Ketamine: Novel Target Engagement in Treatment of Depression and Suicidal Ideation

Paul M. Kim, M.D., Ph.D.
Assistant Professor
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine

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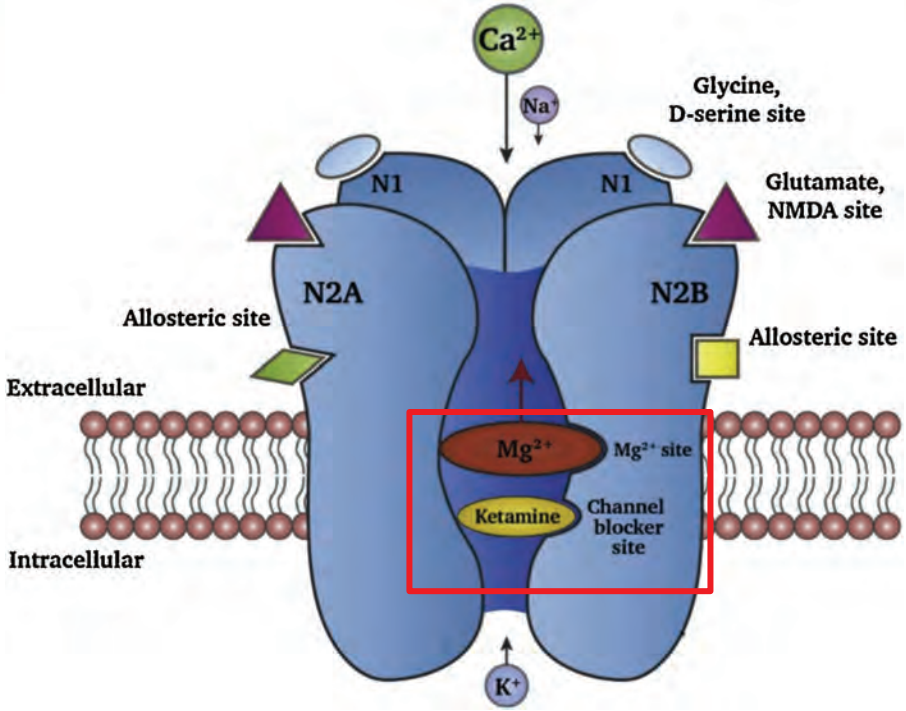
Disclosures

- **No financial disclosure or conflict of interest relevant to the presented materials in this talk**

Outline

- **Background/Science**
- **Clinical Trials and Real-World Outcomes**
- **Future Directions/Considerations**

NMDA/Glutamate Receptor Hypothesis



- In 1959, D-cycloserine, an antibiotic, showed antidepressant effects
- In 1990s, the N-methyl-D-aspartate (NMDA) receptor/glutamatergic signaling hypothesis gained support

Kokane, SS, et. al. J Behav Brain Res, 2020

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

EJP 51446

Functional antagonists at the NMDA receptor complex exhibit antidepressant actions

Ramon Trullas and Phil Skolnick

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

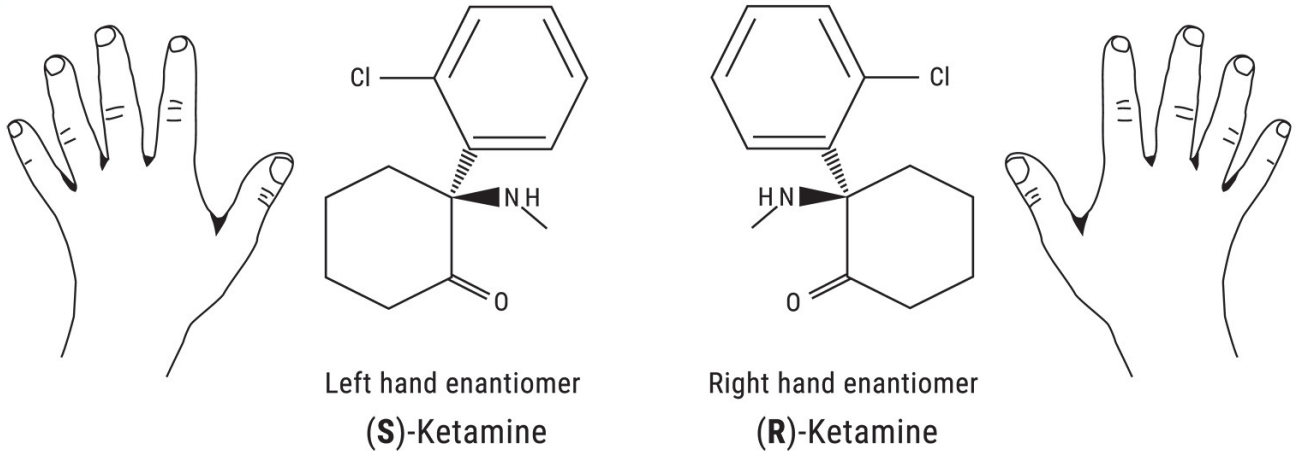
TABLE 1

Effects of AP-7 and MK-801 on swim-induced immobility and ambulatory activity in an open field. MK-801 and AP-7 were administered i.p. to male NIH-HSD mice 15 min and 30 min before testing, respectively. Controls received an equivalent volume of the corresponding vehicle. Immobility (s) during forced swim and ambulatory activity (s) in an open field were measured as described in Methods. Values represent X ± S.E.M. with the number of animals in parentheses. Doses are in mg/kg.

Drug	Dose	Immobility	%δ	Activity	%δ
Control	–	144 ± 6 (28)		145 ± 5 (9)	
AP-7	40	141 ± 21 (7)		144 ± 5 (4)	
	80	153 ± 9 (10)		167 ± 16 (3)	
	100	93 ± 8 [a] (20)	−35	153 ± 5 (11)	
	200	55 ± 13 [b,c] (11)	−62	134 ± 10 (17)	
Control	–	140 ± 12 (8)		150 ± 10 (8)	
MK-801	0.1	80 ± 10 [a] (8)	−43	144 ± 4 (8)	
	0.5	11 ± 4 [a,b] (8)	−92	201 ± 3 [a,b] (8)	+34
	1	64 ± 23 [a] (8)	−54	170 ± 14 (8)	

[a] Significantly different from control group; [b] significantly different from all other groups ($P < 0.05$, Student-Newman-Keuls test).

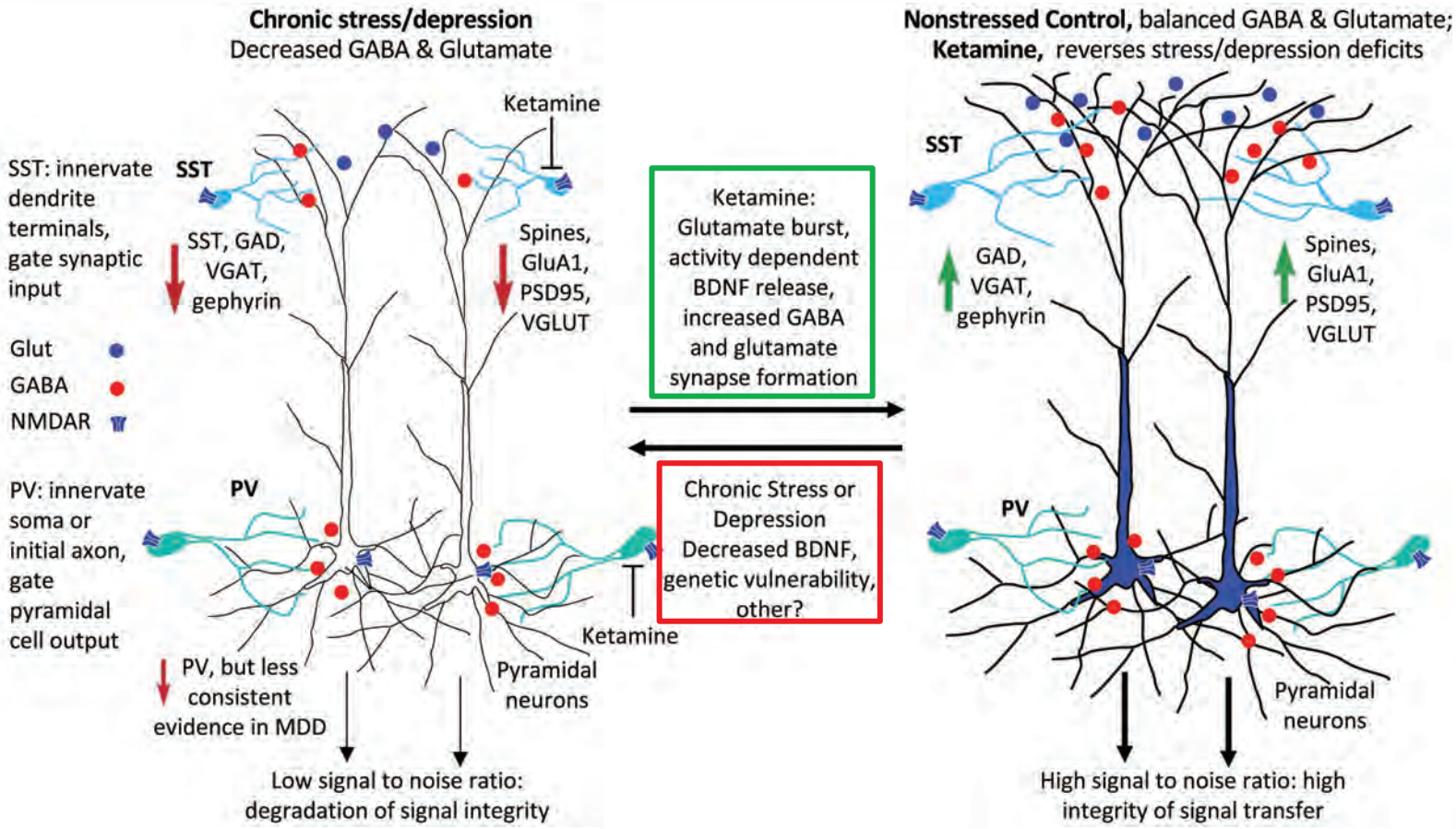
Ketamine



- Ketamine binds to the NMDA receptor
- Inhibits NMDA receptor activation → hallucination/dissociation
- Approved in 1970s as a dissociative anesthetic
- (S)-ketamine (esketamine) has greater binding affinity to the NMDA receptor (R)-ketamine (arketamine) and thus increased potency at NMDA receptor
- In 2019, esketamine (Spravato) was approved for TRD
- In 2020, esketamine was approved for MDD with suicidal ideation and behavior

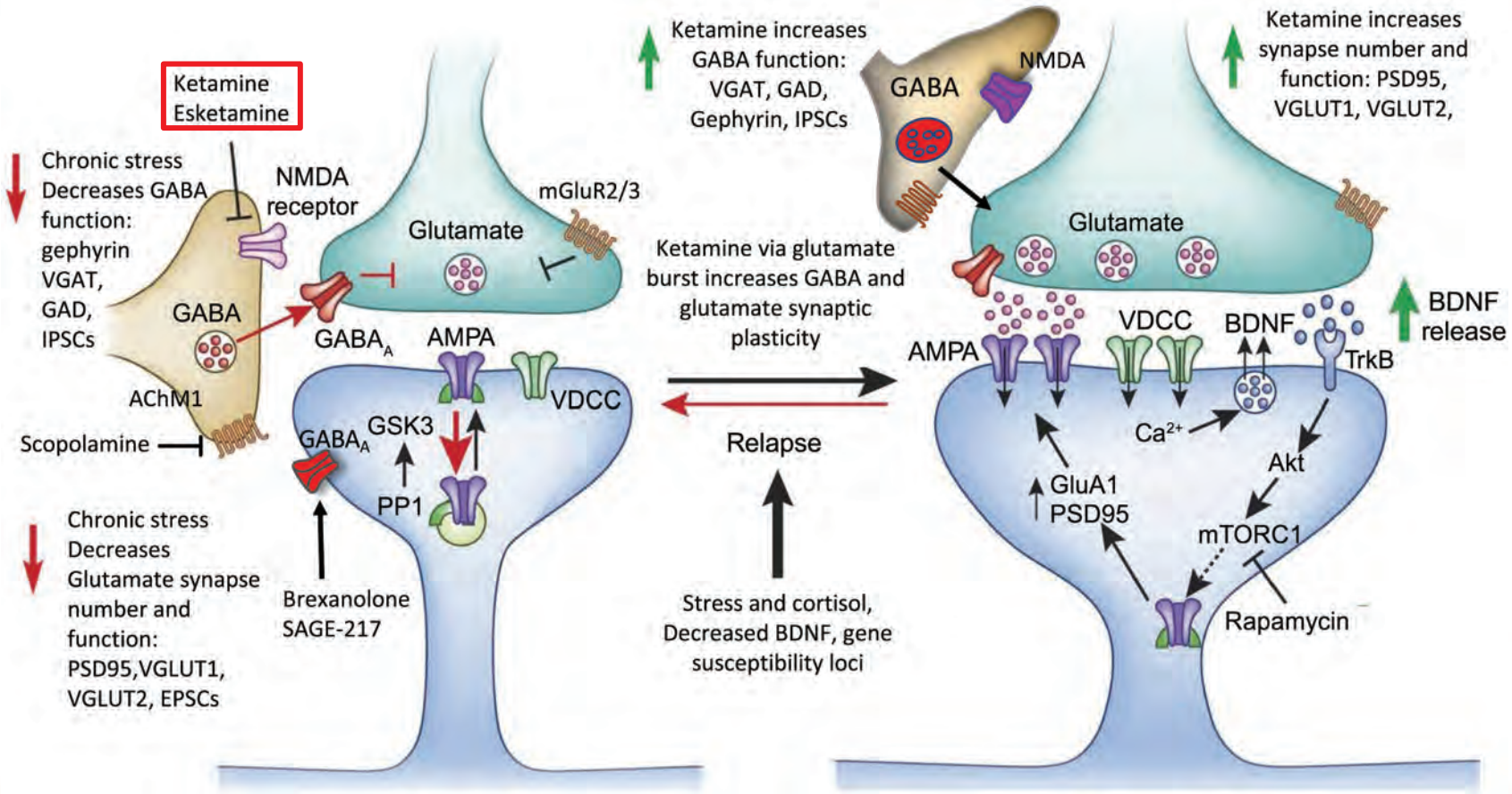
Jalen, LA, et. al. J Psychopharm, 2020

Decreased Glutamate and GABA



Duman, R, et. al. Neuron, 2019

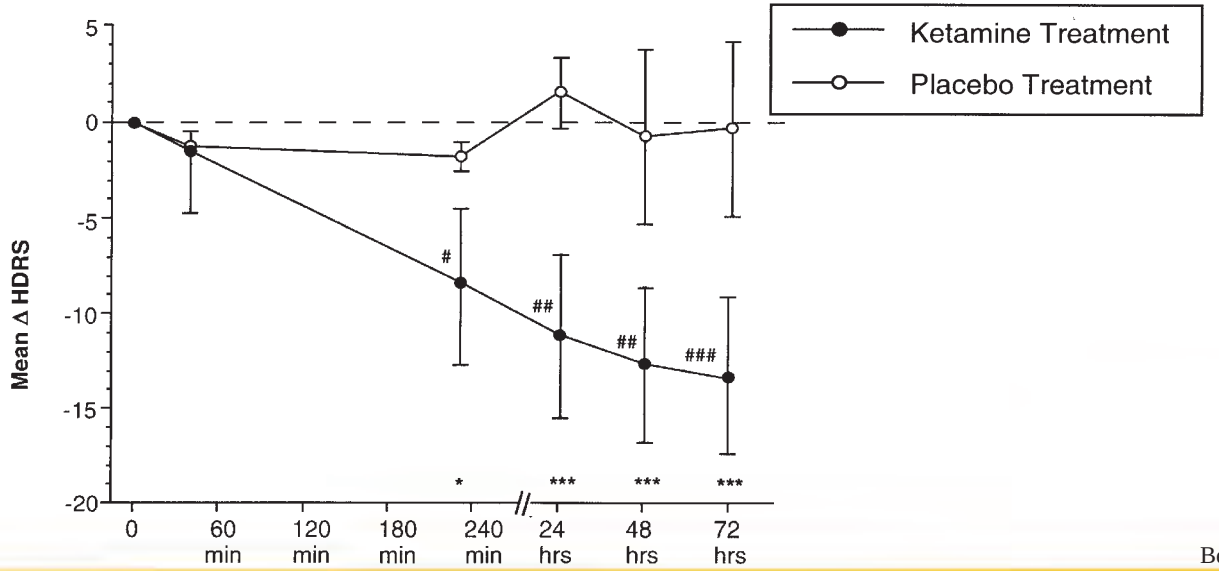
Ketamine Increases Glutamate and GABA



Duman, R, et. al. Neuron, 2019

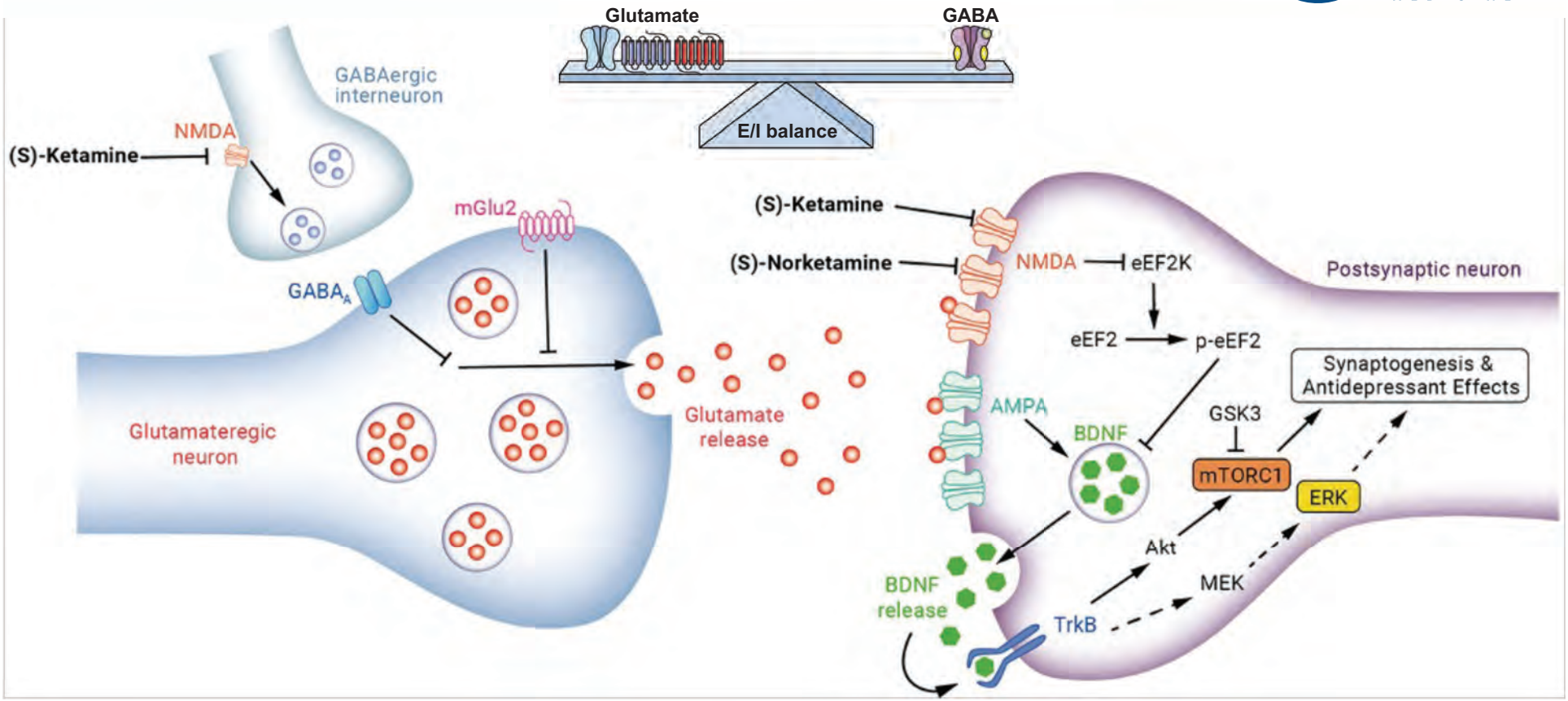
Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal



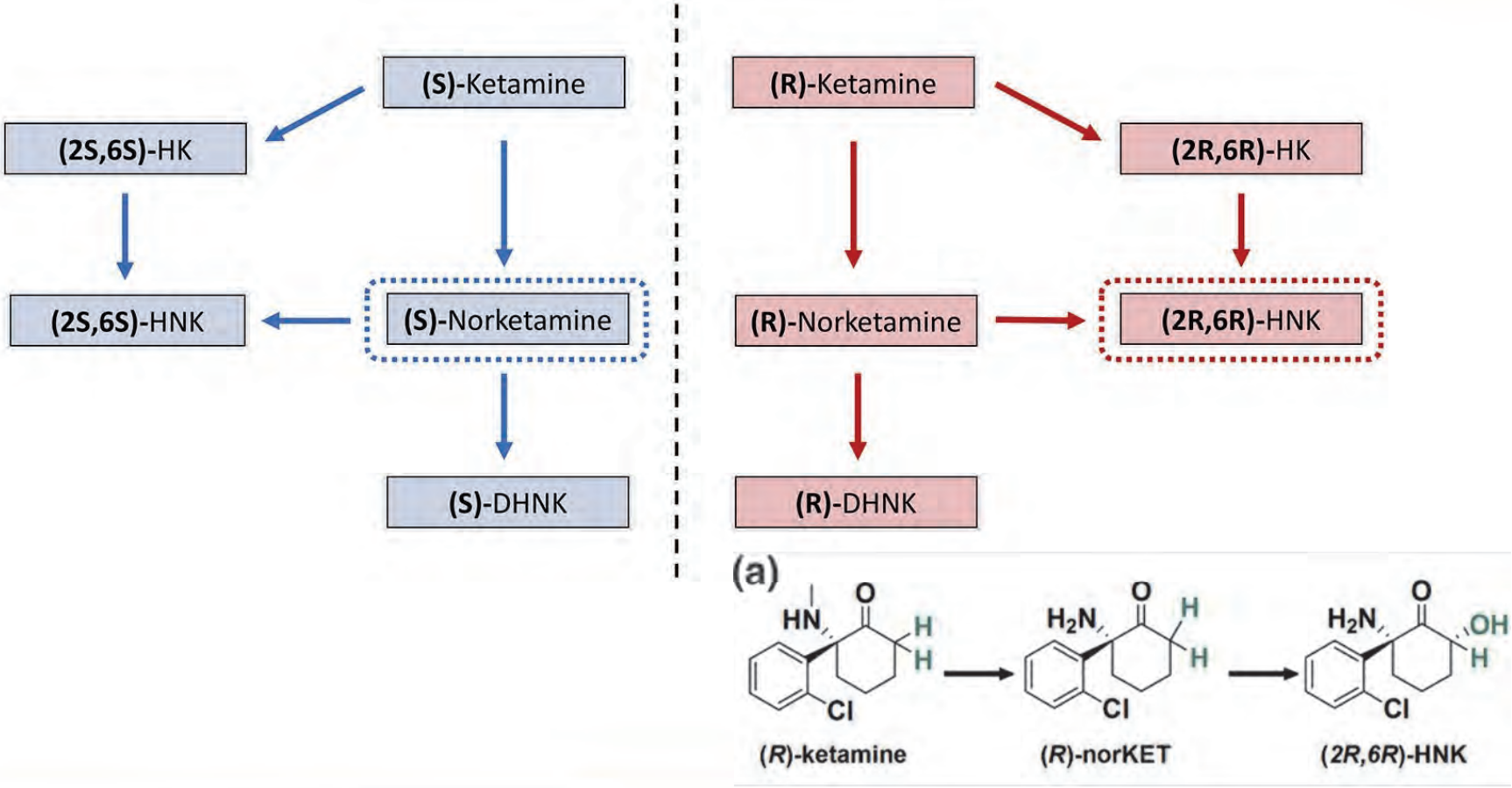
Berman, RM, et. al. Biol Psych, 2000

Possible Ketamine Mechanism



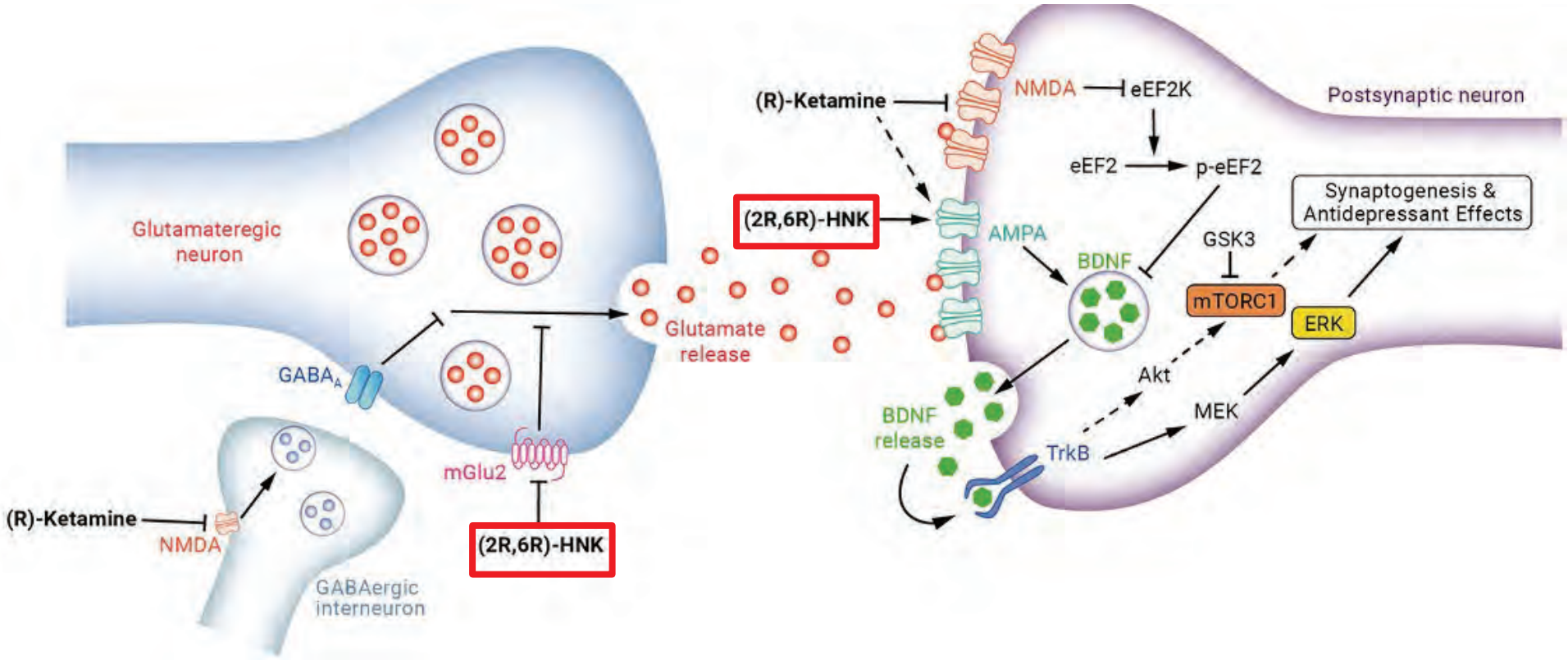
Jalen, LA, et. al. J Psychopharm, 2020
Johnston, JN, et. al. Neuropsychopharm, 2023

Ketamine Metabolism



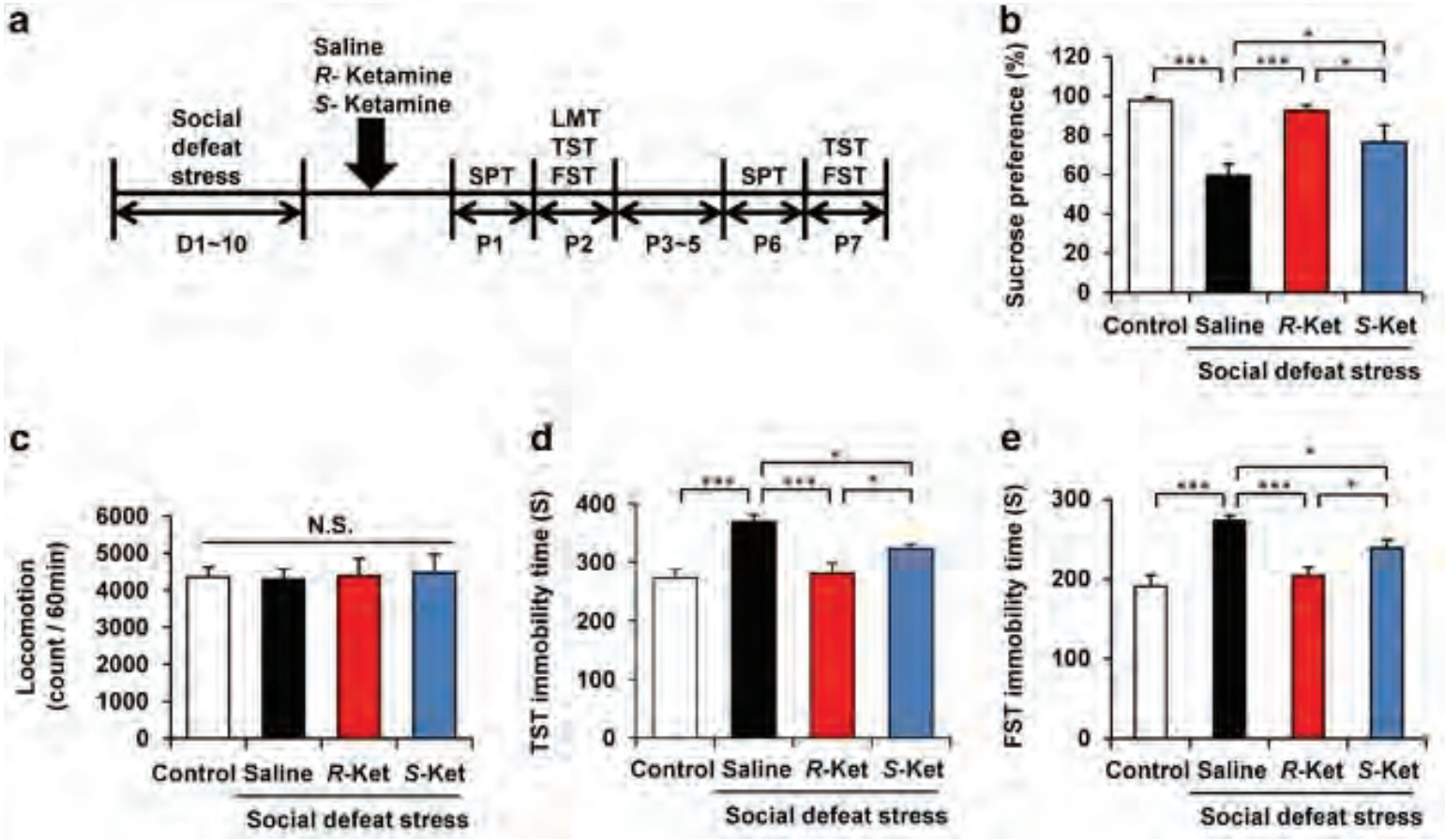
Jalen, LA, et. al. J Psychopharm, 2020

(2R,6R)-HNK Acts on Different Receptors



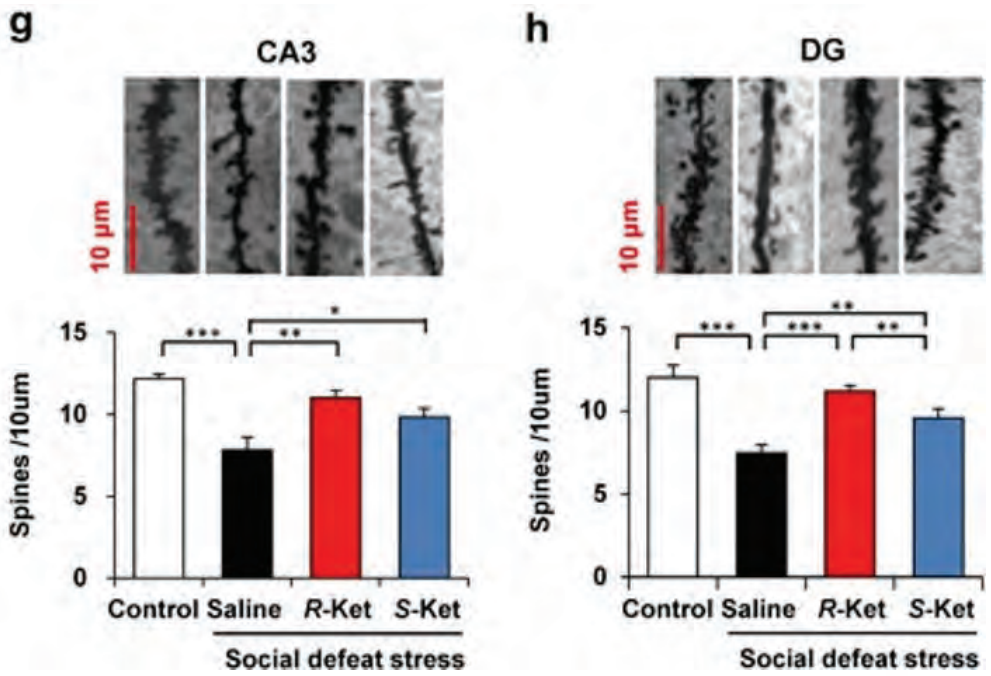
Jalen, LA, et. al. J Psychopharm, 2020

Possible Greater Efficacy of (R)-Ketamine



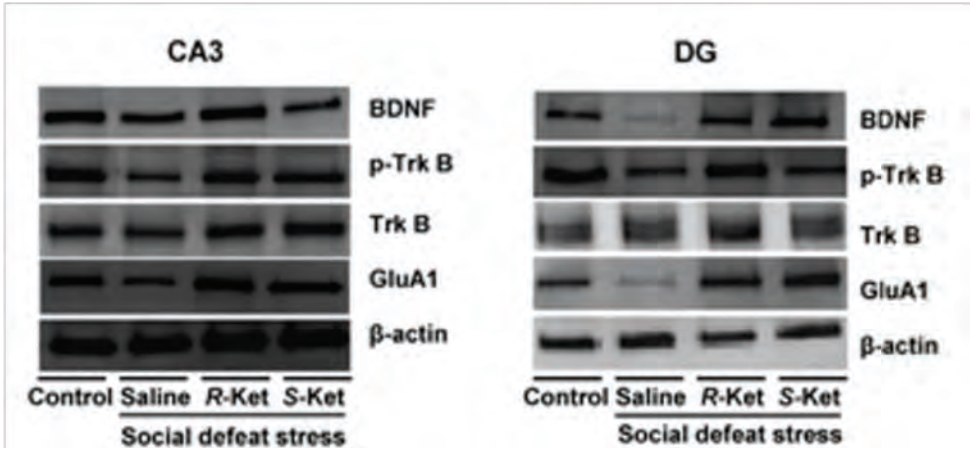
Yang, C. et. al. Transl Psychiatry 2015

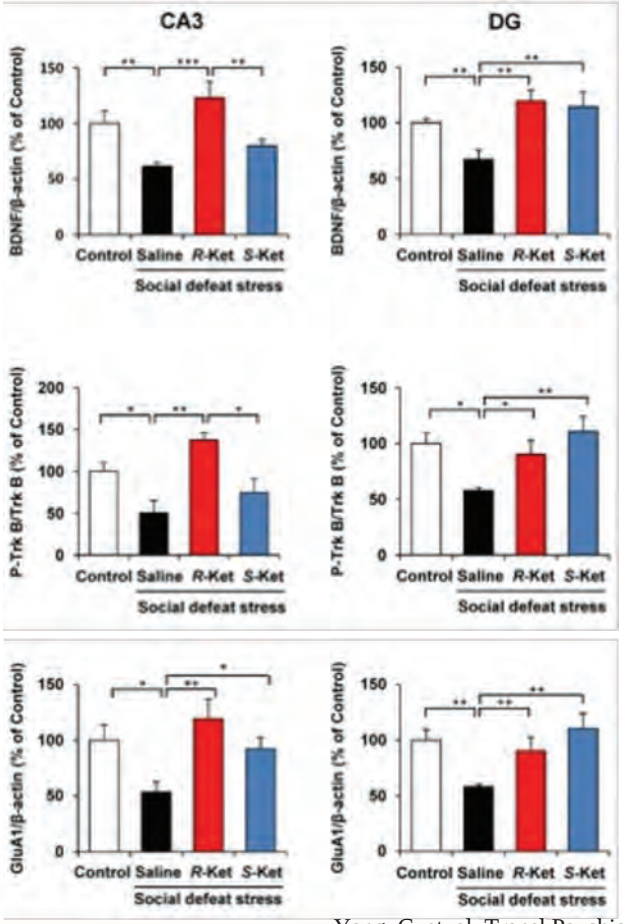
Increased Dendritic Spine Density Post-SDS



Yang, C. et. al. Transl Psychiatry 2015

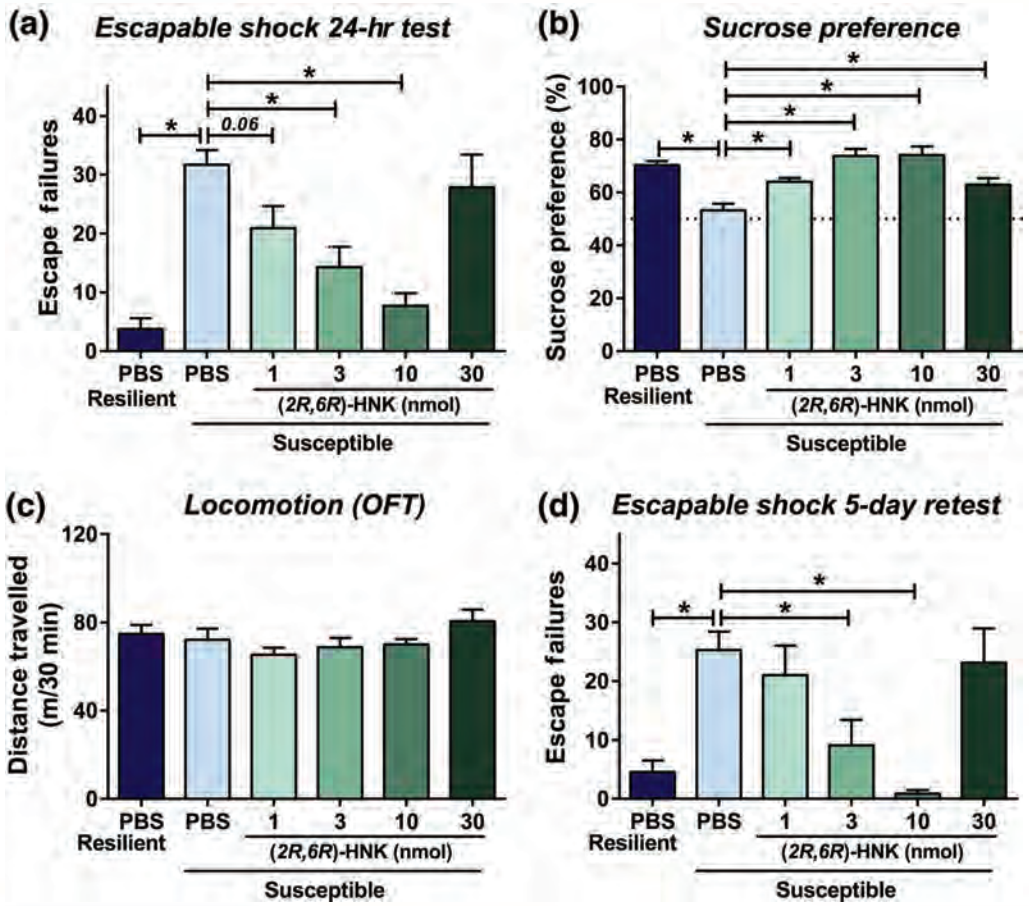
(R)-Ketamine Increases BDNF, TrkB, and AMPA-R





Yang, C. et. al. Transl Psychiatry 2015

(2R,6R)-HNK Has Similar Effect



Zanos, P., et. al. Br J Pharmacol, 2019

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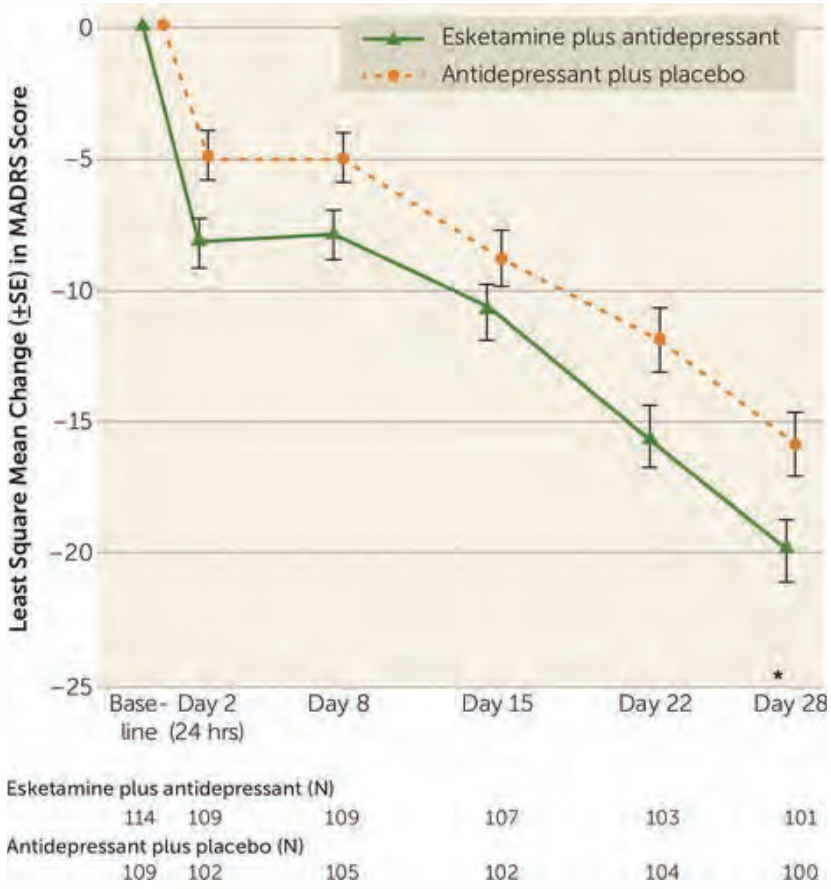
- **Future Directions/Considerations**

Esketamine Phase 3 Trial (TRANSFORM-2)



Popova, V, et. al. AJP, 2019

Esketamine Phase 3 Trial (SUSTAIN-1)

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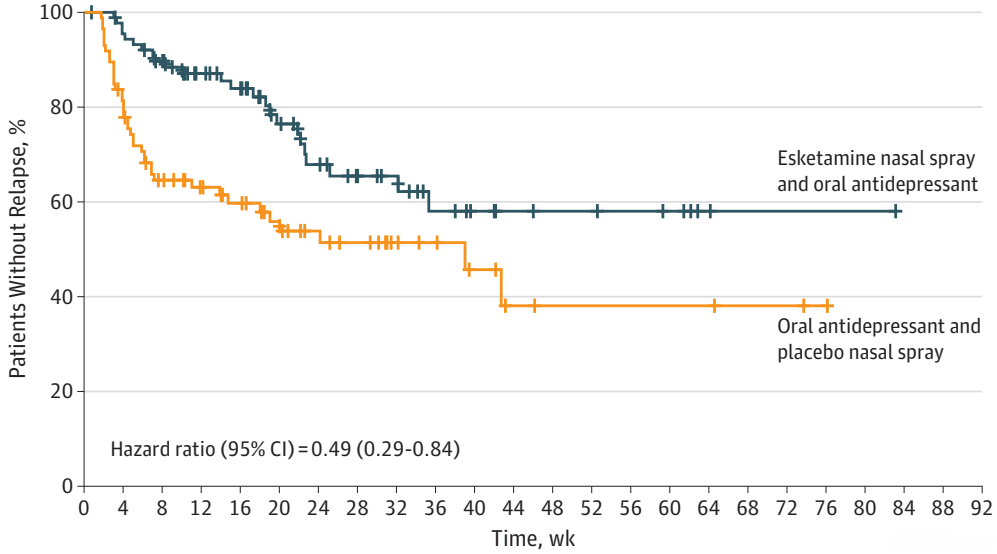
Figure 2. Kaplan-Meier Estimates of Time to Relapse

A Patients who achieved stable remission

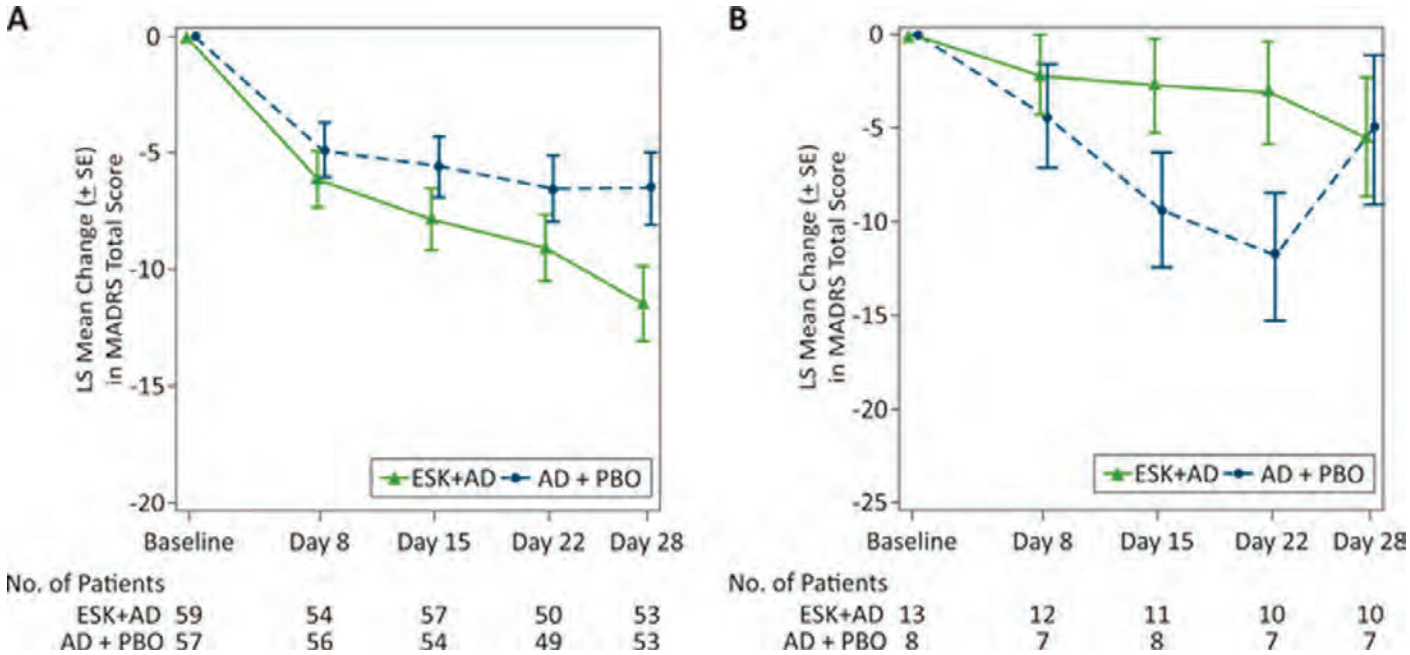


No. at risk

Esketamine nasal spray and oral antidepressant	90	84	74	58	53	39	31	25	20	14	10	8	7	7	6	5	2	1	1	1	1	0
Oral antidepressant and placebo nasal spray	86	69	52	41	34	28	22	19	12	10	7	4	3	3	3	3	3	2	2	1	0	0

Daly, EJ, et. al. JAMA Psych, 2019

Esketamine Phase 3 Trial (TRANSFORM-3)



65-74 years of age **>75 years of age**

Och-Ross, R, et. al. Am J Geri Psych, 2020

Johns Hopkins Esketamine Clinic Outcome

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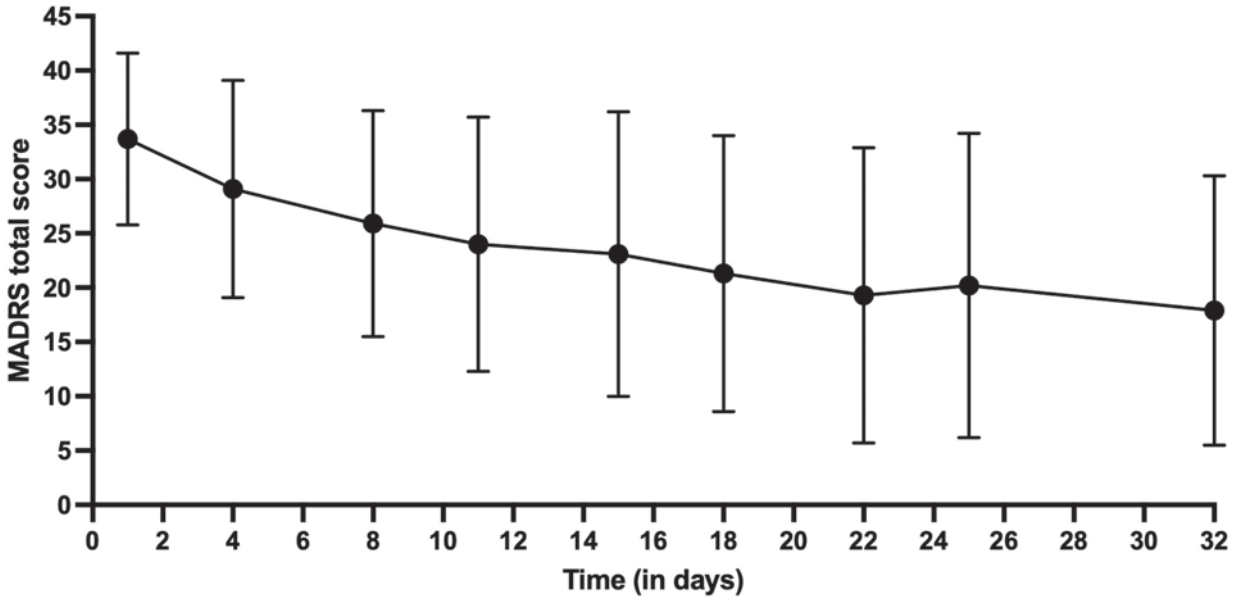
Figure 1. Course of depressive symptoms according to the Montgomery-Asberg Depression Rating Scale (MADRS) in patients with treatment-resistant depression treated with intranasal esketamine (n = 34)



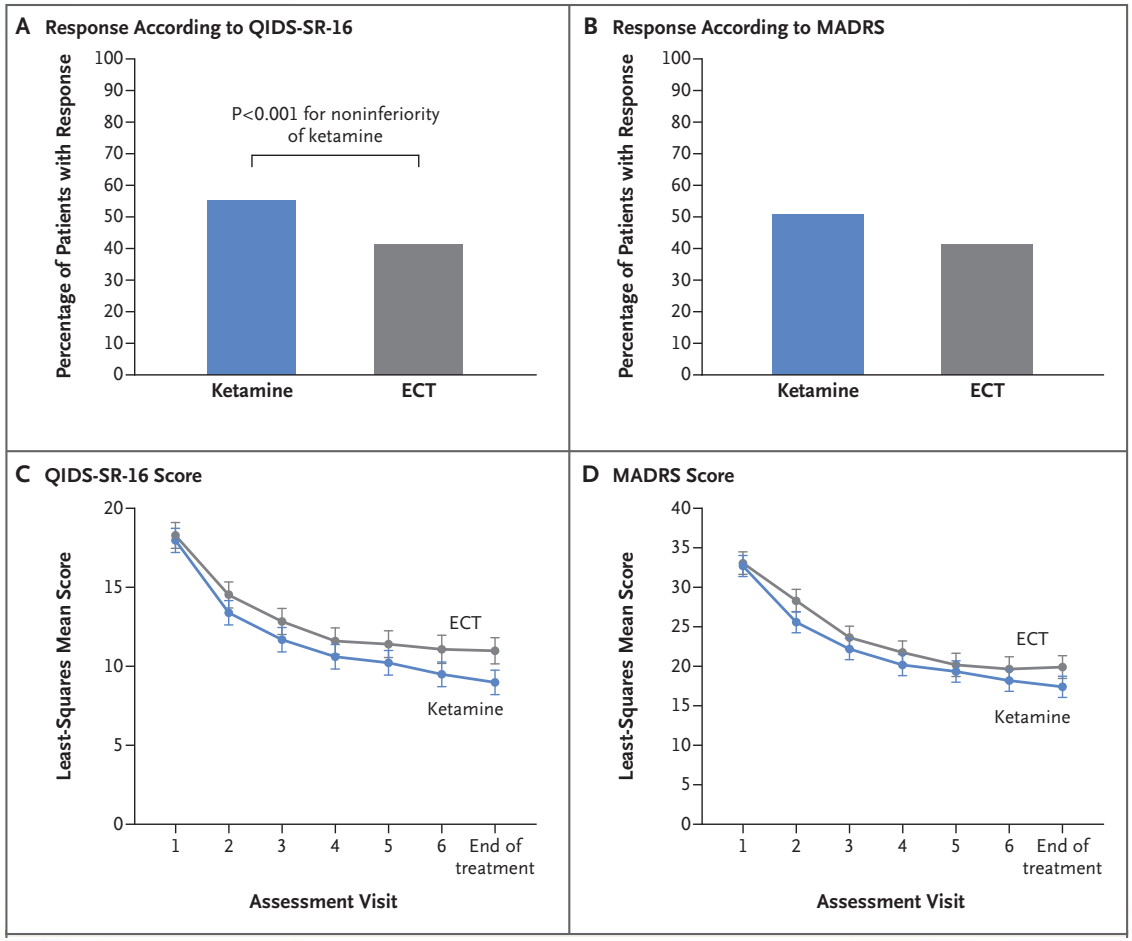
Timepoint	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 32
Mean (SD), MADRS	33.7 (7.9)	29.1 (10.0)	25.9 (10.4)	24.0 (11.7)	23.1 (13.1)	21.3 (12.7)	19.3 (13.6)	20.2 (14.0)	17.9 (12.4)
Mean (SD) dose	54.4 (6.7)	74.4 (16.8)	79.8 (10.2)	82.1 (7.2)	82.1 (7.2)	81.3 (8.4)	83.0 (5.2)	83.0 (5.4)	83.0 (5.4)
Sample size	n = 34	n = 32	n = 33	n = 29	n = 29	n = 31	n = 29	n = 27	n = 27

Table 1. Baseline characteristics and impact of demographics and clinical variables on antidepressant response to intranasal esketamine in patients with treatment-resistant depression (n=34)

Variables	Baseline characteristics Mean (SD) or n (%)	Impact on antidepressant response	
		F	*p*
Demographics			
Age	44.6 (16.1)	F = 3.033	**< .001**
Sex (female)	20 (59%)	F = .191	.992
Race (white)	29 (85%)	F = 1.627	.121
Education (college or more)	23 (68%)	F = .705	.687
Marital status (partnered)	20 (59%)	F = .763	.636
Employment (working and/or studying)	21 (62%)	F = .705	.687
Clinical Variables			
Duration of current episode (months)	114.4 (122.7)	F = 4.110	**< .001**
Number of failed antidepressant treatments (current episode)	7.2 (3.8)	F = 1.373	**.036**
Anxiety disorder (current)	21 (62%)	F = 1.144	.337
Posttraumatic stress disorder (current)	5 (15%)	F = .632	.750
Alcohol use disorder (lifetime)	7 (21%)	F = .525	.837
Substance use disorder (lifetime)	7 (21%)	F = 1.107	.361
Previous psychiatric hospitalization	19 (56%)	F = .445	.892
Previous suicide attempt	10 (29%)	F = .715	.678
Previous treatment with electroconvulsive therapy	13 (38%)	F = .800	.603
Previous treatment with rTMS	10 (29%)	F = .835	.573
Family history of alcohol use disorder	9 (26%)	F = .799	.604
Family history of substance use disorder	7 (21%)	F = 1.745	.092
Average change in systolic blood pressure	5.34 (7.67)	F = 17.092	**< .001**
Average change in diastolic blood pressure	2.29 (4.0)	F = 32.413	**< .001**

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale; rTMS = Repetitive transcranial magnetic stimulation; SD = standard deviation; F = F statistics for repeated measures linear mixed models; p = statistical significance
Bold = statistically significant (p < .05)

Response to ECT vs. Ketamine



Anand, A, et. al. NEJM, 2023

Primary and Secondary Outcomes

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Table 2. Primary and Secondary Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Ketamine (N=195)	ECT (N=170)	Difference (95% CI)†
Primary outcome			
QIDS-SR-16–based response — no./total no. (%)‡	108/195 (55.4)	70/170 (41.2)	14.2 (3.9 to 24.2)
Secondary outcomes			
Effectiveness outcomes — no./total no. (%)			
MADRS-based response‡	99/195 (50.8)	70/169 (41.4)	9.3 (–0.9 to 19.4)‡
Remission§			
QIDS-SR-16–based	63/195 (32.3)	34/170 (20.0)	12.3 (3.4 to 21.2)
MADRS-based	74/195 (37.9)	37/170 (21.8)	16.2 (7.0 to 25.4)
CGI-I score¶			
Much improved or better rating	99/189 (52.4)	78/164 (47.6)	4.8 (–5.6 to 15.3)
Very much improved rating	59/189 (31.2)	35/164 (21.3)	9.9 (0.8 to 19.0)
PGI-I score‖			
Much improved or better rating	84/190 (44.2)	60/164 (36.6)	7.6 (–2.6 to 17.8)
Very much improved rating	37/190 (19.5)	18/164 (11.0)	8.5 (1.1 to 15.9)
Cognitive and behavioral outcomes			
GSE-My score at end-of-treatment visit**	4.2±0.1	3.2±0.1	1.1 (0.9 to 1.2)
SMCQ score at end-of-treatment visit††	0.2±1.4	–8.8±1.5	9.0 (5.1 to 13.0)
Change from baseline in HVLT-R T-score‡‡			
Total	3.2±0.8	–2.1±0.8	5.3 (3.1 to 7.4)
Delayed recall	–0.9±1.1	–9.7±1.2	8.8 (5.7 to 11.9)
Discrimination index	–1.5±1.1	–9.7±1.2	8.2 (5.2 to 11.3)
Change from baseline in the 16-item Quality-of-Life Scale score§§	12.3±1.0	12.9±1.1	–0.6 (–3.4 to 2.1)

Anand, A, et. al. NEJM, 2023

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Future Directions/Considerations

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- **Other NMDA-R antagonists**
  - Without dissociative effects
- **Biomarkers to determine the population that will respond to OAD vs. esketamine or ECT vs. esketamine**
- **Novel therapies that have rapid antidepressant effects**
  - Psychedelics
  - Glutamate/GABA signaling; Allosteric modulators
  - Neuroinflammation
- **Other Applications for esketamine**
  - Bipolar depression, resilience, etc.

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- **Paul Nestadt, M.D.**
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