Why We Should Care About the Opioid Effects of Ketamine

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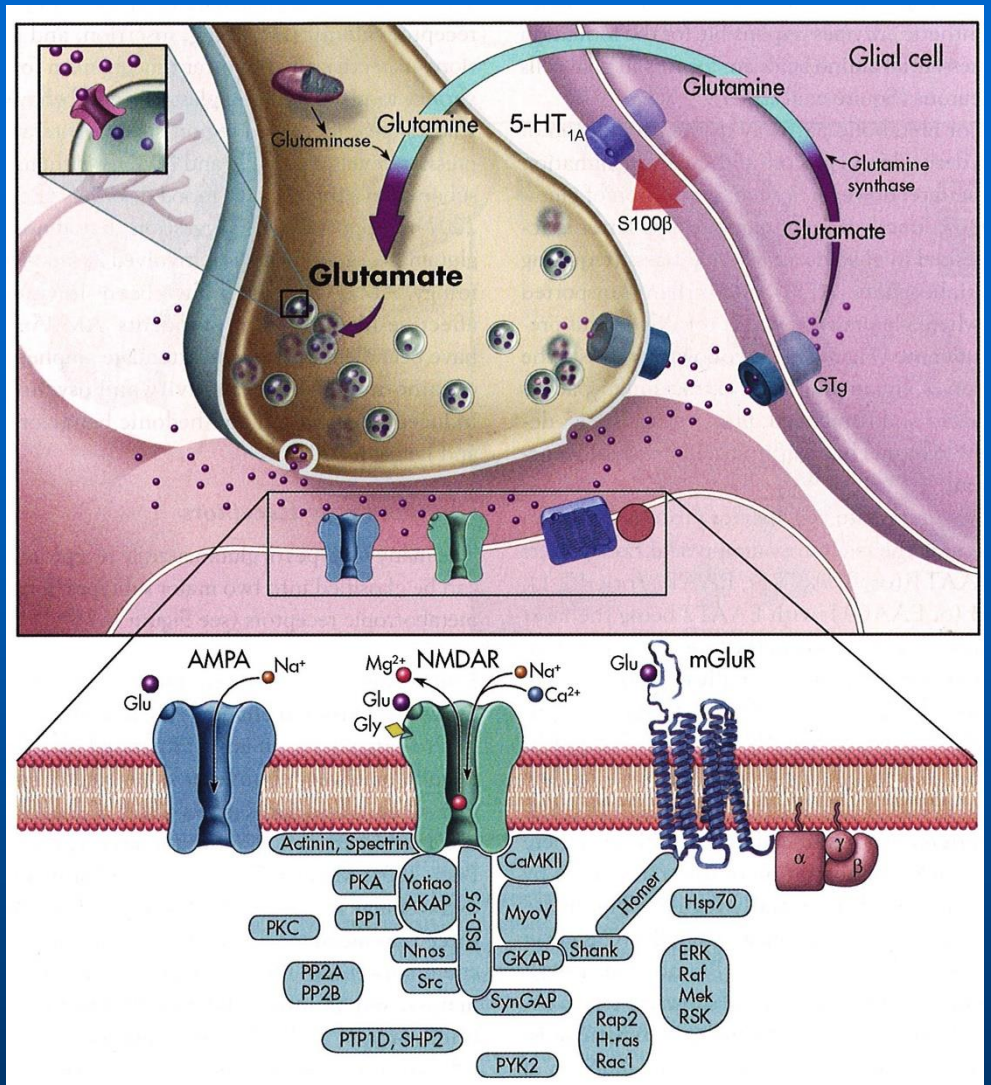
Disclosure

Dr. Schatzberg has in the past 3 years served as a consultant for Alto Neurosciences, ANeurotech, Compass, Delpor, Douglas, Galen, Magnus, McKinsey, NeuraWell, Oryzon, Parexel, Sage Therapeutics, and Signant.

He has equity in Alto Neurosciences, Corcept (co-founder), Delpor, Madrigal, Magnus, NeuraWell, Owl Analytics, Seattle Genetics, Xhale

He has received book royalties from the American Psychiatric Association.



Receptor Subunit Types

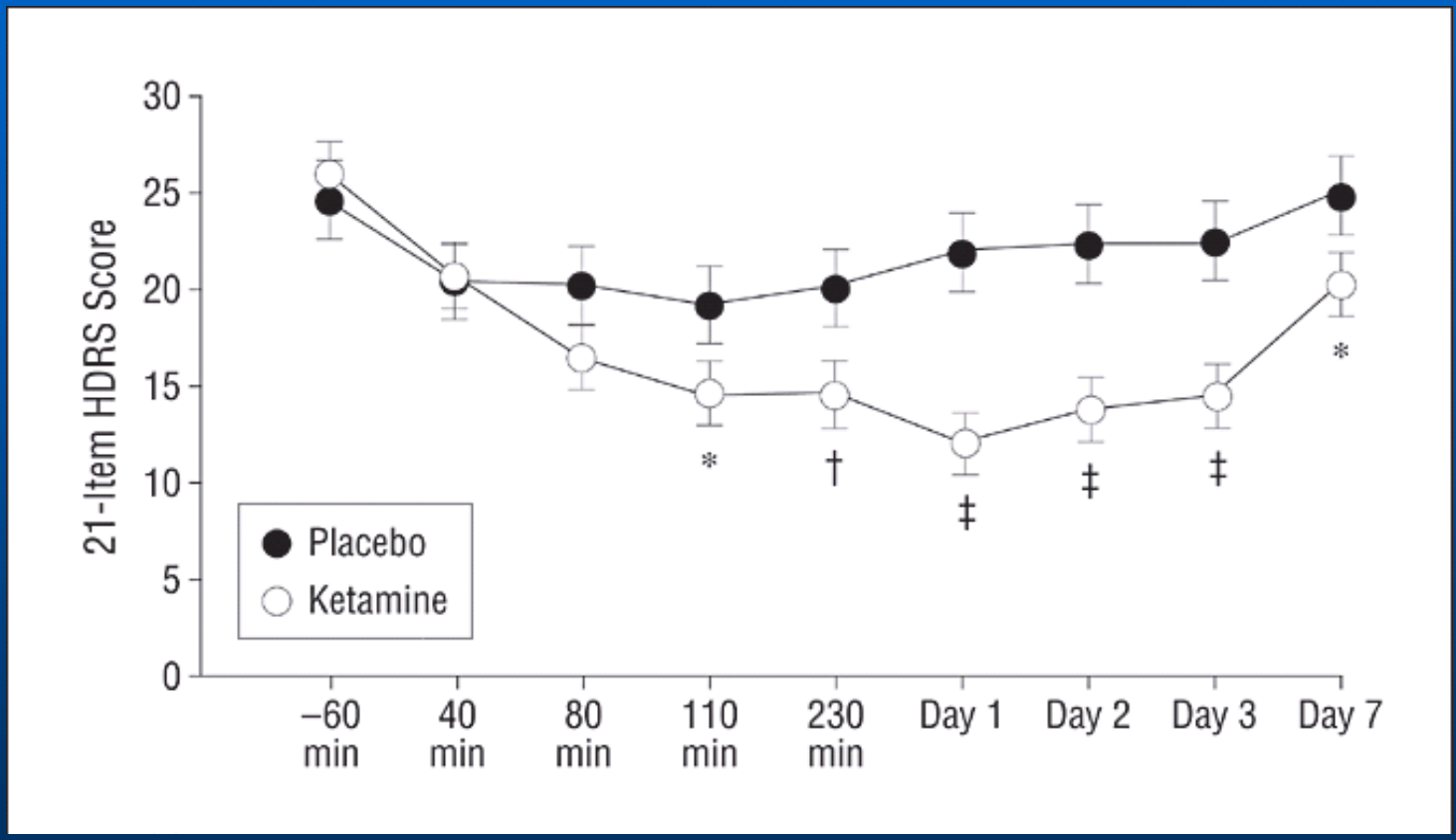
Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
NR1	GluR1	GluR5	mGluR2 a-b-c-d	mGluR2	mGluR4 a-b
NR2 A-B-C-D	GluR2	GluR6	mGluR5 a-b	mGluR5	mGluR6
NR3 A-B	GluR3	GluR7			mGluR7 a-b
	GluR4	KA1			mGluR8 a-b
		KA2			

Drazinic C, et al in Textbook of Psychopharmacology 5th Edition

Ketamine

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist;
- Mu opiod agonist; stimulant (?)
- Psychotomimetic; dissociation
- Acute antidepressant efficacy not sustained

Change in the 21-item Hamilton Depression Rating Scale 28 (HDRS) over 1 week (n = 17)



Zarate, CA et al. Arch Gen Psychiatry 2006; 63:856-864.

Noninferiority Study of Ketamine versus ECT in Nonpsychotic TRD

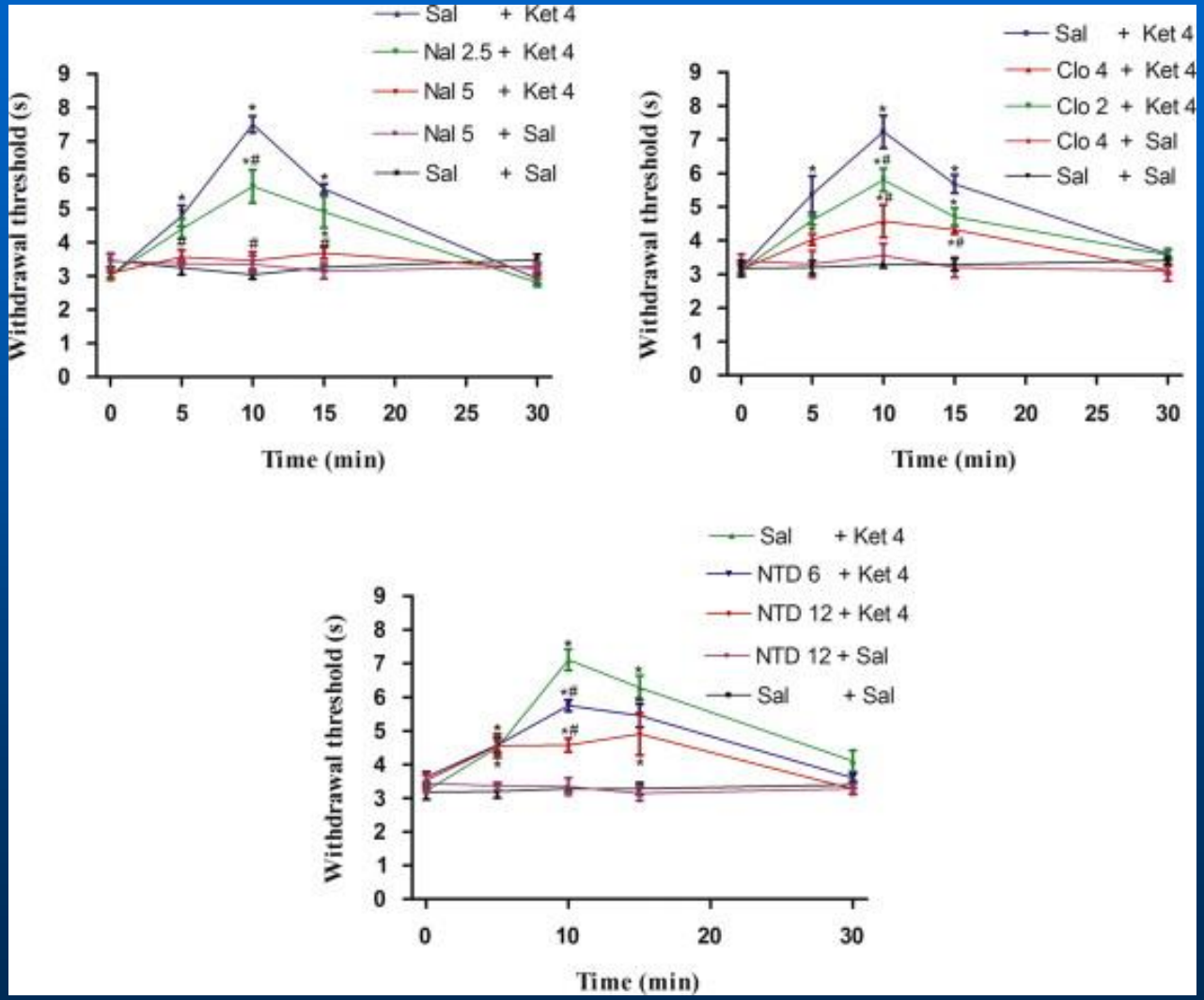
- 403 patients; 365 completed 3 weeks of treatment
- 2x/week of ketamine vs. 3x/week of ECT
- Ketamine response rate on QIDS-SR 55.4% vs. 41.2% for ECT ($p<.001$)
- Higher adverse events % for ECT

Anand et al, N Eng J Med 388: 2315-2325, 2023.

Ketamine and Morphine in OCD

- IV ketamine significantly more effective than placebo in refractory OCD; effects last one week in some patients (Rodriguez C et al Neuropsychopharm 38: 2475-2483, 2013).
- Oral morphine significantly more effective than placebo in refractory OCD; effects seen the next day and last for 5 days (Koran L et al, J Clin Psychopharm 66: 353-359, 2005).

Fig. 2 Antagonism induced by intracerebroventricular administration of naloxone (a), clocinnamox (b) or naltrindole (c) on the central antinociception produced by ketamine



Pachecho et al. Brain Research 1562: 69-75, 2014.

Commentary

A Word to the Wise About Ketamine

Schatzberg, AF. Am J Psychiatry 171:3, 2014

Ketamine: Promising Path or False Prophecy in the Development of Novel Therapeutics for Mood Disorders?

Gerard Sanacora and Alan F Schatzberg

Neuropsychopharmacology (2015) **40,** 1307; doi:10.1038/npp.2014.338

A Word to the Wise About Intranasal Esketamine

Schatzberg, AF. Am J Psychiatry 176:6, 2019

Studying the Possible Opioid MoA of Ketamine (cont'd)

"To explore the effects of ketamine on the opioid system, one could use PET to explore mu opioid binding pre- and post-ketamine in either patients or controls. Mu antagonists such as naloxone could be used to attempt to block the antidepressant effects in animal models, as well as in patients."

Sanacora G, Schatzberg AF: Neuropsychopharmacology 2015; 40: 259-267.

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 Pannu, 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.

Objective: In addition to *N*-methyl-D-aspartate receptor antagonism, ketamine produces opioid system activation. The objective of this study was to determine whether opioid receptor antagonism prior to administration of intravenous ketamine attenuates its acute antidepressant or dissociative effects.

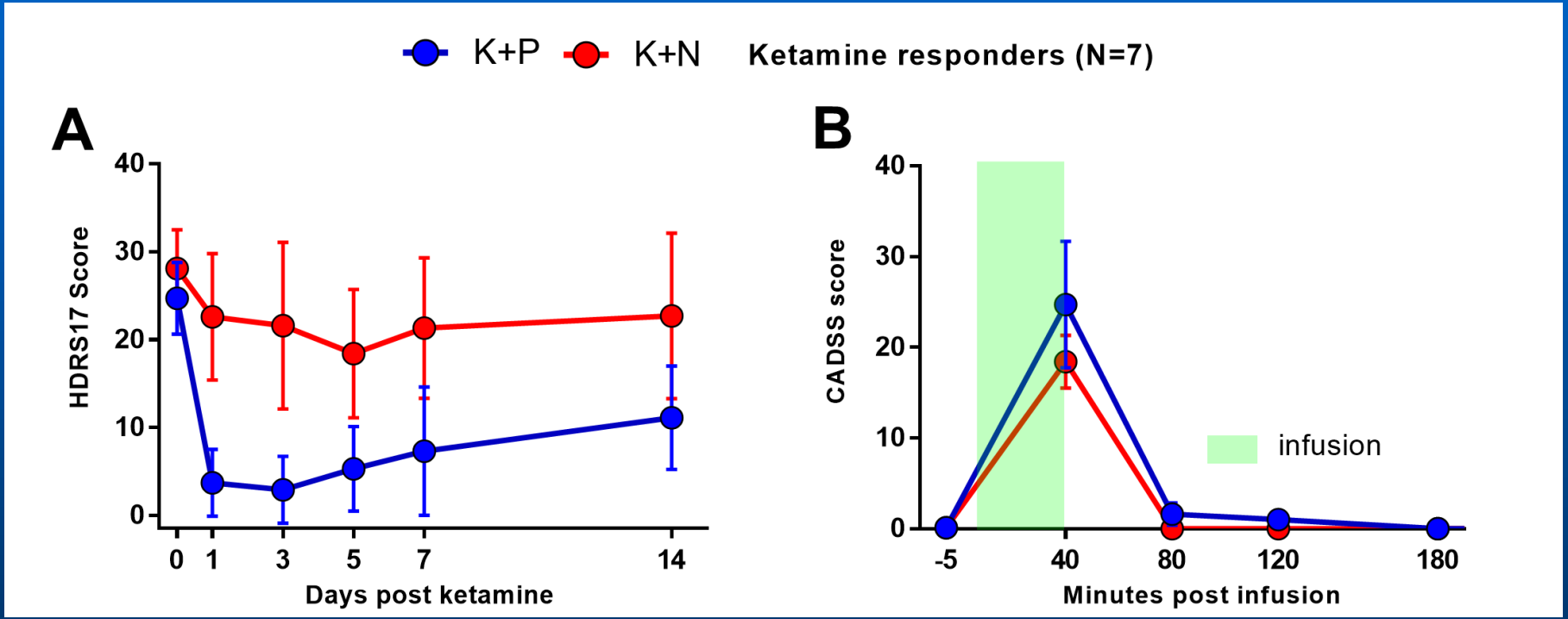
Method: In a proposed double-blind crossover study of 30 adults with treatment-resistant depression, the authors performed a planned interim analysis after studying 14 participants, 12 of whom completed both conditions in randomized order: placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine. Response was defined as a reduction ≥50% in score on the 17-item Hamilton Depression Rating Scale (HAM-D) score on postinfusion day 1.

Results: In the interim analysis, seven of 12 adults with treatment-resistant depression met the response criterion during the ketamine plus placebo condition. Reductions in 6-item and 17-item HAM-D scores among participants in the ketamine plus naltrexone condition were significantly lower than those of participants in the ketamine plus placebo condition on postinfusion days 1 and 3. Secondary analysis of all participants who completed the placebo and naltrexone conditions, regardless of the robustness of response to ketamine, showed similar results. There were no differences in ketamine-induced dissociation between conditions. Because naltrexone dramatically blocked the antidepressant but not the dissociative effects of ketamine, the trial was halted at the interim analysis.

Conclusions: The findings suggest that ketamine's acute antidepressant effect requires opioid system activation. The dissociative effects of ketamine are not mediated by the opioid system, and they do not appear sufficient without the opioid effect to produce the acute antidepressant effects of ketamine in adults with treatment-resistant depression.

Am J Psychiatry 2018; 175:1205–1215; doi: 10.1176/appi.ajp.2018.18020138

Naltrexone Pretreatment Blocks Ketamine's Antidepressant Effects but not Dissociative Symptoms

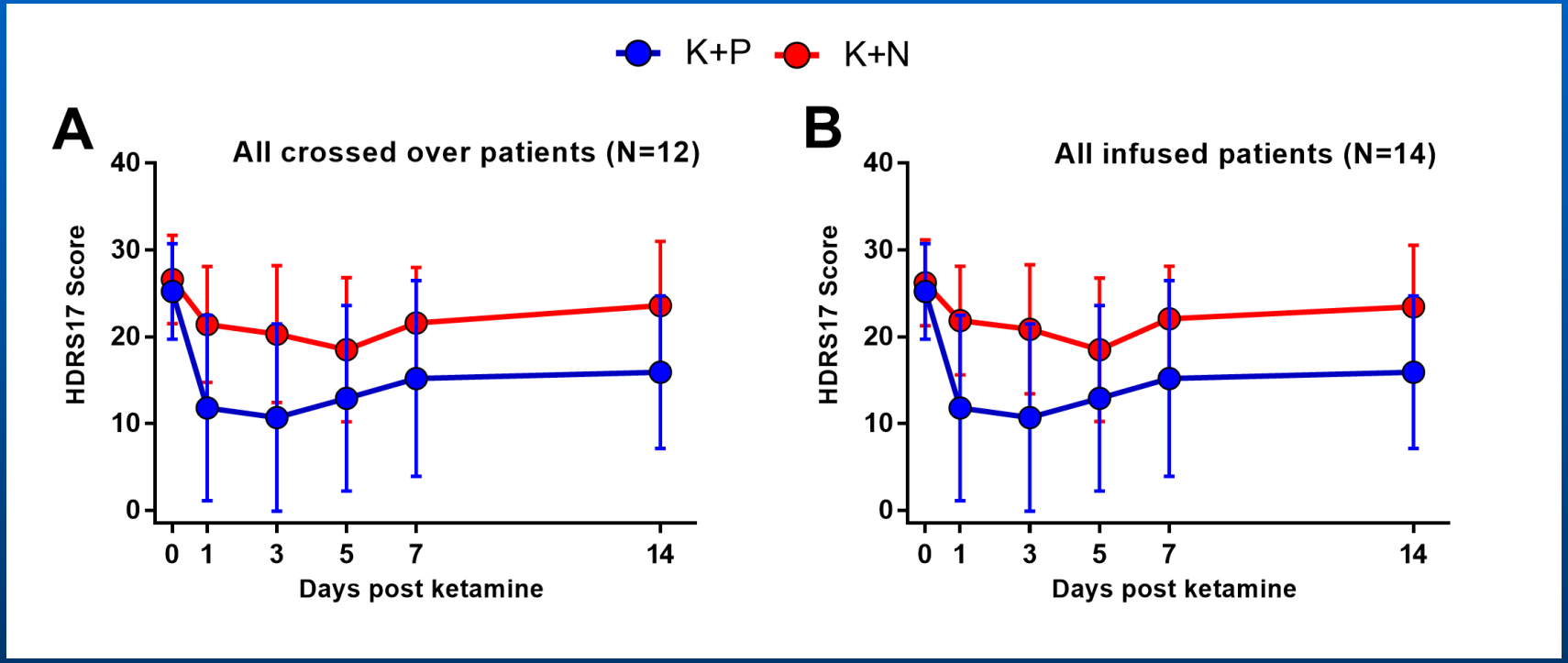


A: Primary outcome at Day 1 was significant (F=43.6, P=0.0006)

B: No significant differences in dissociation measure

Williams N, Heifets B et al, Am J Psychiatry, e-pub, Aug 28, 2018.

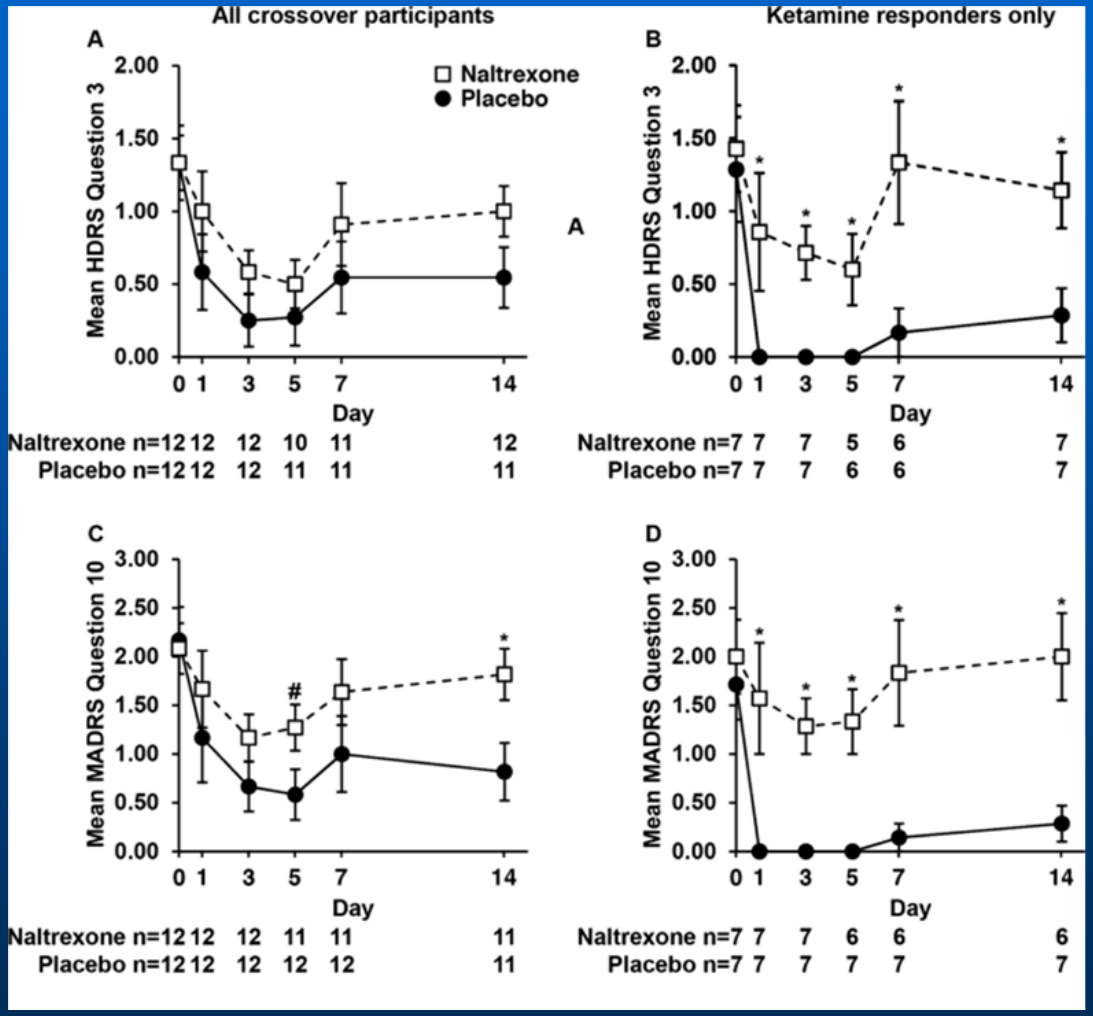
Naltrexone Pretreatment Blocks Ketamine's Antidepressant Effects



A: Significant difference at Day 1 (F=5.4, p=.041)
B: Significant difference at Day 1 (F=6.1, p=.030)

Williams N, Heifets B et al, Am J Psychiatry, e-pub, Aug 28, 2018.

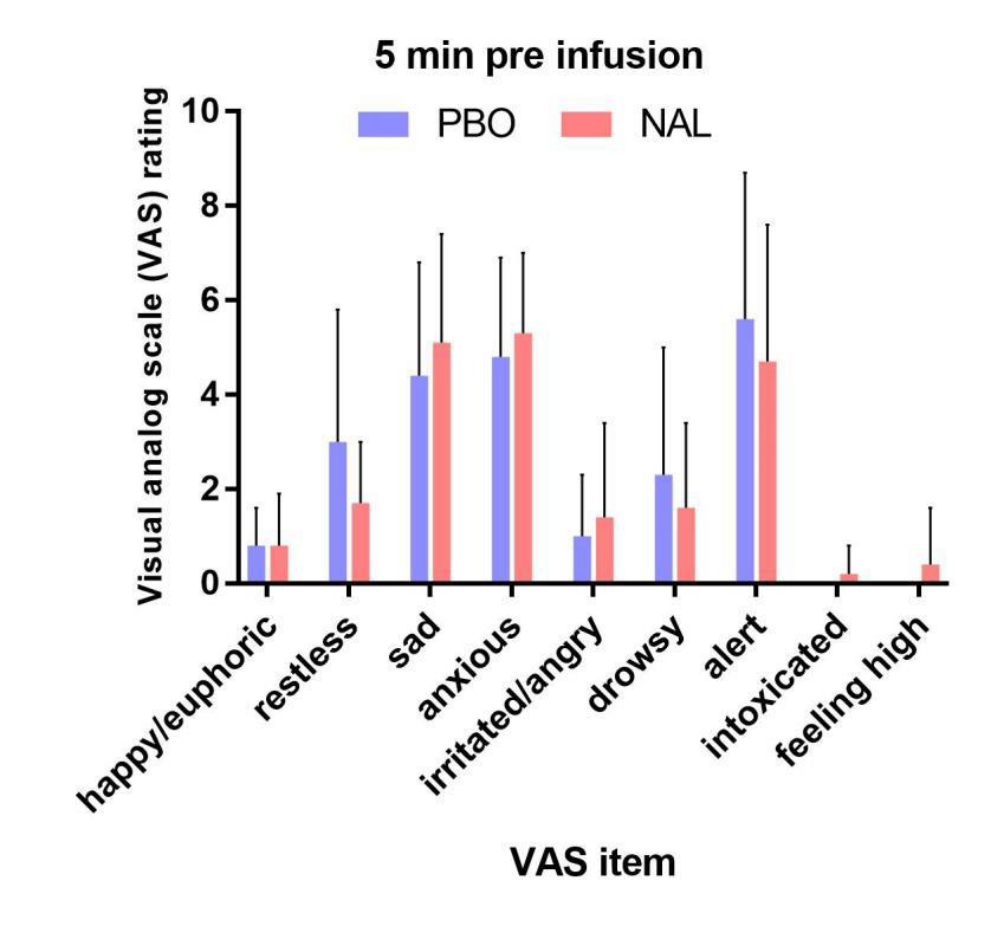
Anti-suicide Effects of Ketamine are Blocked by Naltrexone



#p<0.10, *p<0.05 after Bonferroni correction for multiple comparisons

Williams et al, Mol Psychiatry 2019

VAS Item Scores After Placebo vs. Naltrexone

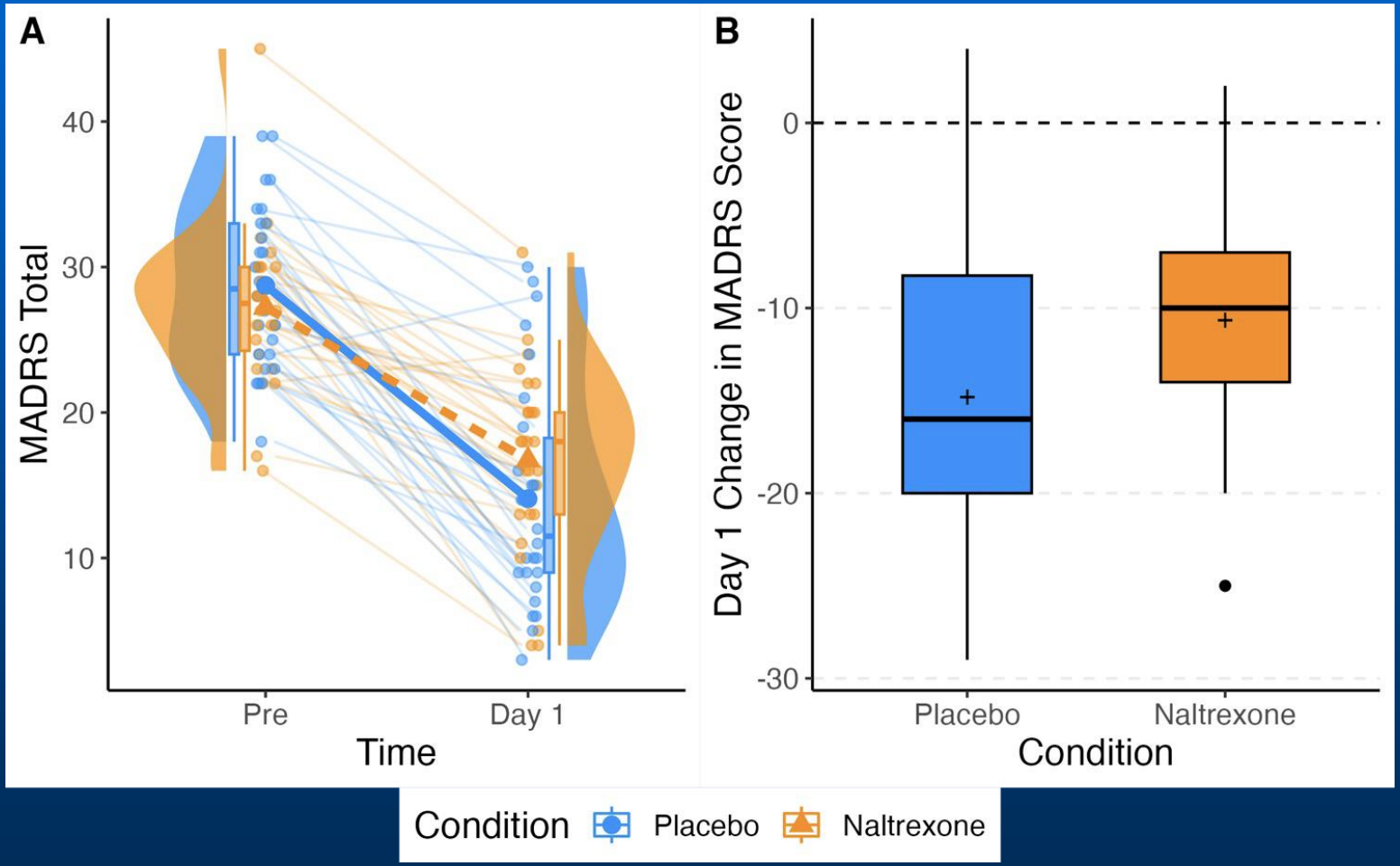


Williams N, Heifets B et al, Am J Psychiatry, e-pub, Aug 28, 2018.

Mu Opioid Antagonists Block Ketamine's Behavioral Effects

- Klein et al – PNAS 2020
- Zhang et al – Pharmacol Biochem Behav 2021
- Bonaventura et al – Mol Psychiatry 2021
- Lucki et al – Psychopharamcology 2022
- Levenstein et al – Biol Psychiatry 2023
- Jelen et al – 2023 ACNP poster (clinical)
- Jiang and Pittenger – Transl Psychiatry 2024
- Di Ianni et al – Nat Commun 2024

Naltrexone Attenuates Antidepressant Effects of Ketamine



Jelen L, ACNP Annual Meeting 2023.

Unanswered Questions Re Ketamine's Opioid Effects

- Degree of endogenous opioid release versus mu opioid binding; significance for placebo response
- Localization of the opioid effect – medial prefrontal cortex primarily? Second messenger effects?
- Risk of abuse and optimal level and frequency of exposure; risk of discontinuation related symptoms
- Significance vis-a-vis developing new, rapidly-acting "glutamatergic" agents
- Sequencing ketamine to mu partial agonists

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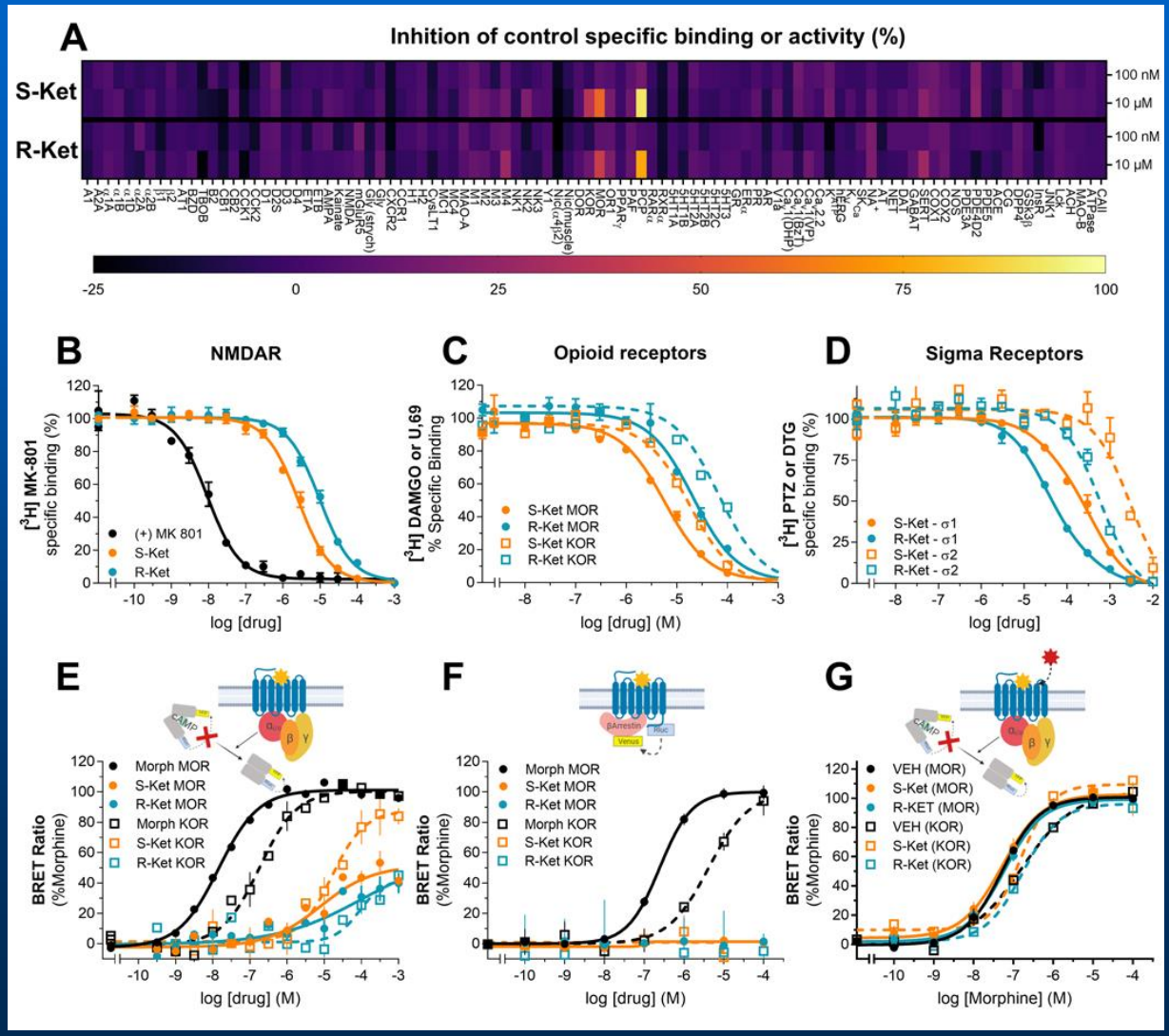
Divergent Pharmacodynamics of Ketamine enantiomers



Bonaventura J et al, Mol Psych 2021.

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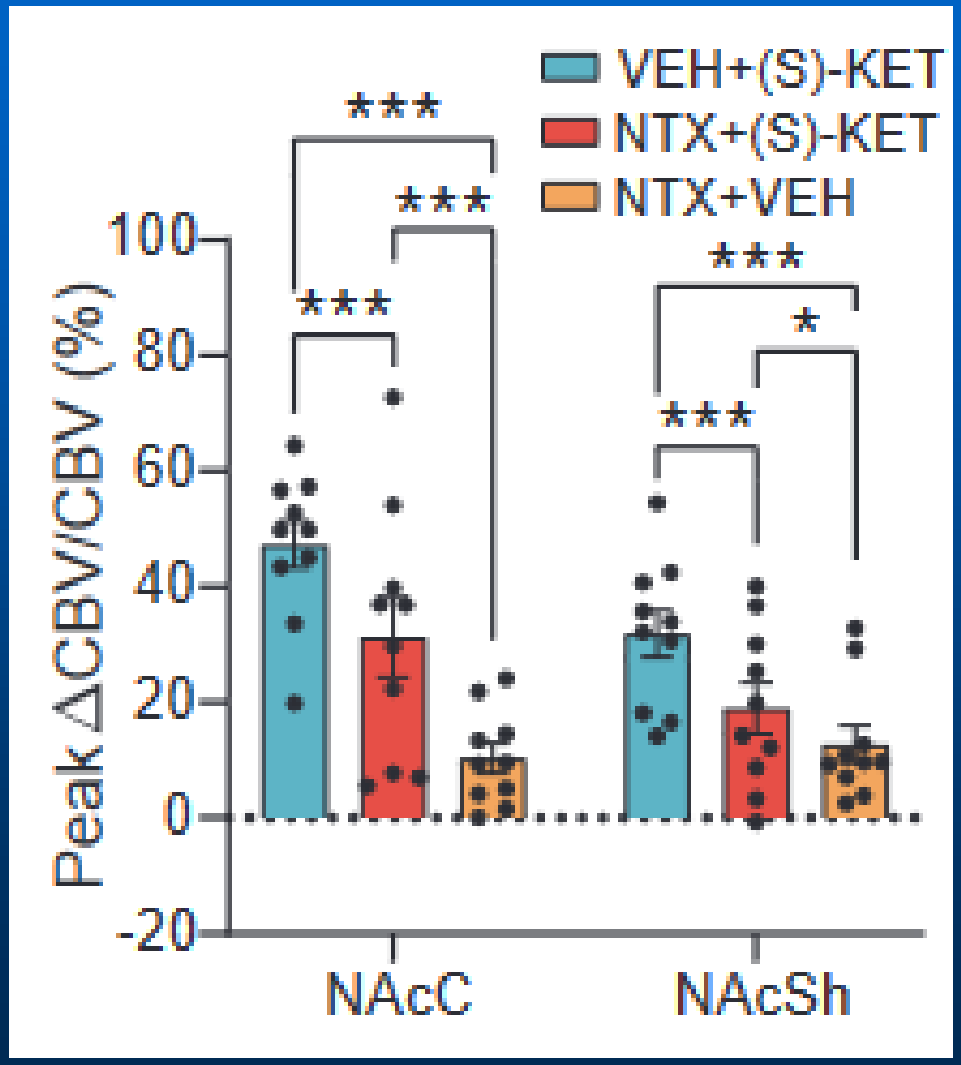
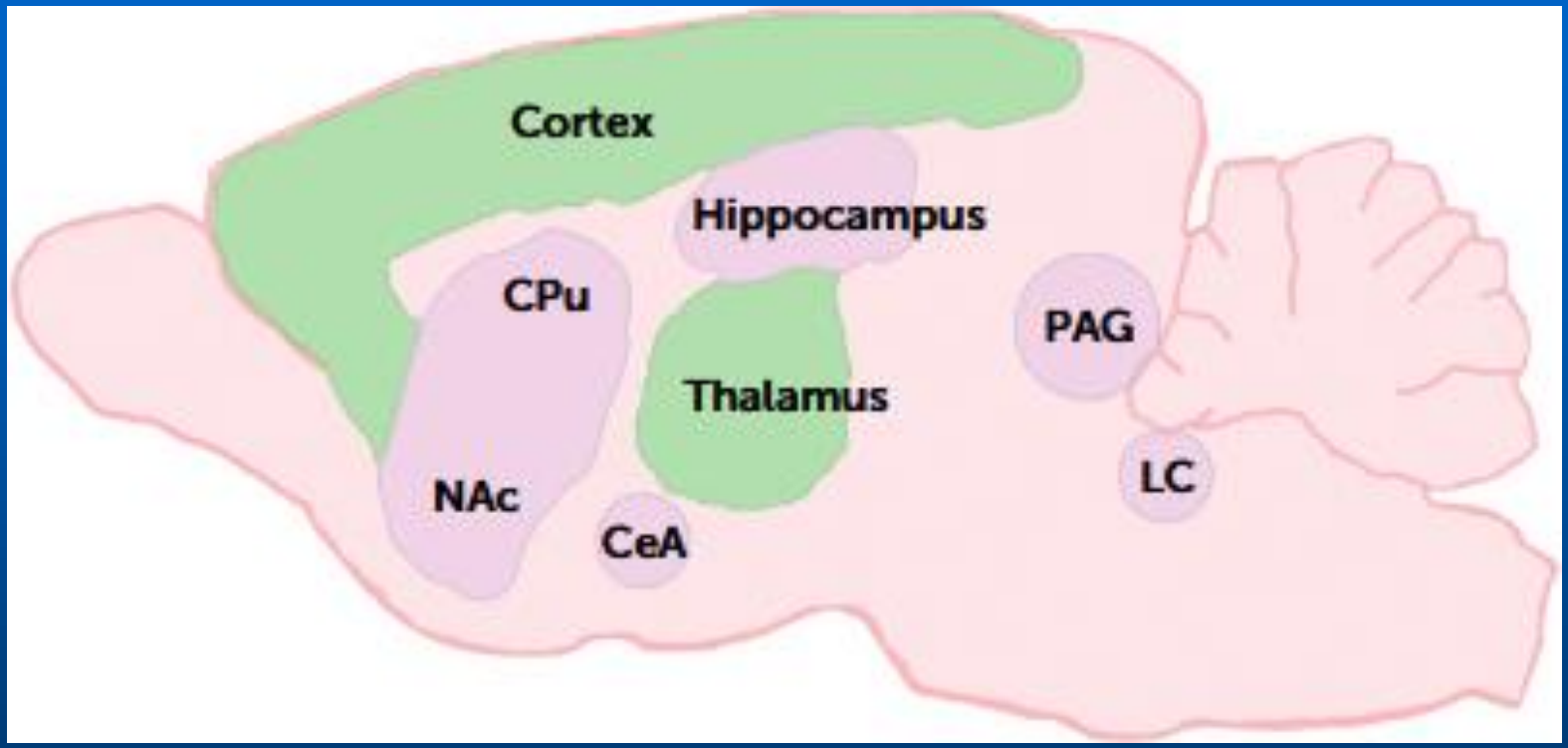
- Di Ianni et al – Nat Commun 2024

Naltrexone Blocks S-ketamine in Nucleus Accumbens



Levinstein et al. Biol Psych, 2023.

Colocalization of NMDARs and MORs[a]



[a] NMDARs and MORs are found on the same or neighboring synapses in many regions throughout the brain. Brain regions in which both NMDARs and MORs are present are depicted in green. Regions where NMDARs and MORs have been shown in the same synapses are in purple. CeA=central nucleus of the amygdala; CPu=caudate putamen; LC=locus coeruleus; MOR=mu-opioid receptor; NAc=nucleus accumbens; NMDAR=N-methyl-D-aspartate receptor; PAG=peri- aqueductal gray

Levinstein MR, et al. Am J Psychiatry. 2025 Mar 01;182(3):247-258.

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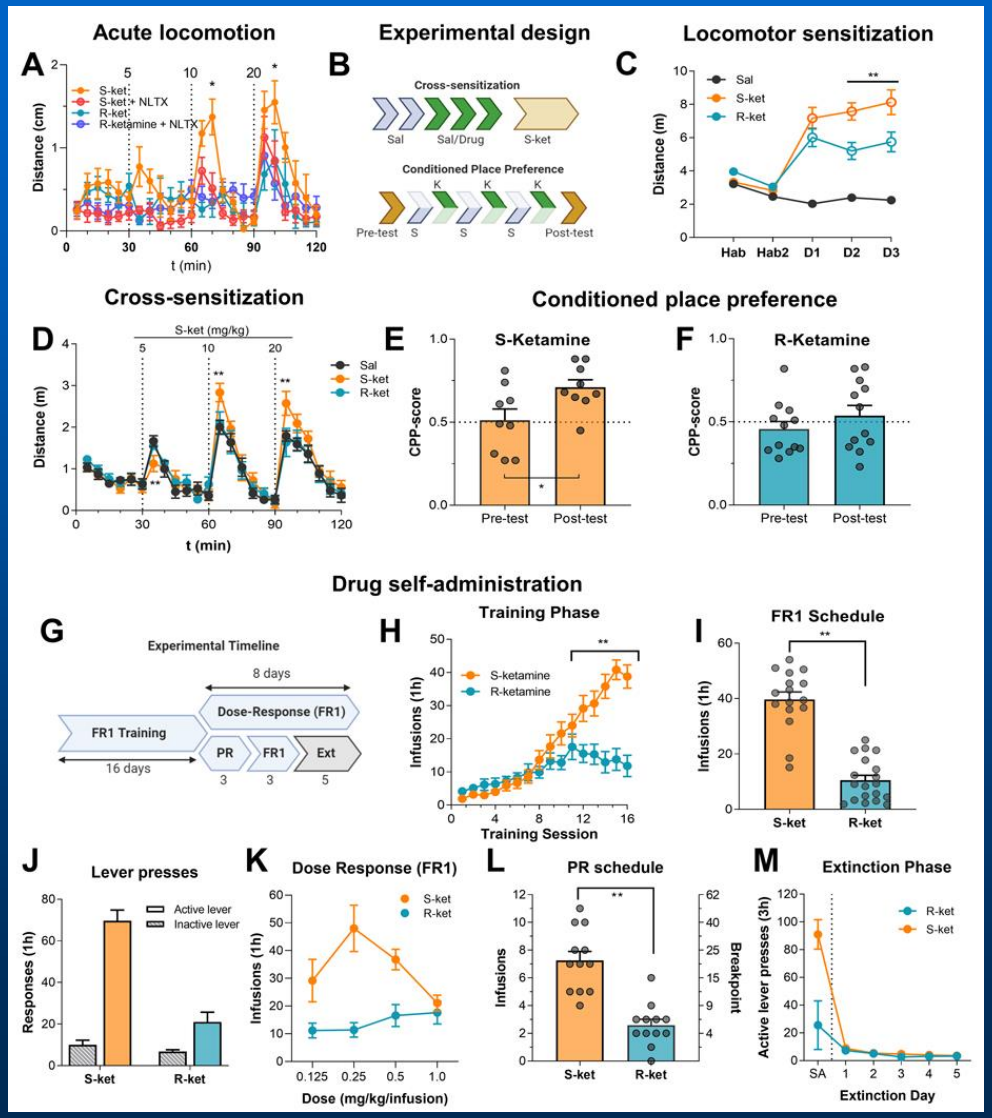
- Localization of the central opioid effect – medial prefrontal cortex primarily?
- Risk of abuse and optimal level and frequency of exposure
- Significance vis-a-vis developing new, rapidly-acting "glutamatergic" agents
- Sequencing ketamine to mu partial agonists

Studying the Possible Opioid MOA of Ketamine

"In fact if we step back for a moment and look at where we are – an intravenously administered agent that is a street drug of abuse, works rapidly and whose enantiomers are being studied by industry for intranasal use – we should be anxious…we need to be as careful and conservative as possible and understand how it is acting and rule out the possibility of whether it acts as an opioid."

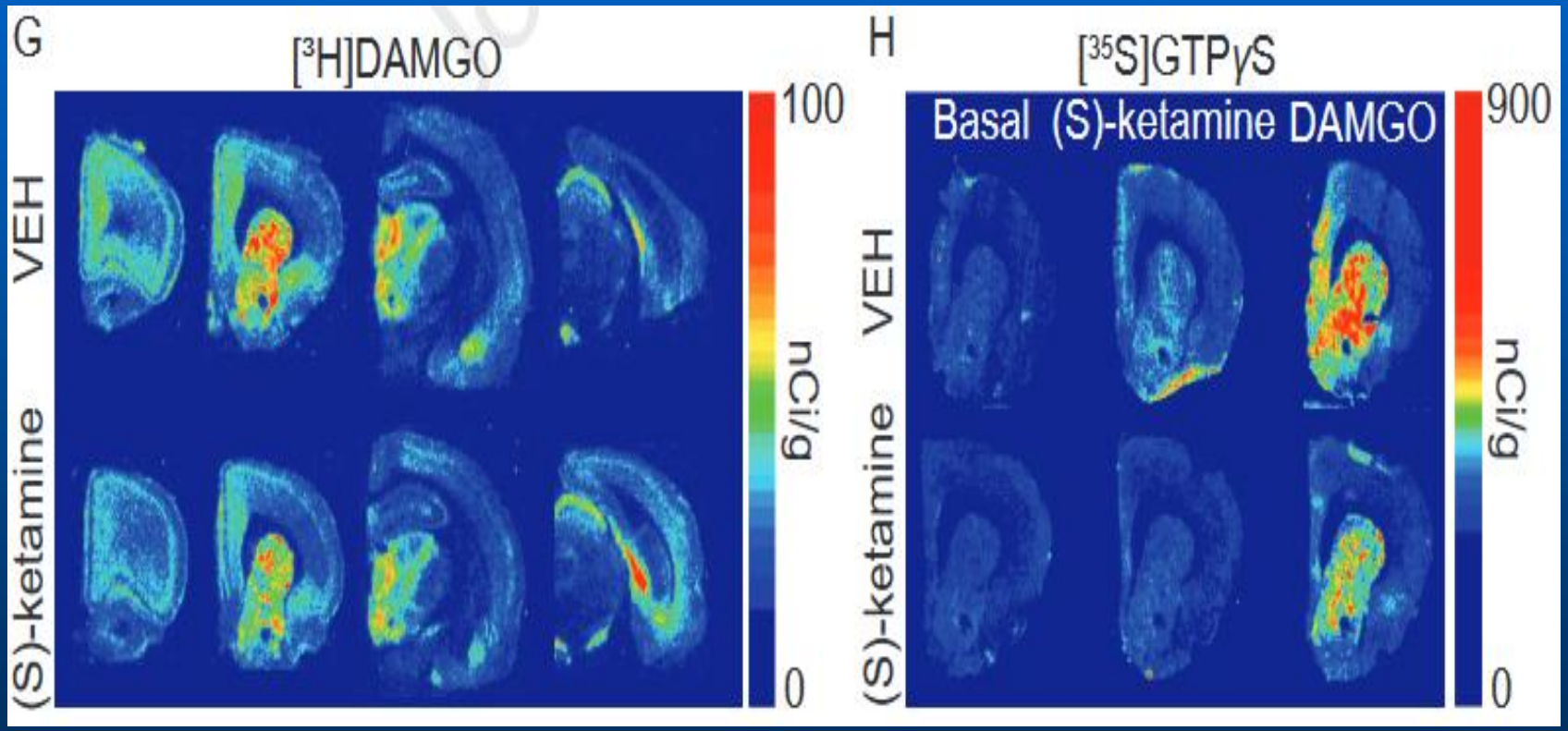
Sanacora G, Schatzberg AF: Neuropsychopharmacology 2015; 40: 259-267.

Functional Brain Imaging Reveals Regional Differences in the Effects of Ketamine Enantiomers



Bonaventura J et al, Mol Psych 2021.

S-ketamine Binds to Mu-opioid Receptors: PET Results



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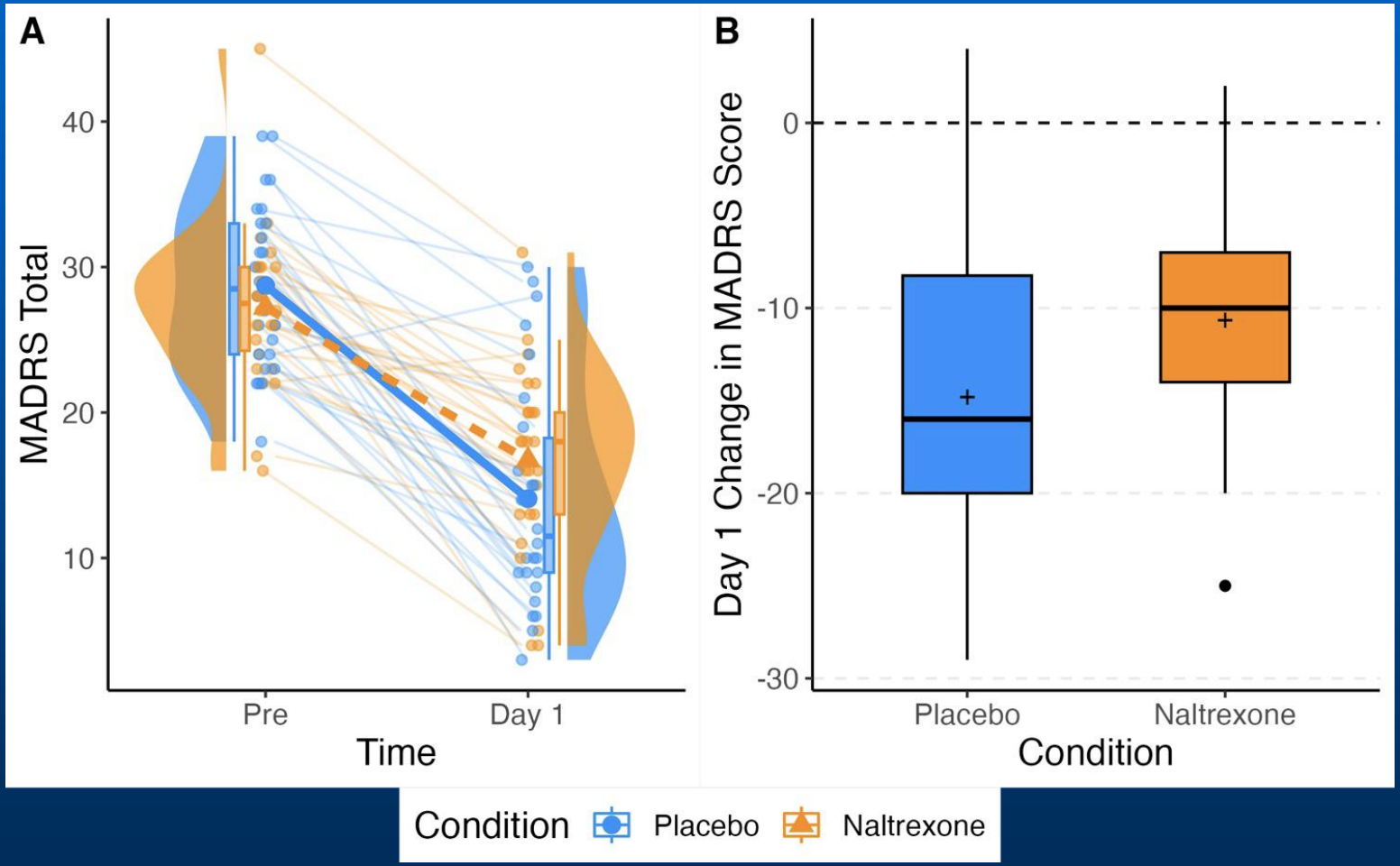


Jelen L, ACNP Annual Meeting 2023.

Recent Issues with Use of Oral Ketamine

- Overdose death of Matthew Perry with serum ketamine plus norketamine level at time of death approximately 10-X levels seen after a typical anti-depressant iv infusion
- Oral ketamine (and buprenorphine) reportedly physician-prescribed as were BZD's
- Patient reportedly also had iv ketamine treatment some 10 days previous

Issues in the Recreational Use of Ketamine

"The Wall Street Journal reported in January that Musk has used drugs, including cocaine, ecstasy, LSD and mushrooms, and that leaders at Tesla and SpaceX were concerned about it, particularly his recreational use of ketamine, for which Musk has said he had a prescription…Musk has attended social gatherings in recent years…where (he) took ketamine recreationally through a nasal spray bottle multiple times…"

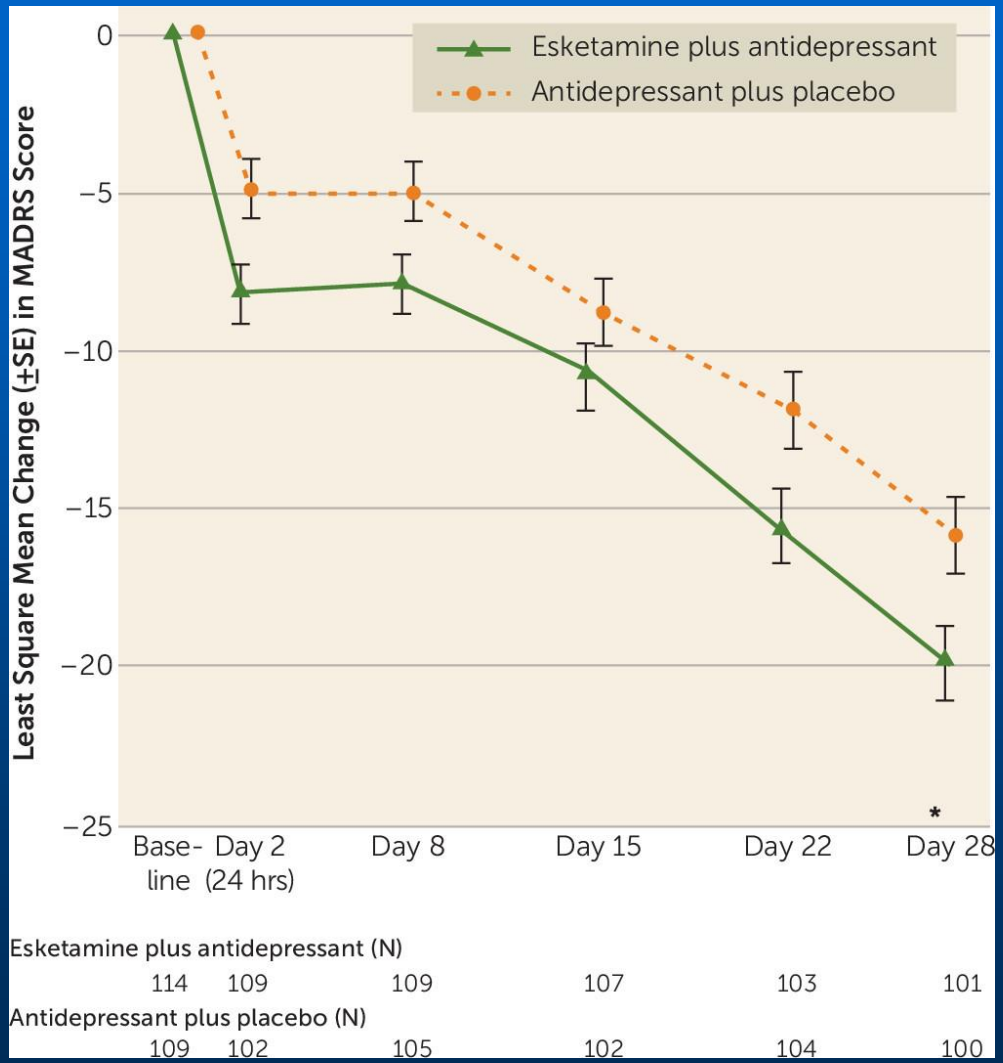
Wall Street Journal February 5, 2024

Phase III Intranasal Esketamine Trials in Refractory Depression

- 1of 3 blinded trials were positive; 2 near positive trials; mild effect sizes
- 1 maintenance discontinuation trial was positive

February 2019 DA Advisory Board Briefing Document

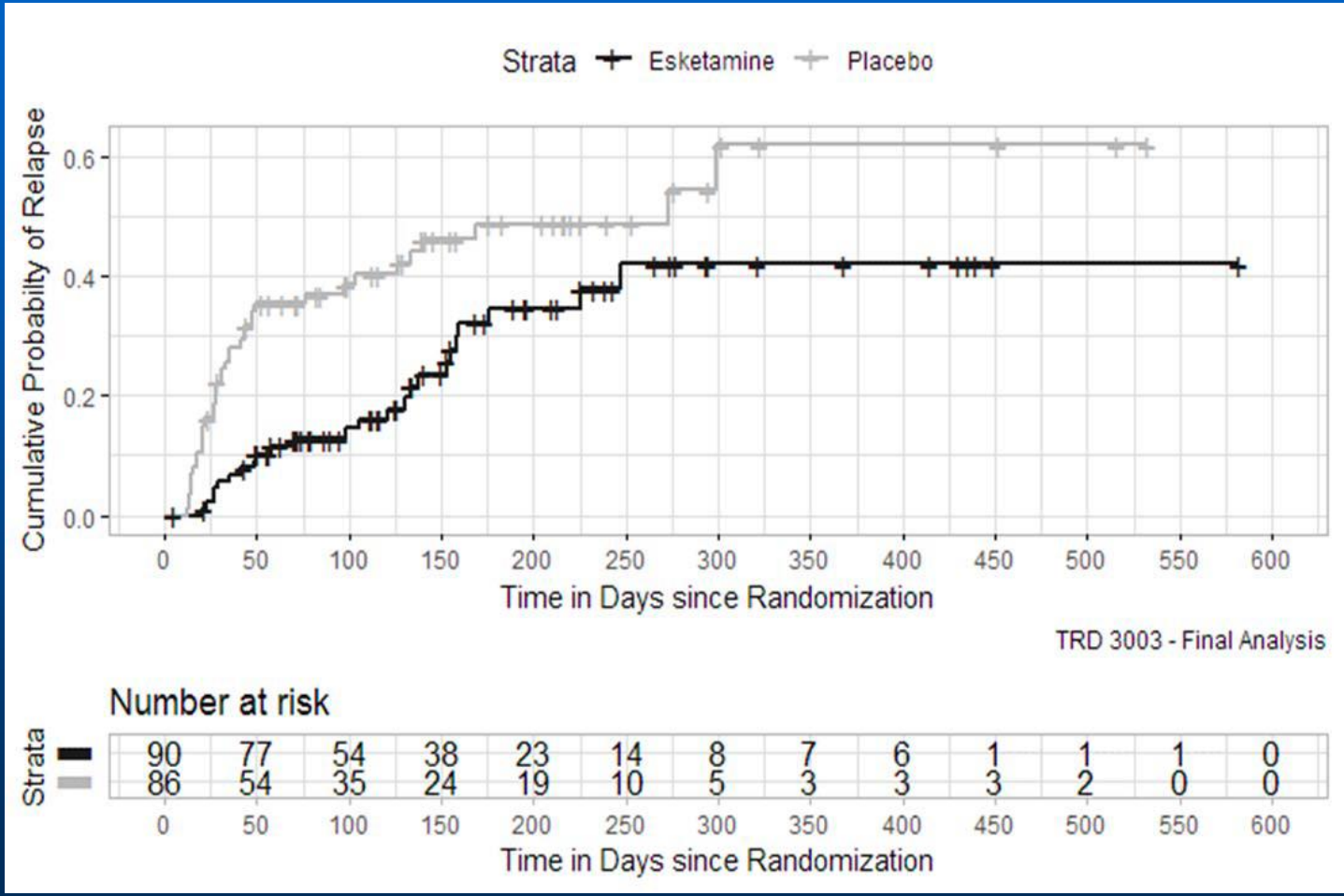
Efficacy of Flexibly Dosed Esketamine Nasal Spray in Treatment-Resistant Depression



*p=0.020

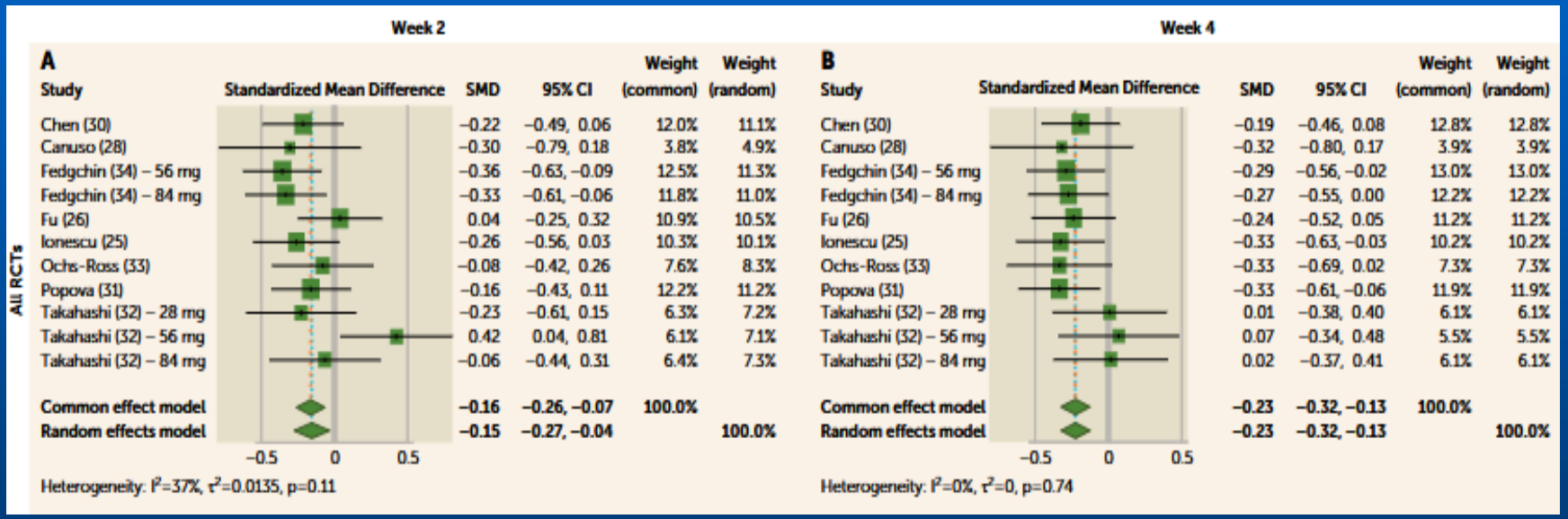
Popova V, et al. Am J Psychiatry, 2019.

Discontinuation from Esketamine in Stable Remitters



FDA Briefing Document, February 12, 2019.

FIGURE 2. Forest plots of results of randomized controlled trials concerning depression at weeks 2 and 4 weeks, and separately for treatment-resistant and non-treatment-resistant depression[a]



[a] Depression was assessed with the Montgomery-Asberg Depression Rating Scale. SMD=standardized mean difference

Fountoulakis KN, et al. Am J Psychiatry. 2025 Mar 01;182(3): 259-275.

Deaths, Serious Adverse Events, Adverse Events Leading to Study Withdrawal

"There were six deaths in the esketamine for treatment-resistant depression development program as of January 8, 2019, all in esketamine-treated subjects. 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. The patients who committed suicide 12 and 4 days after their last dose both appeared to be improving based on their MADRS scores (from baseline of 27 to 9, and 41 to 25, respectively). The patient who committed suicide 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)."

FDA Briefing Document, February 12, 2019.

Interim Results of Esketamine Maintenance Study (SUSTAIN-3) (N=1148)

- Patients followed for a mean of 31.5 months (2,769 patient years)
- 37.6% response + 19.8% remission at end of induction; 31.9% remission at end of maintenance
- Worsening depression in 1.5%; 5 esketamine related deaths
- All cause mortality 0.181/100 patient years was lower than TRD literature 0.79 to 4.6/100 patient years

Zaki N et al. Neurpyschopharm 2023.

Interim Results of SUSTAIN-3 Study: Suicidal Ideation and Behavior

- 4.3% new onset of suicidal ideation
- 10 patients (0.9%) attempted suicide (0.036/100 patient years); 9/10 with known history
- One death by suicide (0.036/100) patients years

Zaki N et al. Neurpyschopharm 2023.

Unanswered Questions Re Ketamine's Opioid Effects

- Degree of endogenous opioid release versus mu opioid binding; significance for placebo response
- Localization of the opioid effect – medial prefrontal cortex primarily? gender effect on response? second messenger effects?
- Risk of abuse and optimal level and frequency of exposure
- Significance vis-a-vis developing new, rapidly-acting "glutamatergic" agents
- Sequencing ketamine to mu partial agonists

NMDA/Opioid Like Agents in Development

- D-methadone
- Bupropion-dextromethorphan combination
- Tianeptine derivatives
- R-ketamine
- Kappa antagonists

D-Methadone in MDD

- Argued to be an NMDA antagonist and not a mu opioid agonist
- L-methadone is largely mu opioid in effect; d-methadone is similarly micromolar at both
- Abuse liability demonstrated at 150mg but not at 25-50mg per day, suggesting 25mg is safer
- Small Phase II study indicated efficacy at 25mg (Fava et al Am J Psychiatry) but three Phase III trials as monotherapy or add-on failed (Remalda press releases 2022 and 2024)

R-Ketamine in MDD

- IV formulation studied in Phase II trial in 102 patients versus placebo
- No significant differences observed on change in MADRS scores (Atai press release 2023)
- Agent was not dissociative

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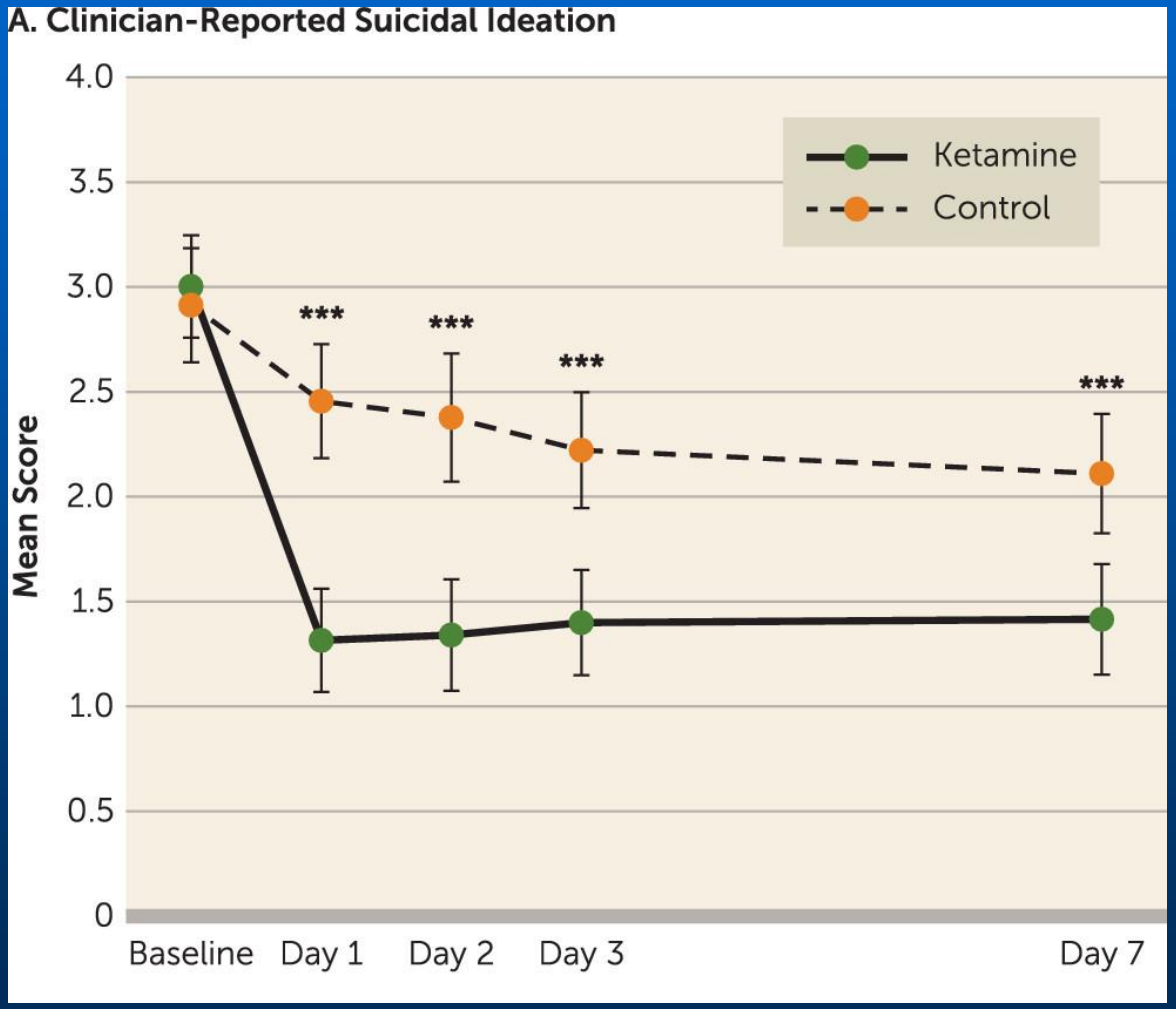
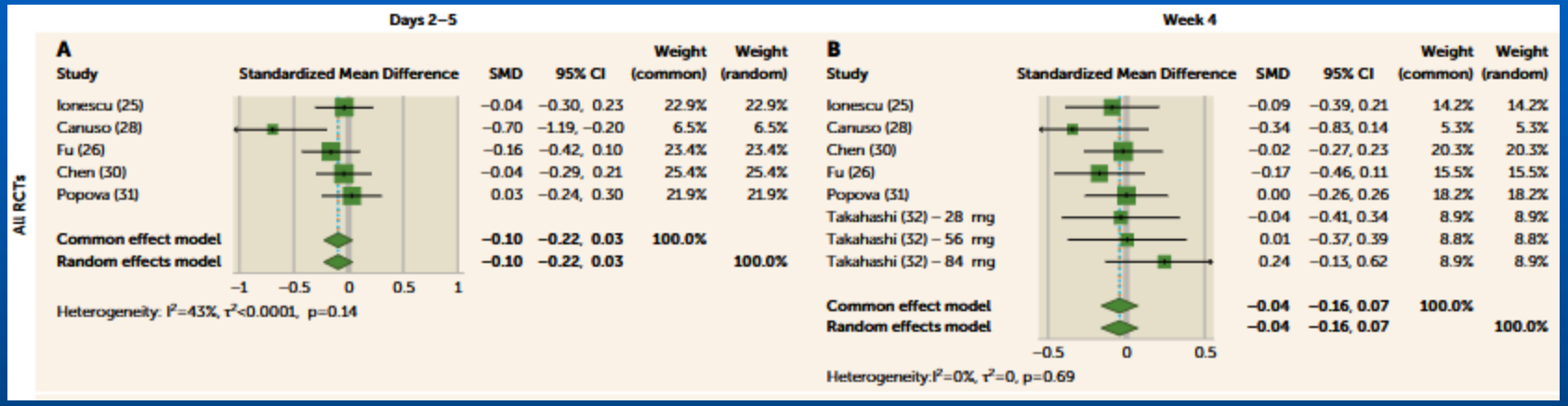
Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Clinician-Administered Measure



Wilkinson et al Am J Psychiatry 2018; 175: 150-158.

FIGURE 3. Forest plots of results of randomized controlled trials concerning suicidality at days 2–5 and 4 weeks, and separately for treatment-resistant and non-treatment-resistant depression[a]



[a]Suicidality was assessed with the Beck Scale for Suicidal ideation, the Clinical global Impressions – Severity of Suicidality – Revised Scale, or the Columbia-Suicide Severity Rating Scale. SMD=standardized mean difference

Fountoulakis KN, et al. Am J Psychiatry. 2025 Mar 01;182(3): 259-275.

Buprenorphine

- Partial mu opioid agonist
- Used at high doses (8-24 mg per day) to block typical opioid effects in substance abusers
- Low doses (<2.0mg per day) have been used to treat refractory depression - Bodkin and Cole 1995
- Ultra low doses of 0.2mg-0.8mg/ day appear to reduce suicidal behavior - Yovell et al 2016

Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial

Yoram Yovell, M.D., Ph.D., Gali Bar, Ph.D., Moti Mashiah, M.D., Amit Lotan, M.D., Amihai Rigbi, Ph.D., Jaak Panksepp, Ph.D.Yehuda Baruch, M.D., Irina Briskman, M.D., Jack Asherov, M.D.

Objective: Suicidal ideation and behavior currently have no quick-acting pharmacological treatments that are suitable for independent outpatient use. Suicidality is linked to mental pain, which is modulated by the separation distress system through endogenous opioids. The authors tested the efficacy and safety of very low dosages of sublingual buprenorphine as a time-limited treatment for severe suicidal ideation.

Method: This was a multisite randomized double-blind placebo-controlled trial of ultra-low-dose sublingual buprenorphine as an adjunctive treatment. Severely suicidal patients without substance abuse were randomly assigned to receive either buprenorphine or placebo (in a 2:1 ratio), in addition to their ongoing individual treatments. The primary outcome measure was change in suicidal ideation, as assessed by the Beck Suicide Ideation Scale at the end of each of 4 weeks of treatment.

Results: Patients who received ultra-low-dose buprenorphine (initial dosage, 0.1 mg once or twice daily; mean final dosage=0.44 mg/day; N=40) had a greater reduction in Beck Suicide Ideation Scale scores than patients who received placebo (N=22), both after 2 weeks (mean difference −4.3, 95% CI=−8.5, −0.2) and after 4 weeks (mean difference=−7.1, 95% CI=−12.0, −2.3). Concurrent use of antidepressants and a diagnosis of borderline personality disorder did not affect the response to buprenorphine. No withdrawal symptoms were reported after treatment discontinuation at the end of the trial.

Conclusions: The time-limited, short-term use of very low dosages of sublingual buprenorphine was associated with decreased suicidal ideation in severely suicidal patients without substance abuse. Further research is needed to establish the efficacy, safety, dosing, and appropriate patient populations for this experimental treatment.

Am J Psychiatry 2016; 173:491–498; doi: 10.1176/appi.ajp.2015.15040535

FIGURE 1. Changes From Baseline in Score on the Beck Scale for Suicide Ideation in Patients With Suicidal Ideation Who Received Buprenorphine or Placebo

Yovell, et al 2016

*p,0.05. **p,0.01.

Study Design for Acute Treatment of Suicidal Behavior

- 60 patients with major depression and active suicidal behavior
- All patients receive one open label, intravenous infusion of ketamine
- Two days later patients are randomized to receive ultra low doses of oral buprenorphine or placebo for 4 weeks
- Clinical and biological assessments weekly