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11TH ANNUAL

CHAIR SUMMIT

CME Outfitters

Master Class for Neuroscience Professional Development

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The Pluses and Minuses of Ketamine for Major Depression

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Learning Objective 1

Weigh the pros and cons for the use of ketamine for the management of treatment-resistant depression and suicide prevention

Learning Objective 2

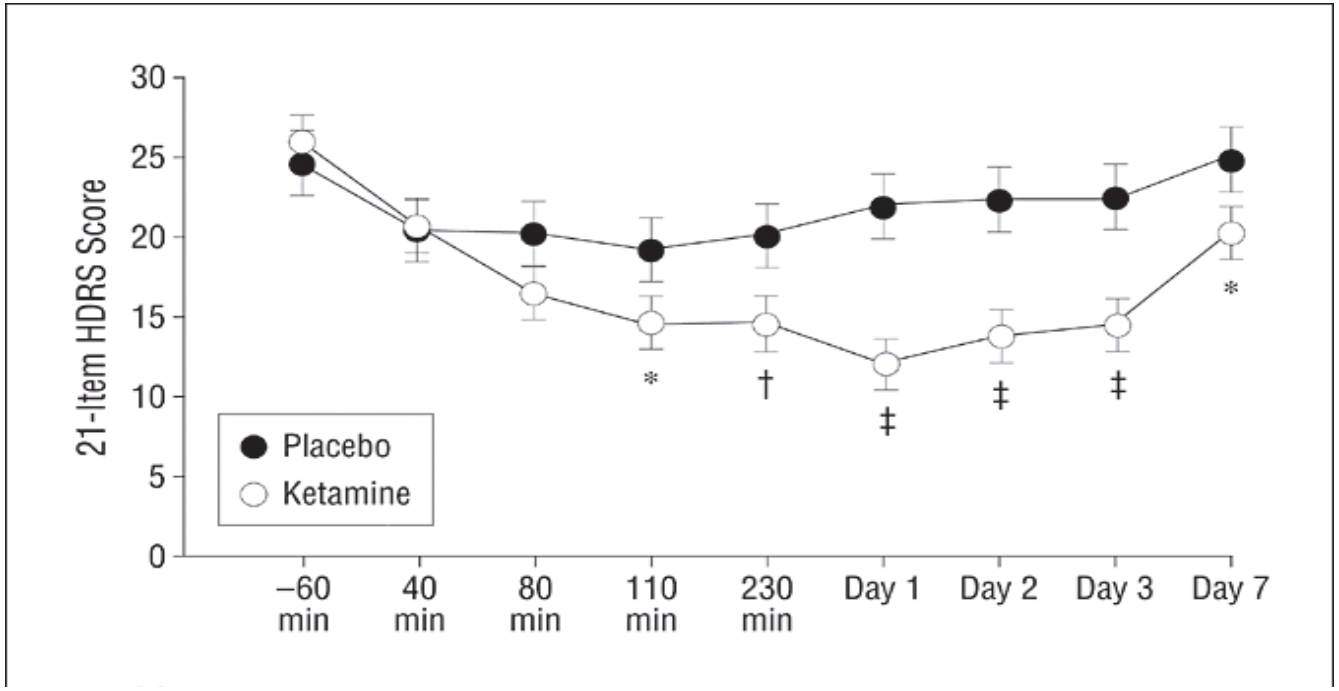
Examine the mechanisms of action of ketamine on the pathophysiology of depression

Ketamine

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

Ketamine Improves Depression Relative to Placebo

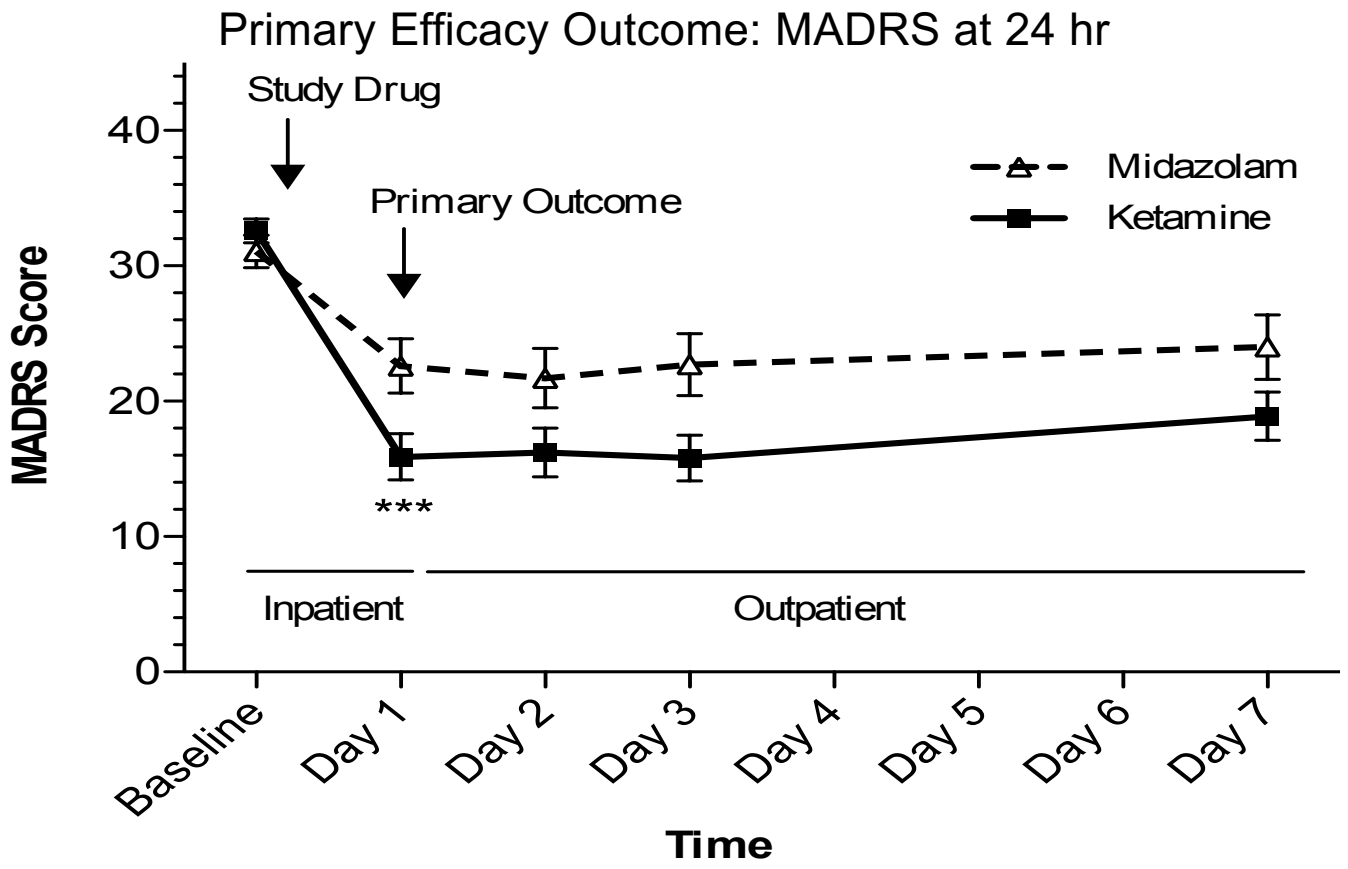
Change in the 21-item Hamilton Depression Rating Scale (HDRS) over 1 week (n = 17)



* indicates $p < .05$; †, $p < .01$; ‡, $p < .001$.

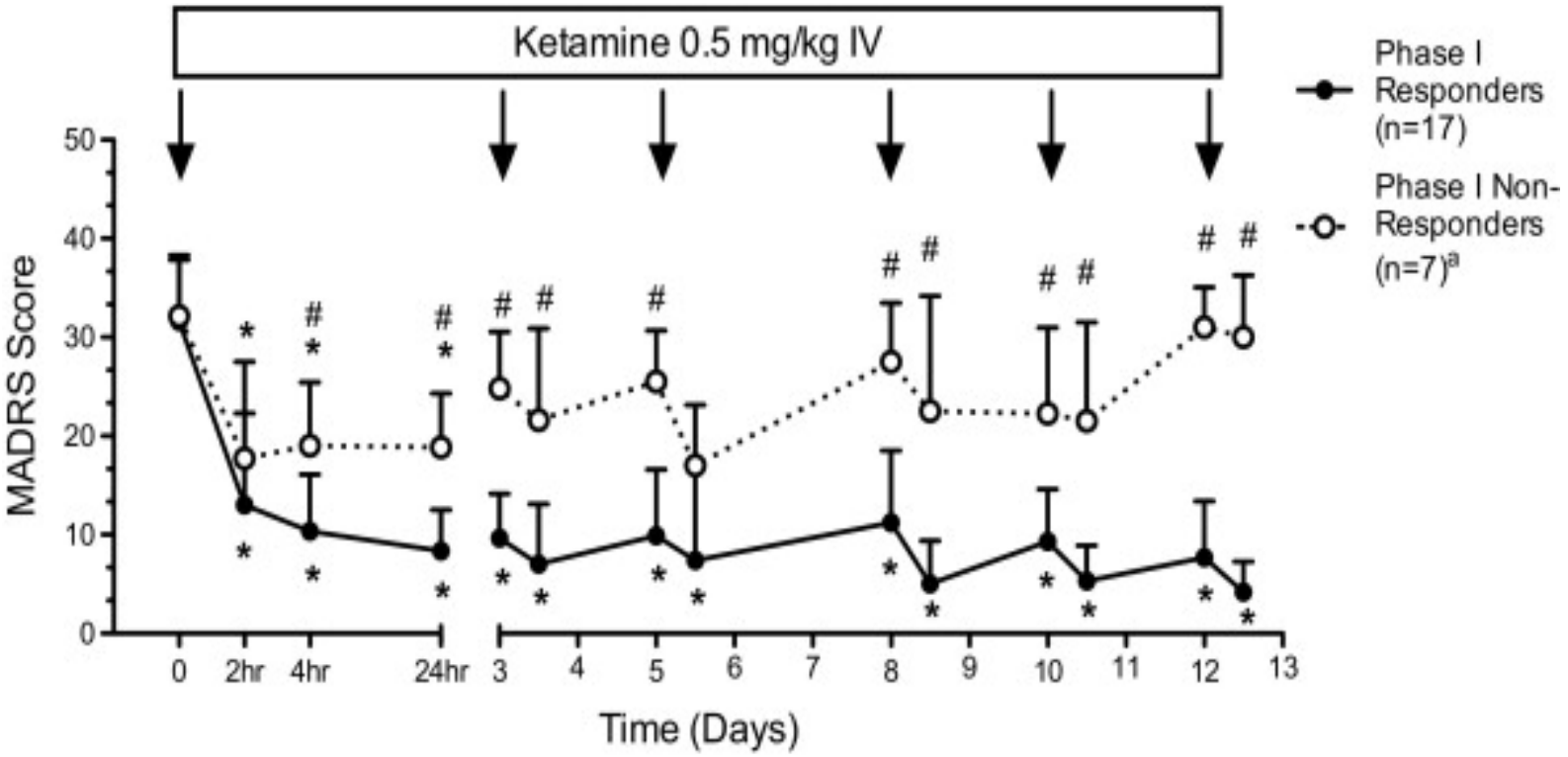
Zarate, CA et al. *Arch Gen Psychiatry.* 2006; 63:856-864.

Ketamine Produces Rapid Antidepressant Effects Compared to Midazolam



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

Response to Repeated Ketamine Infusions



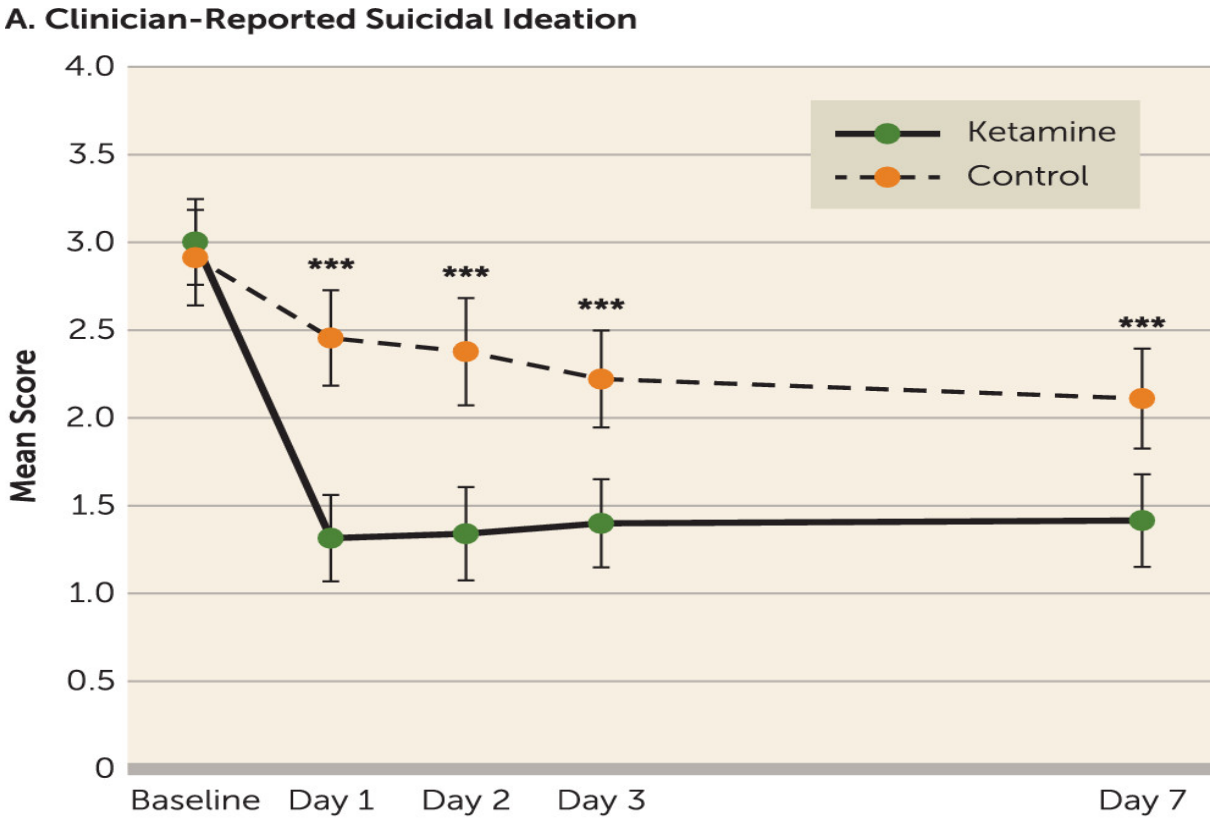
*$p < .05$

#MADRS score significantly different at given time point between responder and non-responder subgroups

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

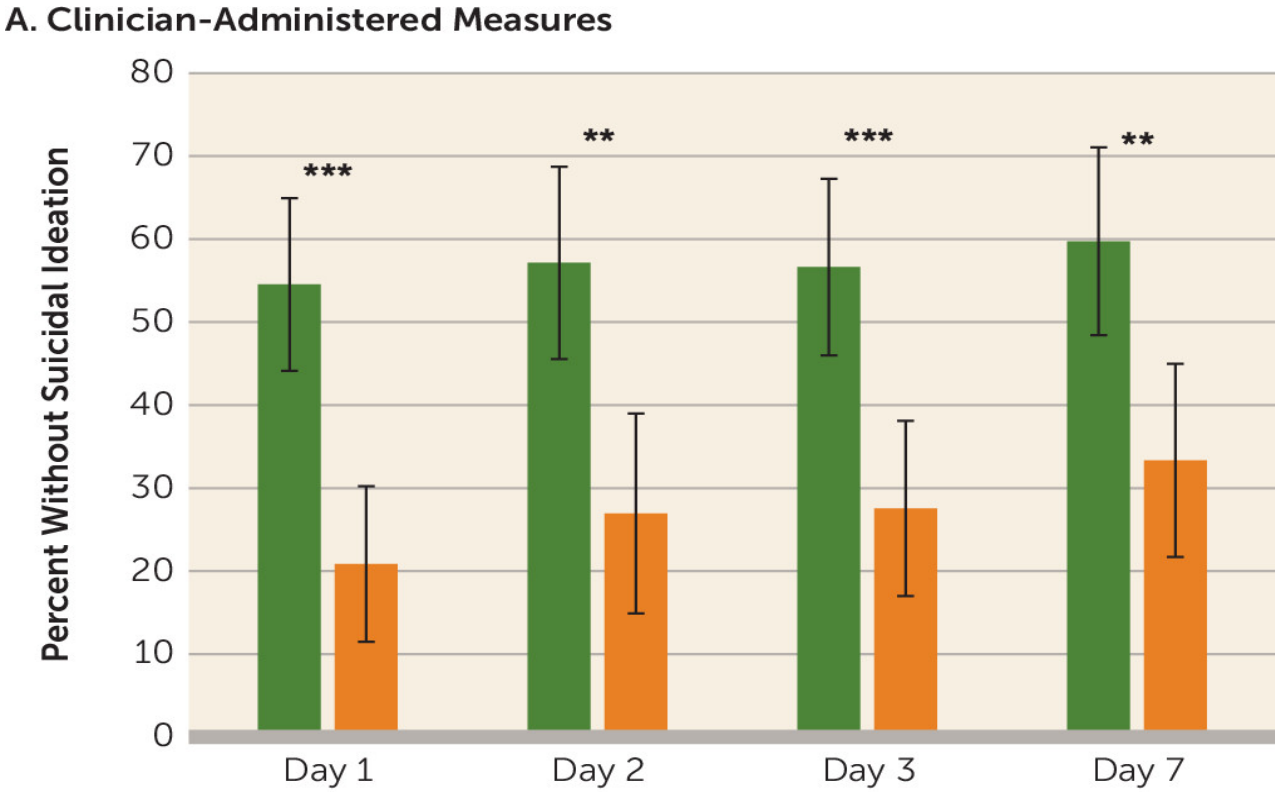
Effect of a Single Dose of Ketamine on Suicidal Ideation as Indicated by Clinician-Administered Measure

***$p < .001$



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

Proportion of Study Subjects Without Suicidal Ideation at Each Time Point After Ketamine Dosing

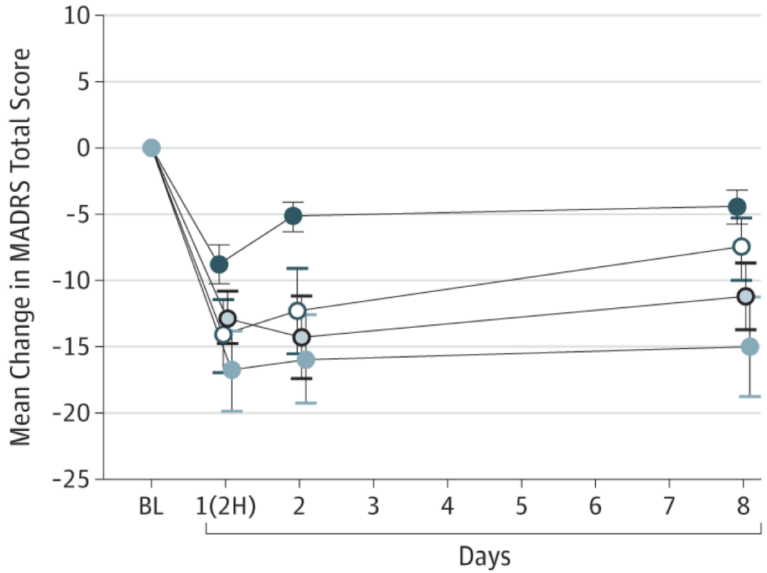


**p <.01
***p <.001

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

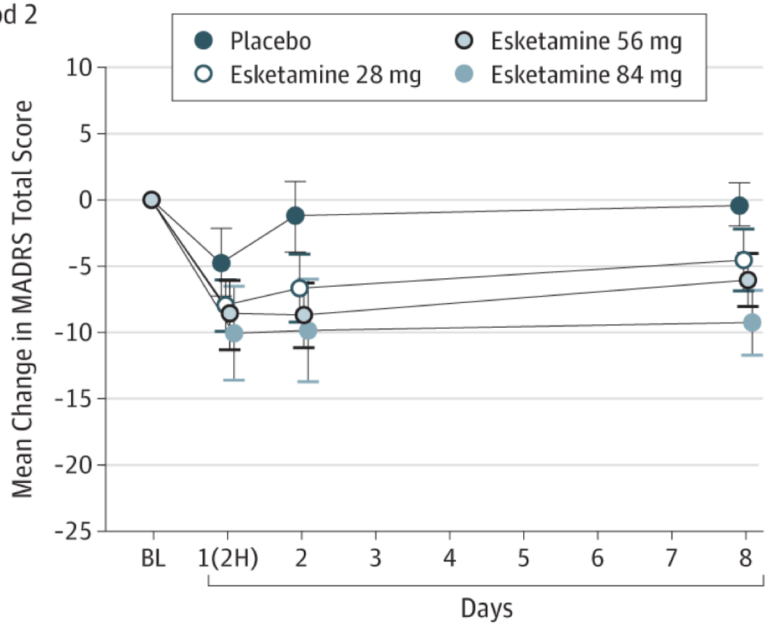
Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time in Double-Blind Phase in Refractory Major Depression

A Period 1



No. of participants				
Placebo	33	33		33
Esketamine 28 mg	11	11		11
Esketamine 56 mg	11	11		11
Esketamine 84 mg	12	12		12

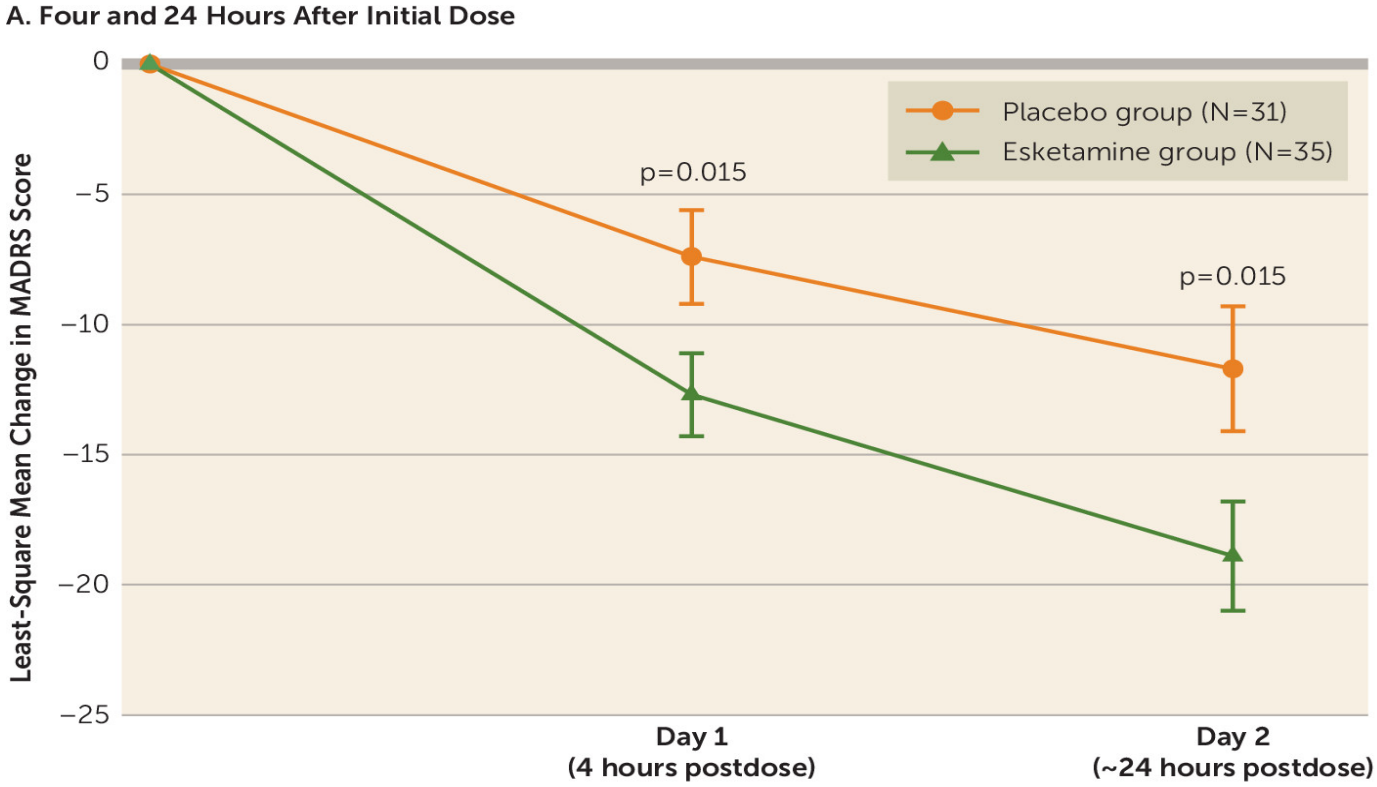
B Period 2



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

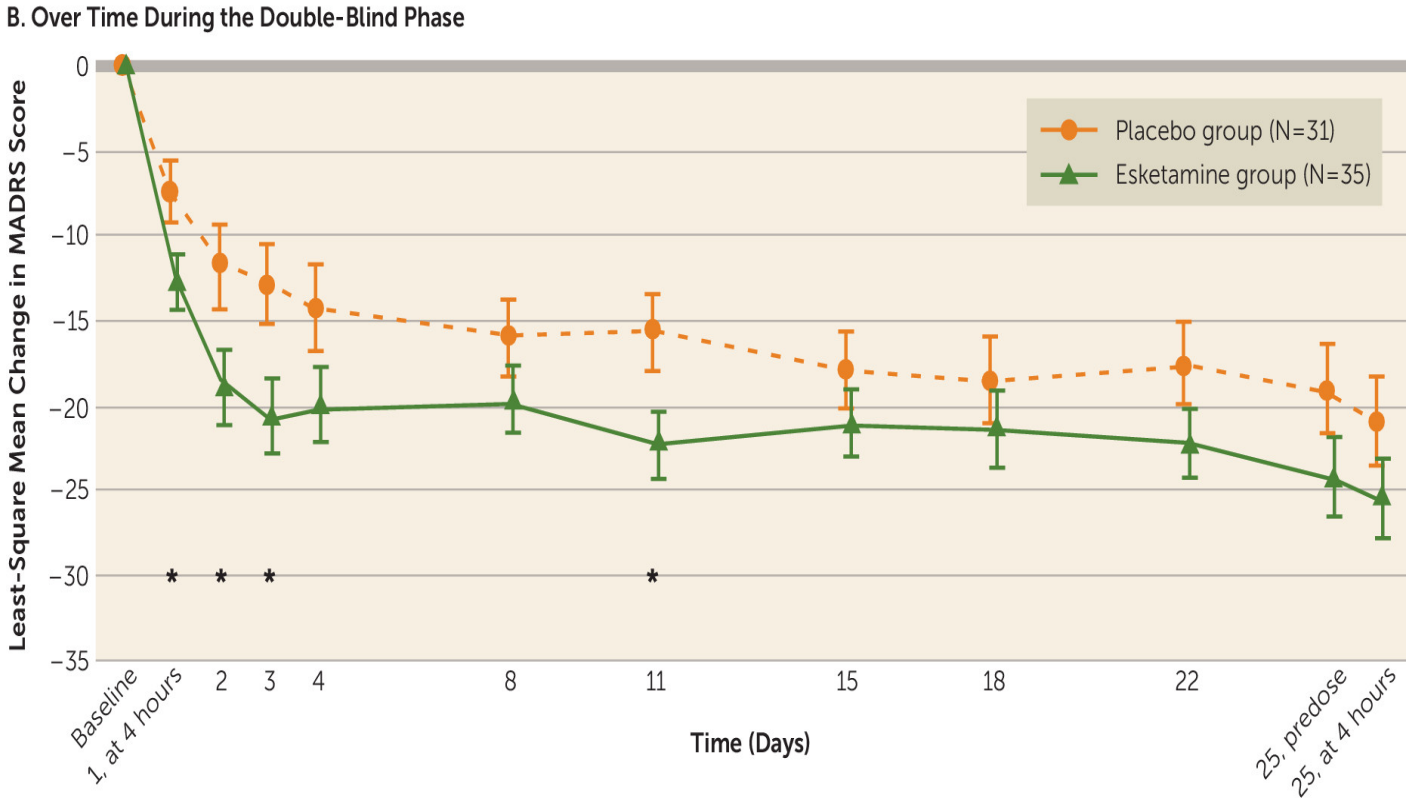
Daly EJ, et al. *JAMA Psychiatry.* 2018;75:139-148.

Intranasal Esketamine for Rapid Reduction of Symptoms in Patients at Imminent Risk for Suicide



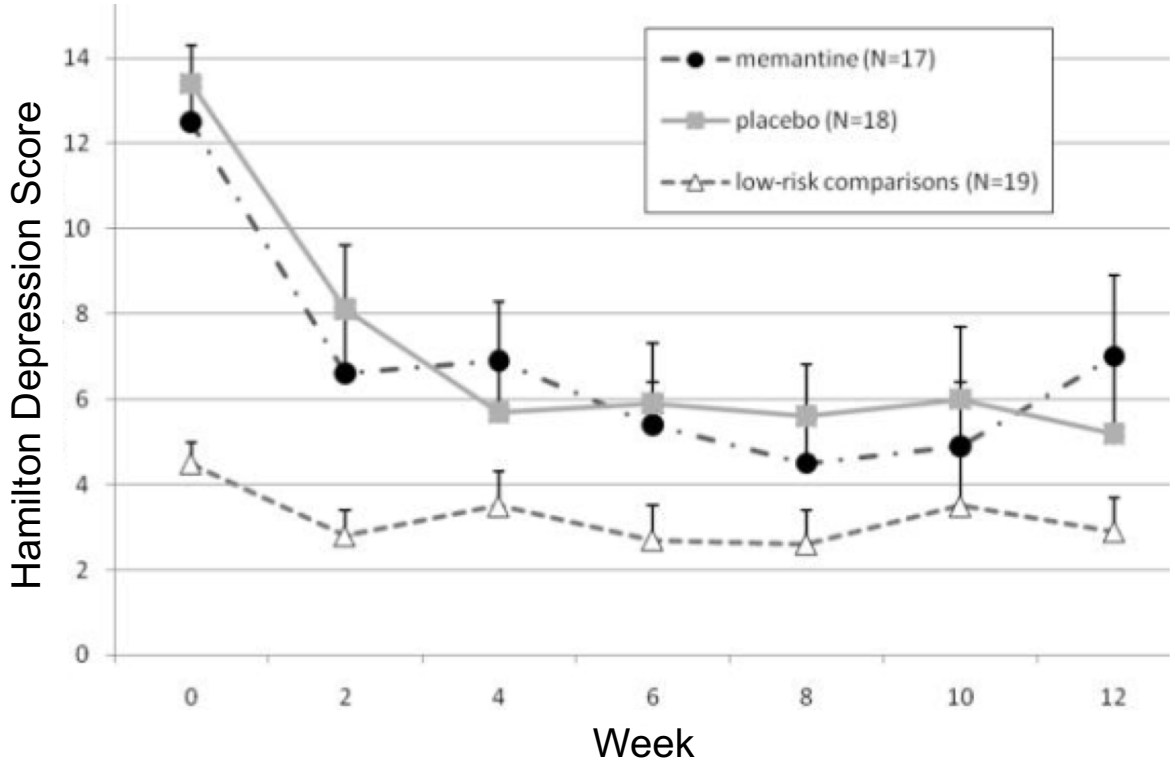
Canuso CM, et al, *Am J Psychiatry*. 2018;175:620-630.

Intranasal Esketamine for Rapid Reduction of Symptoms in Patients at Imminent Risk for Suicide (cont.)



Canuso CM, et al, *Am J Psychiatry*. 2018;175:620-630.

Memantine for Late-Life Depression and Apathy After Disabling Medical Event: HDRS Effect



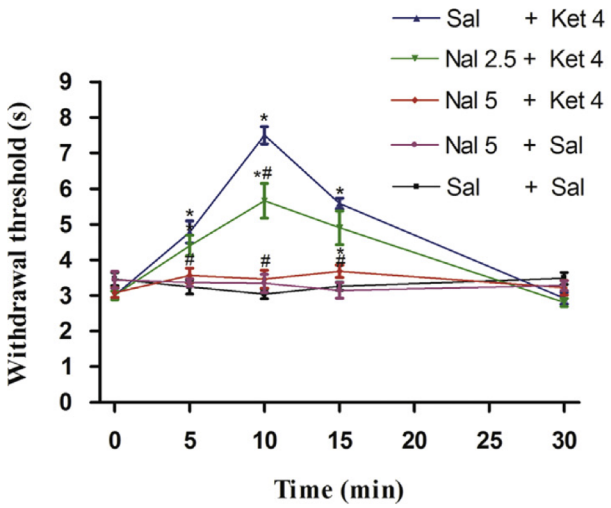
Lenze EJ, et al. *Int J Geriatr Psychiatry.* 2012;27(9):974-980.

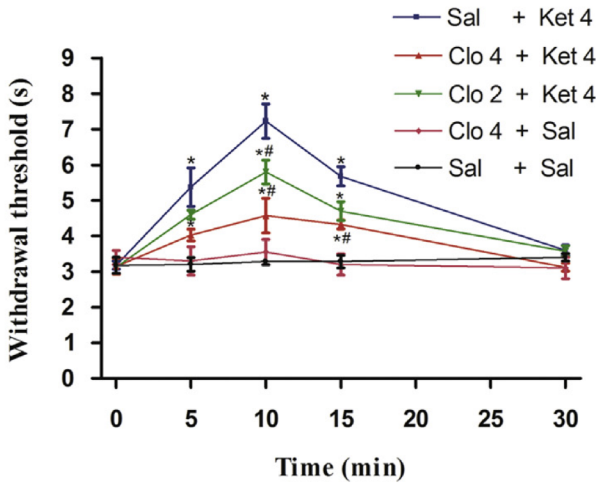
Ketamine and Morphine in OCD

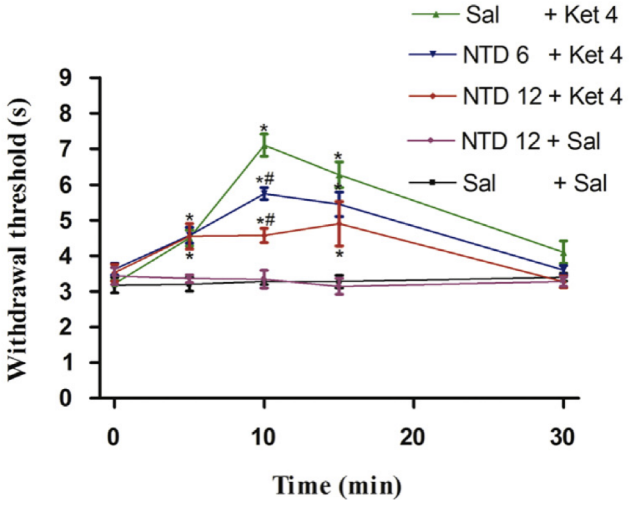
- IV ketamine significantly more effective than placebo in refractory OCD; effects last one week in some patients[1]
- Oral morphine significantly more effective than placebo in refractory OCD; effects seen the next day and last for 5 days[2]

1. Rodriguez C, et al. *Neuropsychopharmacology*. 2013; 38:2475-2483.
2. Koran L, et al. *J Clin Psychiatry*. 2005; 66:353-359.

Antagonism Induced by Intracerebroventricular Administration of Naloxone (a), Clocinnamox (b) or Naltrindole (c) on the Central Antinociception Produced by Ketamine







Nal = naloxone; Clo = clocinnamox; NTD = Naltrindole; SAL = saline

Pachecho DF, et al. *Brain Res*. 2014;1562: 69-75.

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."

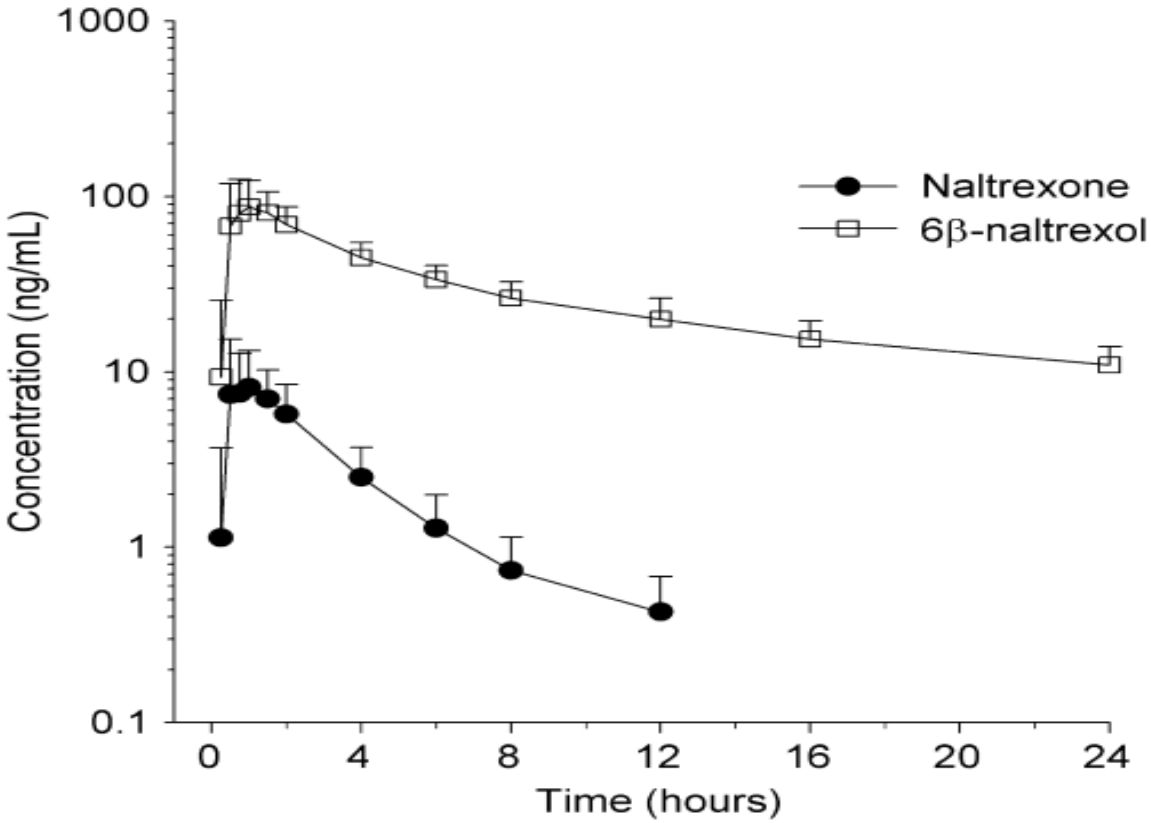
Sanacora G, et al. *Neuropsychopharmacology.* 2015;40:259-267.

Studying the Possible Opioid MOA of Ketamine (cont.)

"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, et a.. *Neuropsychopharmacology.* 2015; 40: 259-267.

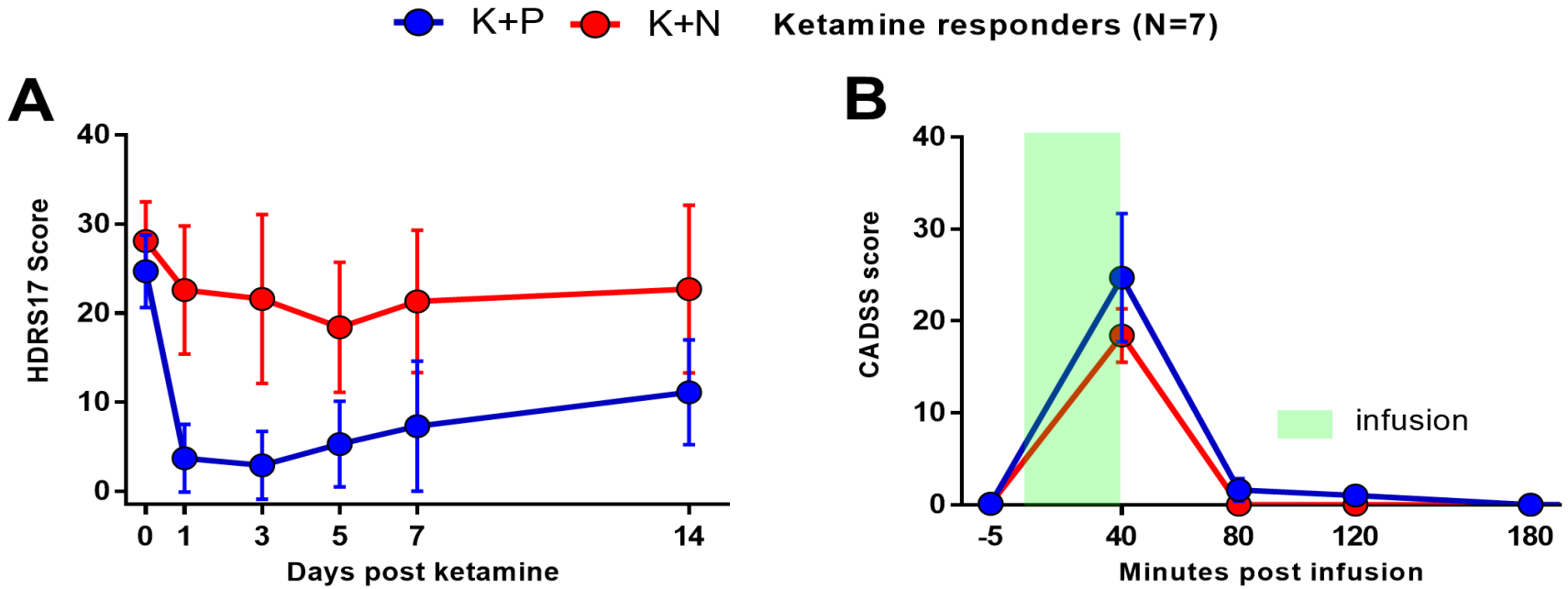
Mean Plasma Concentration of Naltrexone and 6β-naltrexol Following Single Dose Administration of Oral Naltrexone 50 mg



Dunbar JL, et al. *Alcohol Clin Exp Res.* 2006;30(3):480-490.

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

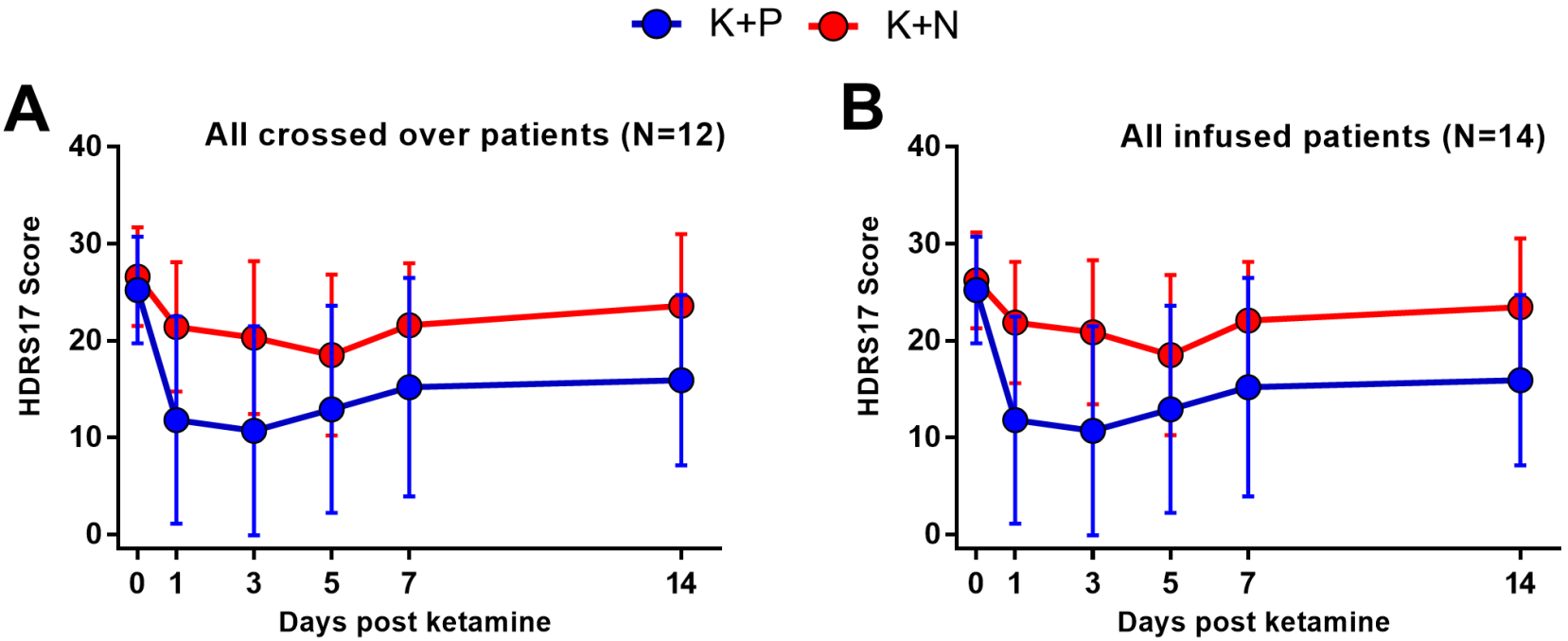
Ketamine + placebo responders



A: Primary outcome at Day 1 was significant (F = 43.6, *p* = .0006)
B: No significant differences in dissociation measure

Williams NR, et al. *Am J Psychiatry.* 2018;175(12):1205-1215.

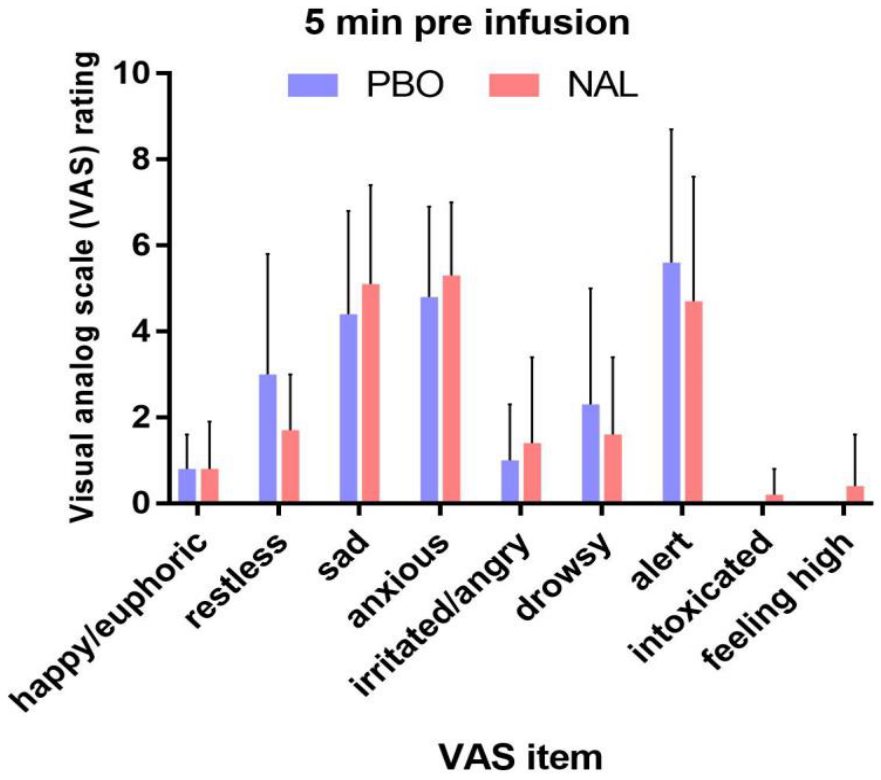
Naltrexone Pretreatment Blocks Ketamine's Antidepressant Effects



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

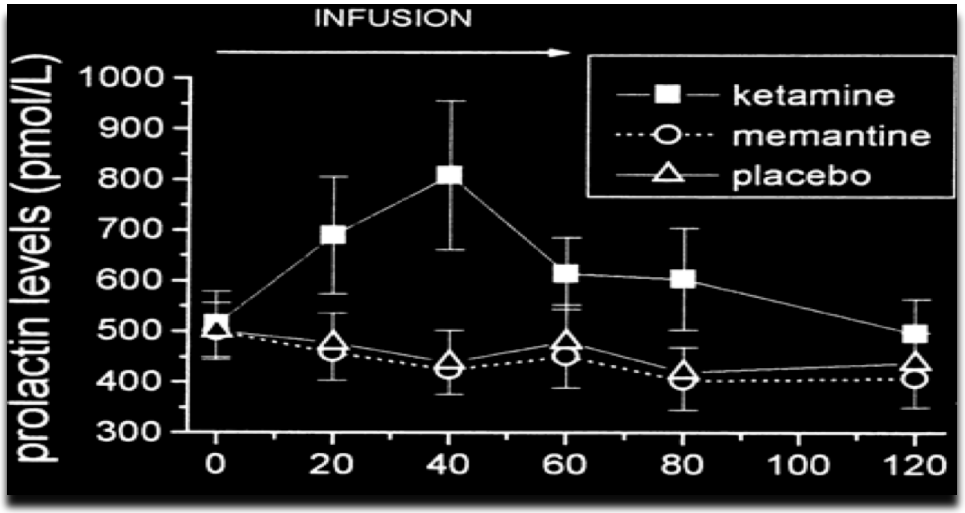
Williams NR, et al. *Am J Psychiatry.* 2018;175(12):1205-1215.

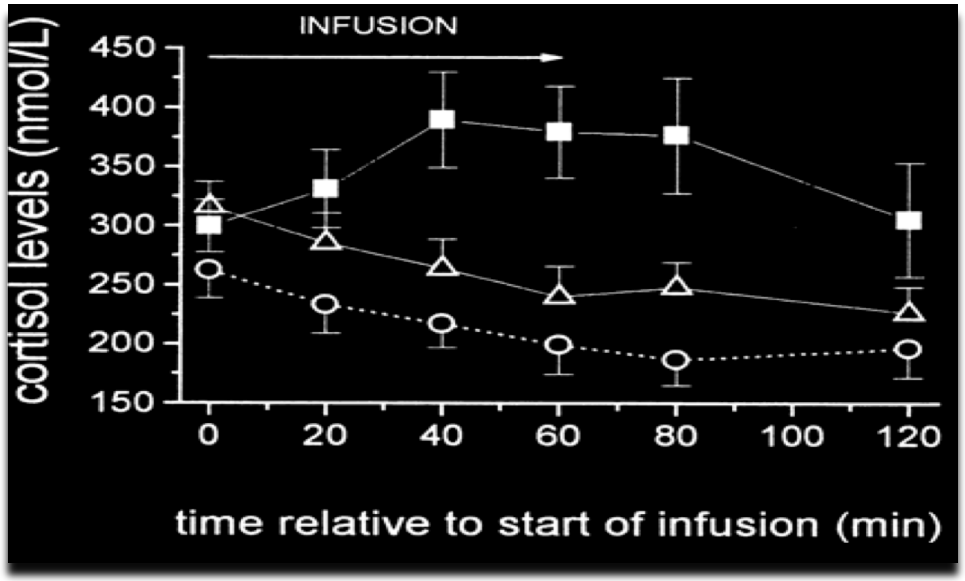
VAS Item Scores After Placebo vs. Naltrexone



Williams NR, et al. *Am J Psychiatry.* 2018;175(12):1205-1215.

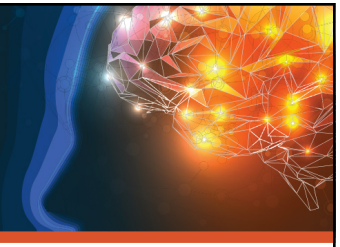
Mean Serum Prolactin (Top Layer) and Cortisol (Bottom Layer) Levels After Ketamine, Memantine and Placebo Infusion (n = 15)





Hergovich N, et al. *Neuropsychopharmacology.* 2001;24:590-593.

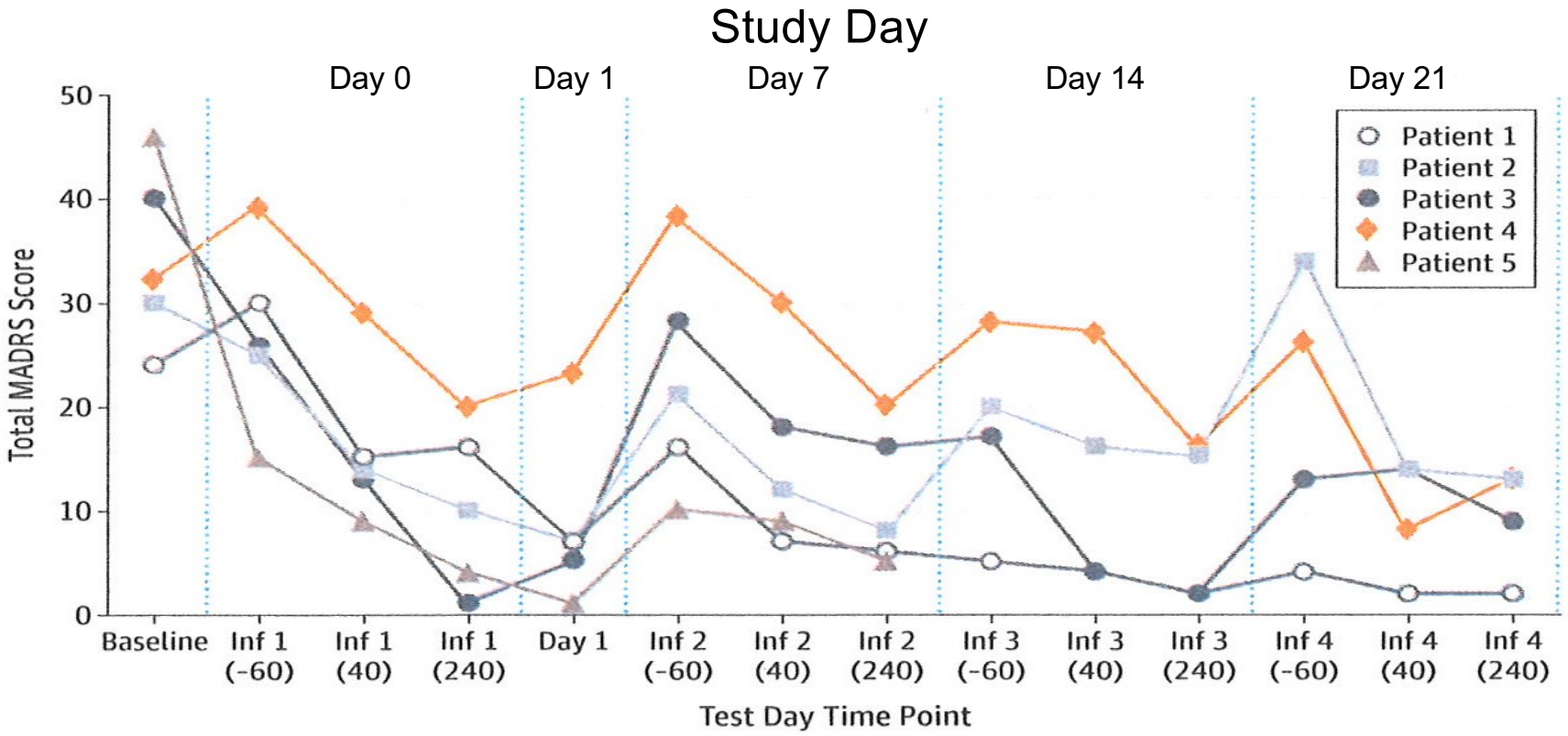
Effects of Naltrexone on Depression and Antidepressants



- **Naltrexone does not exacerbate depressive symptoms**; In normal healthy and depressed individuals, naltrexone does not precipitate depression or cause depressive symptoms.
- **Naltrexone does not block antidepressant action**; Across a number of studies, co-administration of naltrexone with an antidepressant did not block the action of the antidepressant.

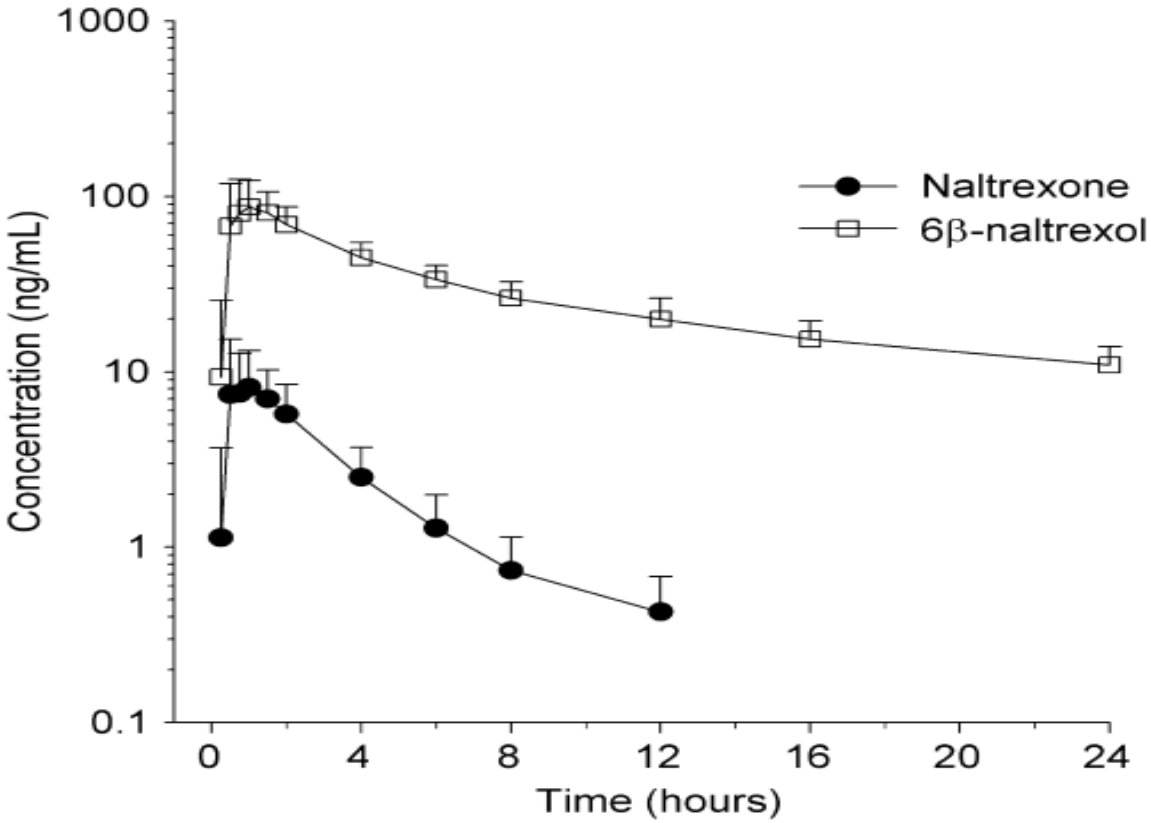
Williams NR, et al. *Am J Psychiatry*. 2018;175(12):1205-1215.

Depressive Symptoms from Baseline to Fourth Ketamine Infusion During the Combination of Naltrexone and Ketamine Treatment



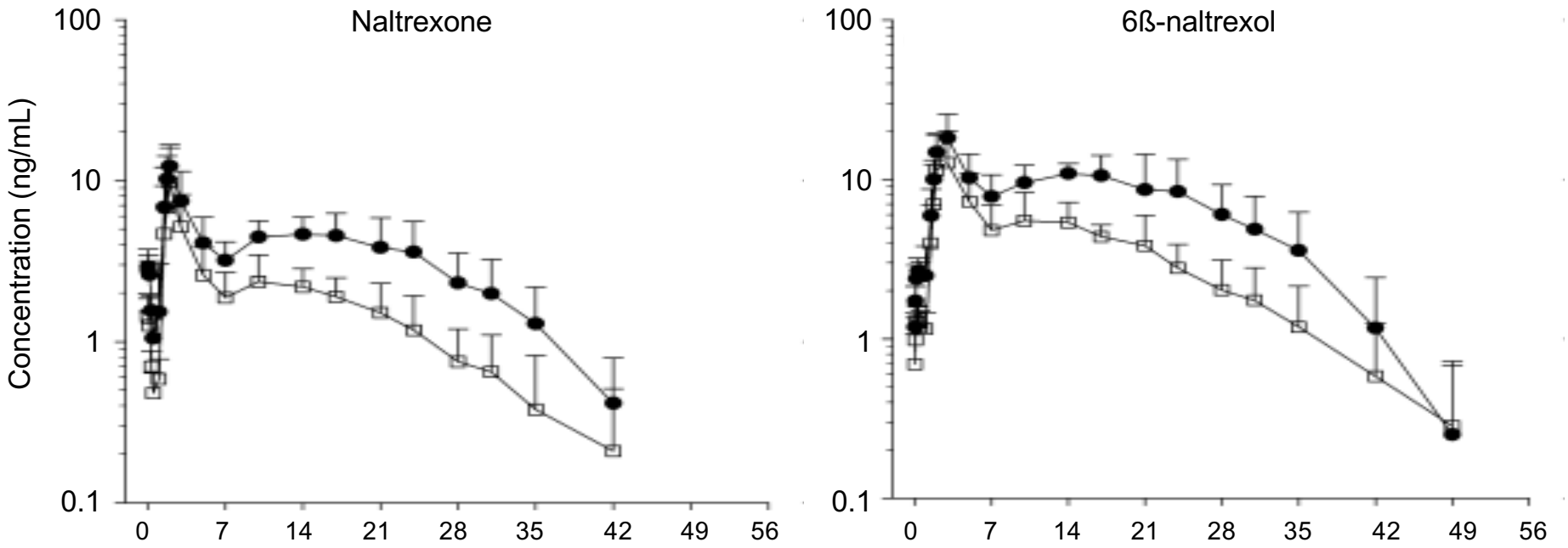
Yoon G, et al., *JAMA Psychiatry.* 2019.

Mean Plasma Concentration of Naltrexone and 6β-naltrexol Following Single Dose Administration of Oral Naltrexone 50 mg



Dunbar JL, et al. *Alcohol Clin Exp Res.* 2006;30(3):480-490.

Mean Plasma Concentration of Naltrexone and 6β-naltrexol Following Single Dose Administration of Long-acting Naltrexone 190 (□) and 380 (•) mg



Dunbar JL, et al. *Alcohol Clin Exp Res.* 2006;30(3):480-490.

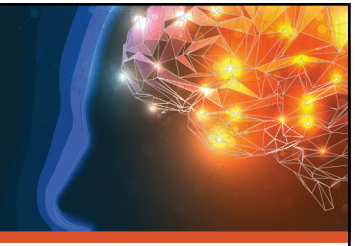
Comparison of Oral and Intramuscular Naltrexone: C_{MAX} and t_{max}

	Oral 50 mg	Intramuscular 380 mg
Naltrexone	10.6 ng/ml	12.9 ng/ml
Naltrexone t_{max}*	1.0 hr	2.0 days
6B-Naltrexol C_{MAX}	109 ng/ml	19.4 ng/ml
6B-Naltrexol t_{max}*	1.0 hr	3.0 days

*t-max median

Dunbar JL et al. *Alcoholism: Clin and Exper Res*. 2006; 480-490.

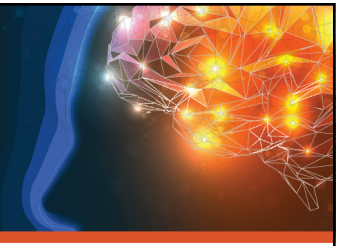
Conclusions



- Ketamine appears to be acutely effective in refractory depression and reducing suicide
- Opioid stimulation rather than NMDA antagonism appears to account for the acute improvement
- NMDA antagonism may confer longer actions
- Little long-term data are currently available on the potential toxicity or efficacy of ketamine

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely



- Utilize the latest clinical data to determine the potential role of ketamine in the management of patients with depression
- Consider ketamine as a viable alternative for suicide prevention in patients with depression

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.