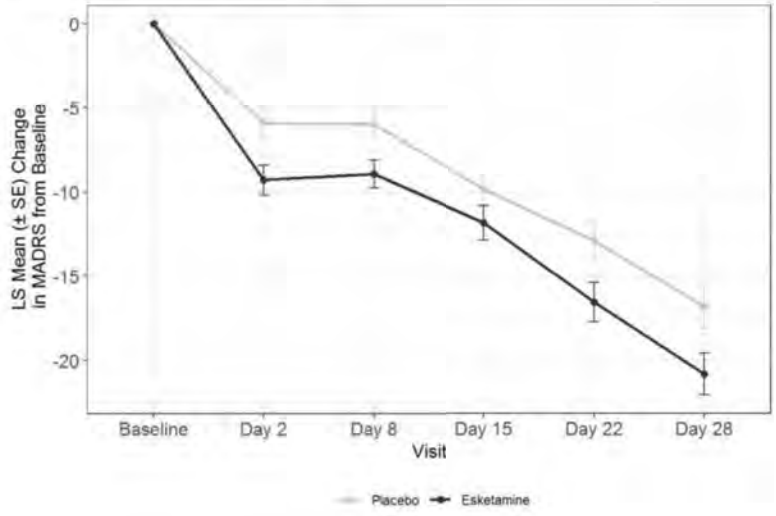


Table 5: Study 3003 Secondary Efficacy Endpoint of Time to Relapse in Stable Responders

	Esketamine + Oral AD	**Placebo + Oral AD**
Number Assessed	62	59
Number Censored	46 (74%)	25 (42%)
Number of Relapses	16 (26%)	34 (58%)
Time to Relapse (Days)		
25% percentile (95% CI)	217 (56 to 635)	24 (17 to 46)
Median (95% CI)	635 (264 to 635)	88 (46 to 196)
Hazard Ratio (HR) (95% CI)	0.30 (0.16 to 0.55)	--
2-sided p-value (<0.05)	**<0.001**	--

Source: Study 3003 CSR, NE=not estimable

Figure 5: Study 3003 Secondary Efficacy Endpoint of Time to Relapse in Stable Responders

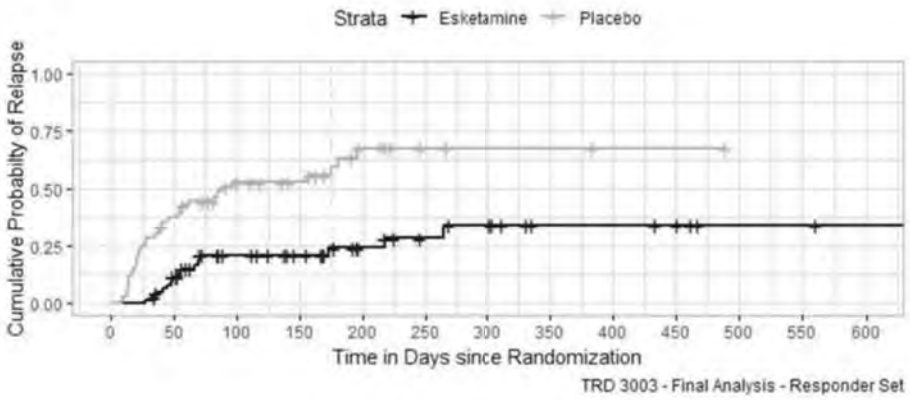
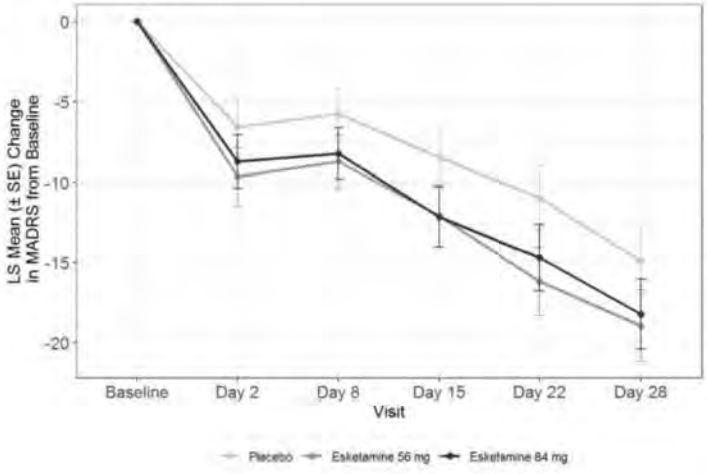


Table 6: Study 3001 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)

Treatment Arm	N	Baseline MADRS Total Score (SD)	LS Mean Change from Baseline (95% CI) at Week 4	LS Mean Difference from Placebo (95% CI) at Week 4	1-Sided *p*-value <0.025
Placebo+Oral AD	113	37.5 (6.2)	-14.9 (-17.4 to -12.4)	--	--
Esketamine 56 mg+Oral AD	115	37.4 (4.8)	-18.9 (-21.4 to -16.4)	-4.1 (-7.7 to -0.5)	*0.013*
Esketamine 84 mg+Oral AD	114	37.8 (5.6)	-18.2 (-20.9 to -15.6)	-3.2 (-6.9 to +0.5)	0.044

Source: Study 3001 CSR and Andrew Potter, PhD, Statistical Reviewer

Figure 8: Study 3001 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)



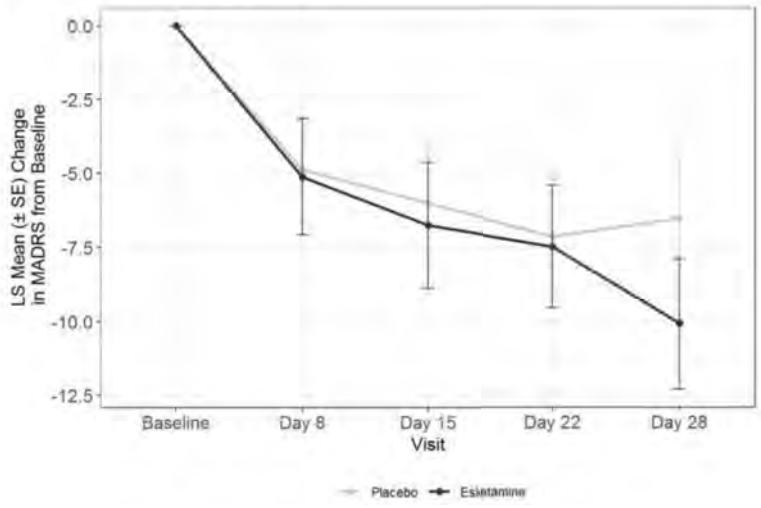
- How Did 3001 Not Meet 1◦ Endpoint?
- The esketamine 84-mg arm was prespecified as the first group to be tested, as it was the higher dose. Because the change from baseline on MADRS was not significantly different, the testing sequence stopped there, and the 56-mg treatment group could not be formally analyzed.
- 84 mg arm had a higher % of subjects with a history of failing three or more antidepressants:
  - 84 mg: 48%, 56 mg: 30%, PBO: 41%
- 56 mg arm did beat PBO.

Table 7: Study 3005 Primary Endpoint MADRS Total Score Change from Baseline at Day 28 Using MMRM (Full Analysis Population)

Treatment Arm	N	Baseline MADRS Total Score (SD)	LS Mean Change from Baseline (95% CI) at Week 4	LS Mean Difference from Placebo (95% CI) at Week 4	1-Sided *p*-value <0.025
Placebo + Oral AD	65	34.8 (6.4)	-6.5 (-9.4 to -3.6)	--	--
Esketamine + Oral AD	72	35.5 (5.9)	-10.1 (-13.1 to -7.1)	-3.6 (-7.2 to 0.07)	0.029

Source: Study 3005 CSR and Andrew Potter, PhD, Statistical Reviewer

Figure 10: Study 3005 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Population)



"Study 3005 does not appear to be supportive of an esketamine effect."

Suspicious to committee that response picked up between day 22 and 28?

Table 9: MADRS Score Change from Baseline for Prior Approved Antidepressants

Indication	Antidepressant	MADRS LS Mean CFB at Primary Endpoint Range	MADRS LS Mean CFB Difference from Placebo/Active Control	Baseline MADRS Score
MDD	Vortioxetine	-13 to -20	-2.8 to -7.1	31 to 34
	Vilazodone	-9.7 to -13	-2.5 to -3.2	31 to 32
	Levomilnacipran	-14 to -17	-1.3 to -4.9	30 to 36
Adjunctive MDD	Aripiprazole	-8.5 to -8.8	-2.8 to -3.0	31 to 32
	Brexpiprazole	-7.7 to -8.5	-1.3 to -3.1	33 to 35
	Quetiapine XR	-14 to -17	-1.6 to -4.1	28 to 32
TRD	Olanzapine + Fluoxetine (fixed-dose combination)	-8.6 to -14	n/a	23 to 30
	Fluoxetine (vs. Olanzapine + Fluoxetine)	-1.2 to -11	-1.4 to -12	"
	Olanzapine (vs. Olanzapine + Fluoxetine)	-2.8 to -10	-0.8 to -11	"
	Esketamine	**-10.1 to -20.8**	**-3.2 to -4.1**	**37 to 38 adult, 35 geriatric**

Source: DPP Antidepressant Study Database from Previously Approved NDAs

Side Effect Profile of Esketamine

Ranked by Incidence in Spravato Group

Symptom > 5%	Spravato	Placebo	Sprav-Pbo
Dissociation*	41%	9%	32.0%
Dizziness*	29%	8%	21.0%
Nausea*	28%	9%	19.0%
Vertigo*	23%	3%	20.0%
Sedation*	23%	9%	14.0%
Headache*	20%	17%	3.0%
Dysgeusia	19%	14%	5.0%
Hypoesthesia	18%	2%	16.0%
Anxiety	13%	6%	7.0%
Lethargy	11%	5%	6.0%
Blood pressure inc.	10%	3%	7.0%
Vomiting	9%	2%	7.0%
Insomnia	8%	7%	1.0%
Diarrhea	7%	6%	1.0%
Nasal discomfort	7%	5%	2.0%
Throat irritation	7%	4%	3.0%

Ranked by Incidence in Spravato-Placebo

Symptom > 5%	Spravato	Placebo	Sprav-Pbo
Dissociation*	41%	9%	32.0%
Dizziness*	29%	8%	21.0%
Vertigo*	23%	3%	20.0%
Nausea	28%	9%	19.0%
Hypoesthesia*	18%	2%	16.0%
Sedation*	23%	9%	14.0%
Anxiety*	13%	6%	7.0%
Blood pressure inc	10%	3%	7.0%
Vomiting	9%	2%	7.0%
Lethargy	11%	5%	6.0%

Management of Side Effects

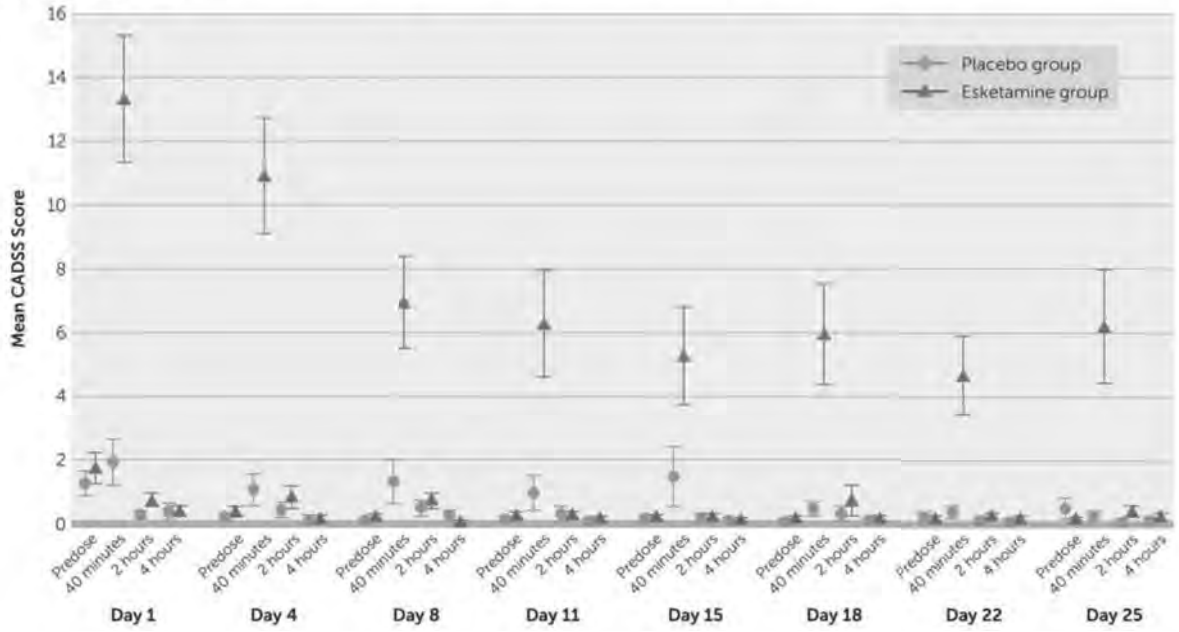
- Nausea (28%):
  - Zofran, Reglan
- Dizziness/Sedation (29%/23%):
  - Quiet room
  - Reclining
  - Enya
- Dissociation (41%):
  - Set expectations
    - 40 min to max, 2 hours to abate
  - Supportive environment

Treatment of Ketamine Overdose Literature

- **Benzodiazepines**: such as lorazepam and diazepam can alleviate **agitation, psychomimetic effects, hypertension, hyperthermia, and seizures.**
  - Lorazepam is typically given 2 to 4 mg IV, or IM, and
  - Diazepam dosing generally is 5 to 10 mg IV.
- **Butyrophenones** including haloperidol have been used to treat **psychotic episodes and agitation**.
  - Haloperidol is typically given in doses of 5 to 10 mg IM and can be administered every 10 to 15 minutes until achieving adequate sedation.
  - However, providers should exercise caution when using haloperidol, as lowered seizure thresholds, QT prolongation and torsades de pointes correlate with the prolonged use of haloperidol.
- **Alpha2-agonists** such as clonidine can treat or prevent ketamine's **psychomimetic side effects, increase hemodynamic stability by decreasing blood pressure**, and provide synergism with ketamine's analgesic effects.
  - Clonidine is typically given at 2.5 to 5 mcg/kg in oral form, though patches are an option for long-duration inpatient infusions and IV clonidine can be used to address acute symptoms.
- **Minimize Stiumulation:** Unnecessary stimulation should be avoided, and the patient's room should be dim and quiet.

Dissociative Side Effects Decrease After First 2-3 Doses

FIGURE 5. Mean Clinician-Administered Dissociative States Scale (CADSS) Scores Over Time During the Double-Blind Phase in a Study of Intranasal Esketamine for Rapid Reduction of Symptoms in Patients at Imminent Risk for Suicide Who Received Standard-of-Care Treatment[a]



Is Death a Side Effect?

- **There were six deaths in the esketamine for treatment-resistant depression development program as of January 8, 2019, all in esketamine-treated subjects. Total number of subjects: 562 Esketamine + 437 Placebo = 999**
- **Three of these deaths were by suicide— two well after the patient's last dose of esketamine (12 and 20 days), and one 4 days after the patient's last dose of esketamine.**
  - 12 days after last dose:
    - Appeared to be improving based on their MADRS scores from baseline of 27 to 9.
    - C-SSRS score of 0, at baseline and at the visit prior to his death.
  - 4 days after last dose:
    - Appeared to be improving based on their MADRS scores from baseline 41 to 25.
    - C-SSRS score was not available.
  - 20 days after his last dose:
    - Was experiencing worsening symptoms from MADRS 7, 13 days prior to death to MADRS 21, 6 days prior to death.
    - C-SSRS score of 0, at baseline and at the visit prior to his death.
  - Given the small number of cases, the severity of the patients' underlying illness, and the lack of a consistent pattern among these cases, it is difficult to consider these deaths as drug related.
- **Of the remaining three cases,**
  - Motorcycle accident:
    - 26 hours after the patient's last dose of esketamine.
    - Given the timing of sedation-related adverse events in the clinical development program and the data from the driving studies,
    - It seems unlikely that esketamine played a role in this accident.
  - Obese 60-year-old man with HTN:
    - died suddenly on study day 113.
    - At his last study visit 5 days prior to death, his blood pressure, heart rate, and pulse oximetry were all within normal limits before and after receiving esketamine.
    - It seems unlikely that this death was drug-related.
  - 74-year-old woman h/o HTN and hyperlipidemia
    - died of myocardial infarction 6 days after last dose of esketamine.
    - Esketamine-induced increases in blood pressure normally last for less than 4 hours post-dose; therefore, the myocardial infarction is not likely related to elevated blood pressure.

Spravato Instructions from the Website: www.spravato.com

- SPRAVATO™ Dosing
  - SPRAVATO™ is taken with a daily oral antidepressant
  - You administer SPRAVATO™ nasal spray yourself under the supervision of a healthcare professional at a certified SPRAVATO™ treatment center
  - SPRAVATO™ is taken twice a week for the first four weeks
  - After the first four weeks, SPRAVATO™ is taken once a week for a month
  - After this, SPRAVATO™ is usually taken either once a week or once every two weeks
- After Treatment
  - A healthcare professional will monitor you for at least two hours.
  - You won't be able to drive or operate machinery that requires you to be completely alert until the next day, following a restful sleep.
  - So you'll need to plan for rides on treatment days.

Instructions for Use

SPRAVATO™
(SPRAH VAH' TOE)
(esketamine)

Important

This device is intended for administration by the patient, **under supervision of a healthcare professional**. Read this Instructions for Use in full before training and supervising patient.

Need help?

For additional assistance or to share your feedback call 800-JANSSEN (800-526-7736).

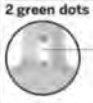
Nasal Spray Device

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)



1 green dot

No green dots
Two sprays (28 mg) delivered

Step 1 Get ready

Before first device only:

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

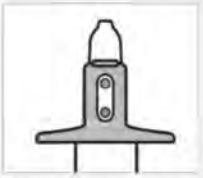
Confirm required number of devices.

56 mg = 2 devices
84 mg = 3 devices

Step 2 Prepare device

Healthcare professional:

- Check expiration date ("EXP"). If expired, get a new device.
- Peel blister and remove device.



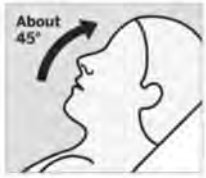
Healthcare professional:

- Do not prime device. This will result in a loss of medication.
- Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.
- Hand device to patient.

Step 3 Prepare patient

Instruct the patient to:

- Hold device as shown with the thumb gently supporting the plunger.
- **Do not** press the plunger.



Instruct the patient to:

- Recline head at about **45 degrees** during administration to keep medication inside the nose.

Step 4 Patient sprays once into each nostril

Instruct the patient to:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.

Instruct the patient to:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.

Instruct the patient to:

- **Sniff gently** after spraying to keep medication inside nose.

Instruct the patient to:

- Switch hands to insert tip into the **second nostril**.
- Repeat Step 4 to deliver second spray.

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.

Disposal

Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Renaissance Lakewood LLC
Lakewood, NJ 08701

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Revised: March 2019

cp-81317v1

janssen

Spravato (esketamine) C-III nasal spray

SPRAVATO™ REMS

Healthcare Setting Enrollment Form

janssen

SPRAVATO™ is only available through the SPRAVATO™ REMS (Risk Evaluation and Mitigation Strategy). Only Pharmacies and Healthcare Settings that are certified in the SPRAVATO™ REMS can receive SPRAVATO™.

To become a SPRAVATO™ REMS certified Healthcare Setting, enroll by following these 3 steps:

STEP 1: REVIEW	STEP 2: COMPLETE AND SIGN	STEP 3: SUBMIT
➤ Designate an Authorized Representative ➤ The Authorized Representative must review the following: • Prescribing Information	➤ The Authorized Representative must complete the Healthcare Setting Enrollment Form ➤ If the designated Authorized Representative changes, the new Authorized Representative must enroll and complete these 3 steps	➤ Submit the Healthcare Setting Enrollment Form either: • Online at www.SPRAVATOrems.com. or • Print and fax completed form to 1-877-778-0091

SPRAVATO™ REMS Fact Sheet

What is the SPRAVATO™ REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has determined that a REMS is necessary to ensure that the benefits of SPRAVATO™ outweigh the potential risks.

The goal of the REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO™ administration, and abuse and misuse of SPRAVATO™ by:

- Ensuring that SPRAVATO™ is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients
- Ensuring pharmacies and healthcare settings that dispense SPRAVATO™ are certified
- Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrollment of all patients in the REMs (registry) to further characterize the risks and support safe use

SPRAVATO™ is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after SPRAVATO™ administration. SPRAVATO™ must never be dispensed directly to a patient for home use.

What are the SPRAVATO™ REMS requirements?

SPRAVATO™ is available only through a limited distribution program that is part of the SPRAVATO™ REMS. All healthcare settings and pharmacies are required to enroll in the SPRAVATO™ REMS via a designated authorized representative before they can purchase product from a distributor, dispense, or supervise administration of SPRAVATO™. All patients must also be enrolled in the SPRAVATO™ REMS before they can receive SPRAVATO™.

How can healthcare settings and/or pharmacies obtain SPRAVATO™ for patients?

To order, dispense, prescribe, and/or supervise administration of SPRAVATO™, the healthcare setting and/or pharmacy must be certified in the SPRAVATO™ REMS.

To become certified, the healthcare setting or pharmacy must:

1. Designate an "authorized representative" to complete the ***SPRAVATO™ REMS Healthcare Setting Enrollment Form*** and/or ***SPRAVATO™ REMS Pharmacy Enrollment Form*** and submit it to the SPRAVATO™ REMS.
2. Healthcare settings and pharmacies must establish appropriate policies and procedures, and train relevant staff involved in the prescribing, dispensing and administering, and handling of SPRAVATO™ to ensure that product is delivered/dispensed directly to a healthcare provider at the site of care and not dispensed directly to a patient to take home.
3. Healthcare settings must further establish policies and procedures and train relevant staff on the following steps to comply with REMS requirements:
    a. Counsel and enroll patients in the SPRAVATO™ REMS
    b. Ensure that administration of SPRAVATO™ is under the direct observation by a healthcare provider
    c. Ensure that patients are monitored by a healthcare provider for at least 2 hours post-administration
    d. Report relevant information back to the SPRAVATO™ REMS using the *Patient Monitoring Form*

Patient Information

First Name*:	MI:	Last Name*:	Birthdate*: (MM/DD/YYYY):	Sex*: ☐ M ☐ F ☐ Other

Email*: (Email is required for online enrollment only)	Phone Number*:
Address 1*:	Address 2:

City*:	State*:	ZIP*:

Patient Agreement

By signing this form, I understand and acknowledge that:

Before my treatment begins, I will:

- Enroll in the SPRAVATO™ REMS by completing this *Patient Enrollment Form* with my healthcare provider. Enrollment information will be provided to the REMS.
- Agree to receive counseling on the risks and the need for monitoring for resolution of sedation and dissociation, and for any changes in my vital signs.

During treatment I will:

- Use the SPRAVATO™ nasal spray myself under the direct observation of a healthcare provider.
- Be observed at the healthcare setting where I get SPRAVATO™ for at least 2 hours after each treatment until the healthcare provider determines I am ready to leave the healthcare setting.

I understand:

- Sedation and dissociation can result from treatment with SPRAVATO™ and I must stay after each treatment. Until these effects resolve, I may feel:
  - sleepy and/or
  - disconnected from myself, my thoughts, feelings and things around me.
- I should make arrangements to safely leave the healthcare setting and get home.
- I should not drive or use heavy machinery for the rest of the day on which I receive SPRAVATO™.
- I should contact my doctor or inform him/her at my next visit if I believe I have a side effect or reaction from SPRAVATO™.
- In order to receive SPRAVATO™, I am required to be enrolled in the REMS, and my information will be stored in a database of all patients who receive SPRAVATO™ in the United States.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may contact me via phone, mail, fax, or email to support administration of the REMS.
- Janssen Pharmaceuticals, Inc. and its agents, including trusted vendors, may use, disclose, and share my personal health information for the purpose of the operations of the REMS, including enrolling me into the REMS and administering the REMS, coordinating the dispensing of SPRAVATO™, and releasing and disclosing my personal health information to the Food and Drug Administration (FDA), as necessary, and as otherwise required by law.

Authorized Representative Information

First Name*:	MI:	Last Name*:

Credentials*:
☐ Physician ☐ Physician Assistant ☐ Nurse Practitioner ☐ Pharmacist ☐ Nurse ☐ Other: _____

Telephone Number*:	EXT:	Fax*:	Email Address*:

Alternate Contact

First Name:	Last Name:

Telephone Number:	EXT:	Fax:	Email Address:

Healthcare Setting Authorized Representative Agreement

I am the Authorized Representative designated by my Healthcare Setting to oversee implementation and coordinate the activities of the SPRAVATO™ REMS.

By signing this form, I agree, on behalf of myself and my Healthcare Setting, to comply with the following requirements:

I will:

- Review the SPRAVATO™ Prescribing Information.
- Enroll in the SPRAVATO™ REMS by completing this *Healthcare Setting Enrollment Form* and submitting this form to the SPRAVATO™ REMS.
- Have a prescriber onsite during SPRAVATO™ administration and monitoring.
- Have a healthcare provider(s) onsite to monitor each patient for at least 2 hours following administration of SPRAVATO™ for resolution of sedation and dissociation, and changes in vital signs.
- **Train** all relevant staff involved in prescribing, dispensing, and administering SPRAVATO™ and **establish processes and procedures** to ensure that the following take place in my Healthcare Setting:
  - A healthcare provider counsels the patient on the need for enrollment, monitoring, and risks of sedation and dissociation, and changes in vital signs prior to receiving SPRAVATO™.
  - All patients are enrolled in the SPRAVATO™ REMS by completing and submitting the *Patient Enrollment Form*.
  - Verify the patient is enrolled in the REMS before dispensing SPRAVATO™ for patient self-administration.
  - The patient self-administers SPRAVATO™ under the direct supervision of a healthcare provider.
  - A healthcare provider monitors every patient for at least 2 hours for resolution of sedation and dissociation and changes in vital signs after every dose.
  - A *Patient Monitoring Form* is submitted to the SPRAVATO™ REMS for every patient within 7 calendar days following administration of every dose.
  - SPRAVATO™ is not dispensed for use outside the Healthcare Setting.
- Have any new Authorized Representative enroll in the REMS by completing the *Healthcare Setting Enrollment Form*.
- Do not distribute, transfer, loan, or sell SPRAVATO™.
- Maintain records documenting staff's completion of training.
- Maintain records that all processes and procedures are in place and are being followed.
- Maintain records on all shipments of SPRAVATO™ received and dispensing information including the patient name, dose, number of devices and date administered.
- Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

Spravato™ (esketamine) CIII nasal spray

SPRAVATO™ REMS
Patient Monitoring Form

janssen pharmaceutical companies of Johnson & Johnson

Patient Information (PRINT)			
First Name*:	Middle Initial:	Last Name*:	Birthdate* (MM/DD/YYYY):

Concomitant Medication		
Is the patient currently taking any of the following concomitant medication(s) that may cause sedation or blood pressure changes?		
• benzodiazepines	☐ Yes	☐ No
• non-benzodiazepine sedative hypnotics	☐ Yes	☐ No
• psychostimulants	☐ Yes	☐ No
• monoamine oxidase inhibitors (MAOIs)	☐ Yes	☐ No

Healthcare Setting and Healthcare Provider Information (PRINT)		
First Name*:	Last Name*:	
Phone*:	Email*:	
Healthcare Setting Name*:		
Healthcare Setting Address 1*:	Healthcare Setting Address 2:	
City*:	State*:	ZIP*:

Treatment Session Information

Date _____MM/ _____DD/_____YYYY		Dose _____28 mg _____56 mg _____84 mg
Time at start of administration: _____:_____ AM / PM	**Patient must be monitored for at least 2 hours**	Time of discharge: _____:_____ AM/PM

☐ I confirmed vital signs (BP, HR, RR) were in an acceptable range **prior to SPRAVATO™ administration.**

☐ I confirmed vital signs were in an acceptable range **prior to patient discharge.**

BP prior to administration	BP 40 minutes post administration	BP prior to discharge
_____mmHg	_____mmHg	_____mmHg

Was the patient clinically ready for discharge **prior to the required 2 hours**? ☐ Yes ☐ No

If Yes, when was the patient ready for discharge? _____minutes from start of administration

If No, use the below sections to describe as appropriate

Sedation and Dissociation

Did the patient experience sedation or dissociation?

Sedation ☐ Yes ☐ No	If yes, indicate onset of symptoms from start of administration ☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins Did symptom resolve within 2 hours of administration? ☐ Yes ☐ No If greater than 2 hours, specify total time since administration _____
Dissociation ☐ Yes ☐ No	If yes, indicate onset of symptoms from start of administration ☐ 1-29 mins ☐ 30-59 mins ☐ 60-89 mins ☐ 90-120 mins Did symptom resolve within 2 hours of administration? ☐ Yes ☐ No If greater than 2 hours, specify total time since administration _____

Serious Adverse Events

Did the patient experience a serious adverse event during this treatment session or since the last treatment session? A serious adverse event is one which is any undesirable experience associated with the use of SPRAVATO™ that resulted in patient hospitalization, a disability or permanent damage, death, required medical intervention, or was life threatening.

Serious Adverse Event	Occurrence	Date of Event MM/DD/YYYY	The event resulted in: (check all that apply)	Did the event resolve?
	☐ During this treatment session ☐ Since the last treatment session		☐ Hospitalization ☐ Disability or permanent damage ☐ Medical Intervention ☐ Life threatening ☐ Death	☐ Yes ☐ No ☐ Unknown
	☐ During this treatment session ☐ Since the last treatment session		☐ Hospitalization ☐ Disability or permanent damage ☐ Medical Intervention ☐ Life threatening ☐ Death	☐ Yes ☐ No ☐ Unknown
	☐ During this treatment session ☐ Since the last treatment session		☐ Hospitalization ☐ Disability or permanent damage ☐ Medical Intervention ☐ Life threatening ☐ Death	☐ Yes ☐ No ☐ Unknown

Janssen Pharmaceuticals, Inc., Safety Department may follow-up to obtain more information about these events.

Future Directions: The Known Unknowns

- Will Esketamine continue to be effective in real world clinical use?
- Will Esketamine lead to increased drug use disorders?
- What is safety of Esketamine when patient population goes from 1000 to 100,000? TRD vs SI MDD?
- Known Patient Populations:
  - How long should Esketamine be used/tapered? Optimal dosing strategy? Optimal patient population? Predictors of response? Tx Combinations--Lock in benefits?
- Other Patient Populations:
  - BPAD, SCZ, Psychotic Mood Disorders, SUD +/- Mood Disorders, Chronic Pain, Others?
- Mechanism of Action:
  - How important is anti-inflammatory component of effect.
  - What of immune-mediated MDD?
  - How similar to ECT is Ketamine?

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- Cody Benoit-RC
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- **Manisha Hong-** IDS
- Mike Amy-ORA

Questions?

- AK@JHMI.EDU