Psychedelics and Potential Drugs of Abuse as Antidepressants

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Disclosure

Dr. Schatzberg has in the past 3 years served as a consultant for Alkermes, Alto Neurosciences, ANeuroTech, Avanir, Axsome, Boehringer-Ingelheim, Bracket, Compass, Delpor, Douglas, Magnus, McKinsey, NeuraWell, Neuronetics, Otsuka, Owl, Analytics Pfizer, Sage Therapeutics, Signant, Takeda.

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.

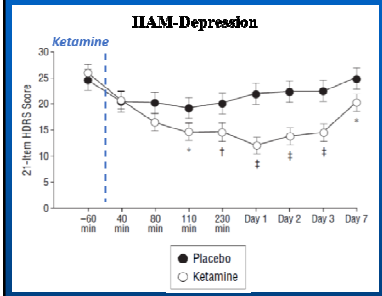
Learning Objectives

- Review recent data on current drug development from a Mechanism of Action (MoA) perspective--Hallucinatory Serotonin 2a agonists, MDMA, and Ketamine/Esketamine
- Discuss how MoA's can affect risk-benefit ratio of Opioid Modulators
- Knowledge of efficacy and side effect data of new anti-depressants and those under development

Mechanisms of Action of Known or Putative Antidepressants

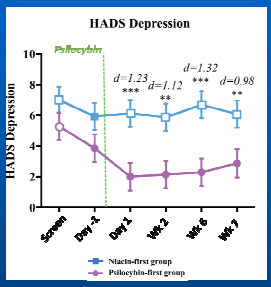
- Enchanced NE and 5-HT Monoaminergic Synaptic Activity
- Hallucinatory Serotonin 2a agonists
- Glutamatergic Transmission
- GABA-ergic neurosteroids
- Opioid Modulators

KETAMINE



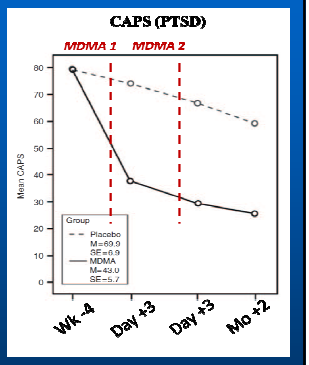
Zarate et al, 2006 Arch Gen Psych

PSILOCYBIN



Ross et al, 2016 J Psychopharmacol;
See also: Griffiths et al, 2016;
Carhart-Harris et al, 2016, 2018, 2021;
Davis et al, 2020

MDMA

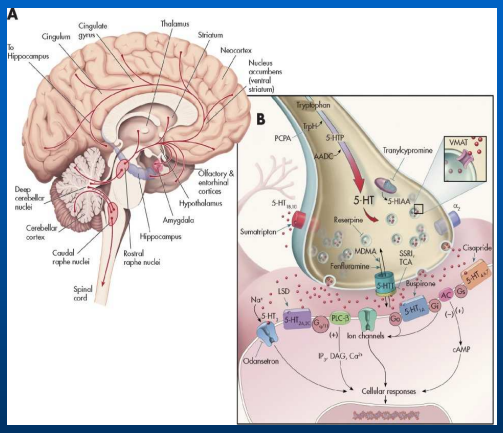


Mithoefer et al, 2011 J Pscyhopharmacol

Psychotherapy with Psychedelics and Ketamine (FDA registration trials)

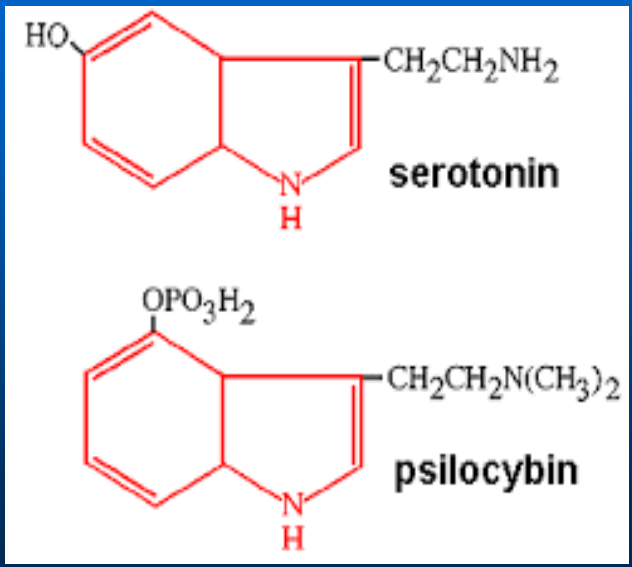
- Psilocybin – Psychotherapy Assisted Psychopharmacology
- MDMA – Psychopharmacology Assisted Psychotherapy
- Ketamine and esketamine – Supportive Assistance (non psychotherapy)
- Non FDA registration trials may use other combination approaches

The Serotonin System



Drazinic C et al: Neurotransmitters and Receptors in Schatzberg AF, Nemeroff CB (Eds.): Textbook of Psychopharmacology, Fifth Edition, Washington, 2017.

Psilocybin



Psilocybin

- 5HT2a Agonist
- Mushroom psychedelic
- Low abuse liability in animal models
- Used for centuries by indigenous people
- Studied as an adjunct to psychotherapy in the 1950s and 1960s
- Research largely halted in 1970 after Nixon era criminalization of psychedelics

Double-blind Studies of Psilocybin in Cancer Patients with Comorbid Depression and Anxiety

- Two positive double-blind studies
- Niacin or low dose psilocybin as controls
- Full doses of psilocybin were 0.3 mg./Kg or 22 to or 30 mg./70 kg
- Both studies demonstrated sustained responses at full doses

R. Griffiths et al, Psychopharm 30: 1181-1197, 2016; S. Ross et al, Psychopharm 30: 1165-1180, 2016.

Open Label Psilocybin in Refractory Major Depression

- 12 treatment refractory depressives
- 10 mg. on day 1 and 25 mg. on day 8
- 8 of 12 patients responded at one week; 7 of the 12 maintained response at 3 months

Carhart-Harris R et al, Lancet Psychiatry 3: 619-627, 2016.

Psilocybin vs Escitalopram Study

- 59 patients with moderate to severe MDD
- Double-blind random assignment; 6 weeks
- Escitalopram daily for 6 weeks with 1mg psilocybin given twice 3 weeks apart versus psilocybin 25mg given twice three weeks apart with placebo daily
- Numerical but not statistical superiority on primary endpoint change in QIDS-SR at 6 weeks for the 25mg psilocybin group

Carhart-Harris R New Eng J Med 384: 1402-1411, 2021

Psilocybin Plus Escitalopram Study, con't.

- Secondary measures were statistically significant in favor of 25mg but not corrected for multiple comparisons
- No inquiry re the blind
- 29% in both groups had previous psilocybin exposures

Carhart-Harris R New Eng J Med 384: 1402-1411, 2021

Multicenter Controlled Trial of Psilocybin with Supportive Psychotherapy in TRD

- 22 centers
- Phase 2b trial
- N=216
- Randomized to 1mg, 10 mg, 25 mg
- Standardized psychedelic psychotherapy

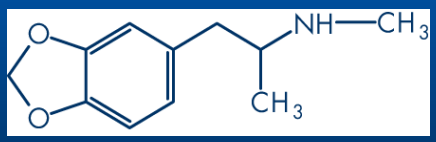
Double Blind Psilocybin Study in Refractory Depression

- 25mg dose showed statistically significant superiority on primary endpoint of change in MDRS at 3 weeks, p<.001
- 25mg superior to other 2 doses in % responders on MDRS at 3 weeks – 36.7% vs 18% with numerical superiority seen at weeks 9 and 12
- Suicidal behavior seen in 6% of patients treated with 10mg or 25mg per day

Compass Therapeutics Press Release 2021

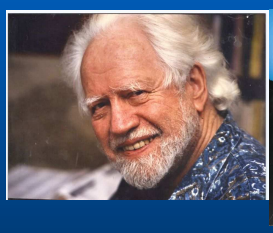
±3,4-Methylenedioxymethamphetamine (MDMA)

MDMA is a synthetic amphetamine **derivative**



- Euphoria
- Trust
- Emotional openness
- Empathy
- Bond between therapist and patient
- …and abuse potential

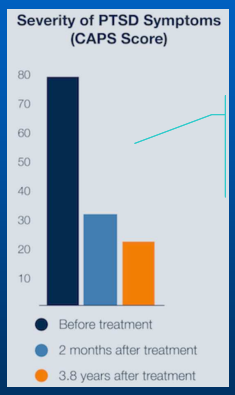
MDMA rediscovered: ~1976



For him the effect was like a particularly lucid alcohol buzz; he called it his "low-calorie martini." He was intrigued, though, by the drug's unique combination of intoxication, disinhibition and clarity. "It didn't have the other visual and auditory imaginative things that you often get from psychedelics," he said. "It opened up a person, both to other people and inner thoughts, but didn't necessarily color it with pretty colors and strange noises." He decided that it might be well suited for psychotherapy.

- NYT, 2005

MDMA Assisted Psychotherapy

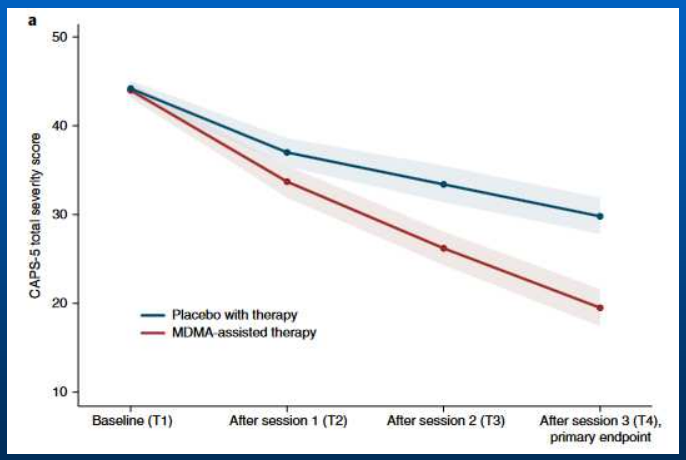


3.8 years after treatment

- Tested in PTSD, social anxiety in autistic adults
- Enhances feelings of trust, emotional openness and empathy
- May work by strengthening the bond between therapist and patient
- PTSD effect through enhancing fear extinction responses to treatment

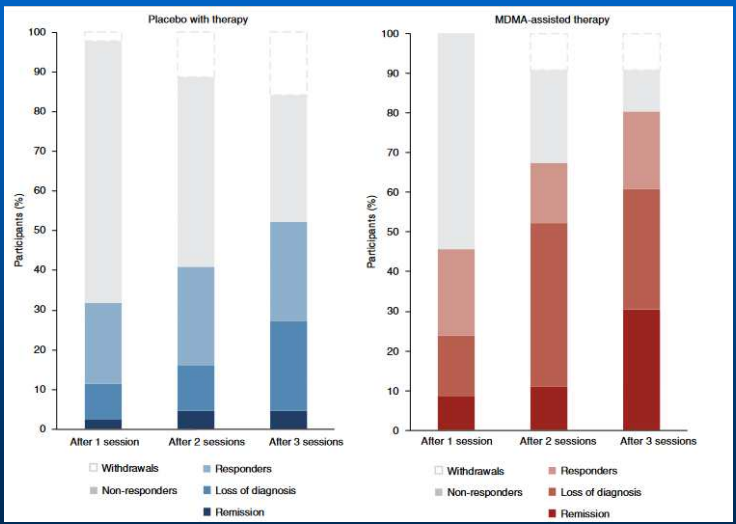
Mithoefer et al, 2010 & 2013. J Psychopharm

Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. Change in CAPS-5 total severity score from T1 to T4 (P < 0.0001, d = 0.91, n = 89 (MDMA n = 46)), as primary outcome.

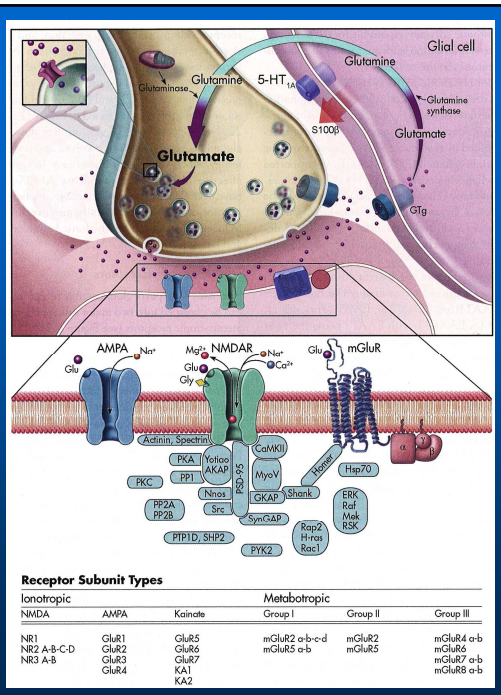


Mitchell et al, Nat. Med. 27(6): 1025-1033, 2021.

Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, n = 46; placebo, n = 44)



Mitchell et al, Nat. Med. 27(6): 1025-1033, 2021.



Receptor Subunit Types

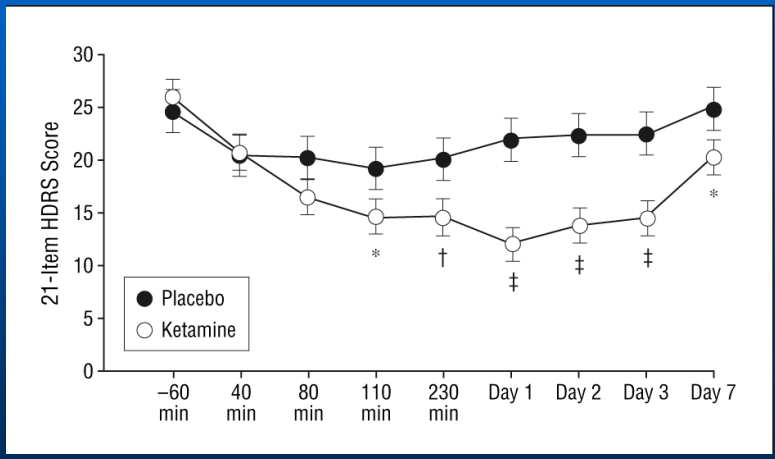
Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
NR1 NR2 A-B-C-D NR3 A-B	GluR1 GluR2 GluR3 GluR4	GluR5 GluR6 GluR7 KA1 KA2	mGluR2 a-b-c-d mGluR5 a-b	mGluR2 mGluR5	mGluR4 a-b mGluR6 mGluR7 a-b mGluR8 a-b

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

Ketamine

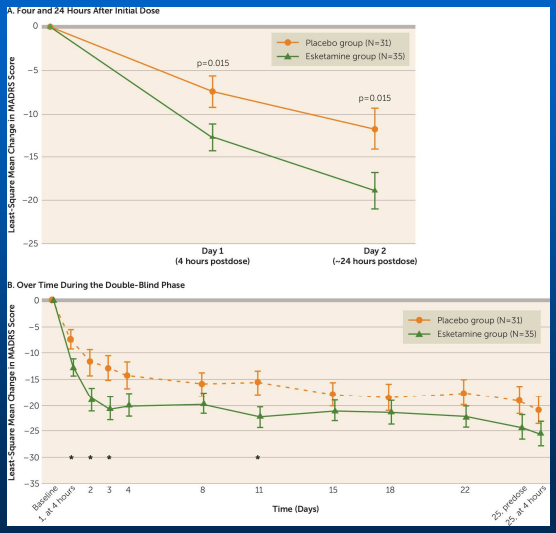
- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist;
- Mu opioid agonist; stimulant (?)
- Psychotomimetic; dissociation
- Acute antidepressant efficacy not sustained

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.

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



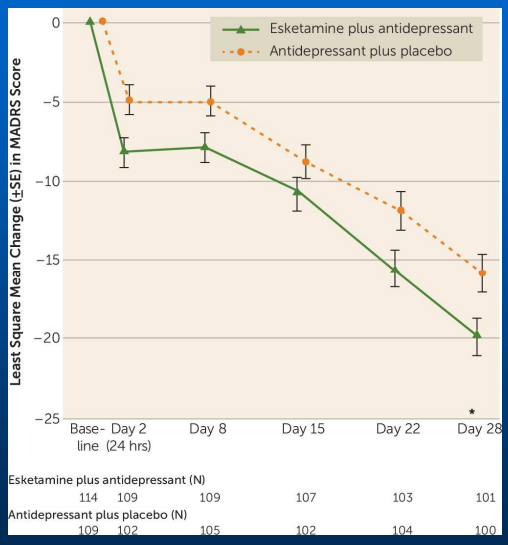
Canuso et al, Am J Psychiatry 2018; 175: 620-630.

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



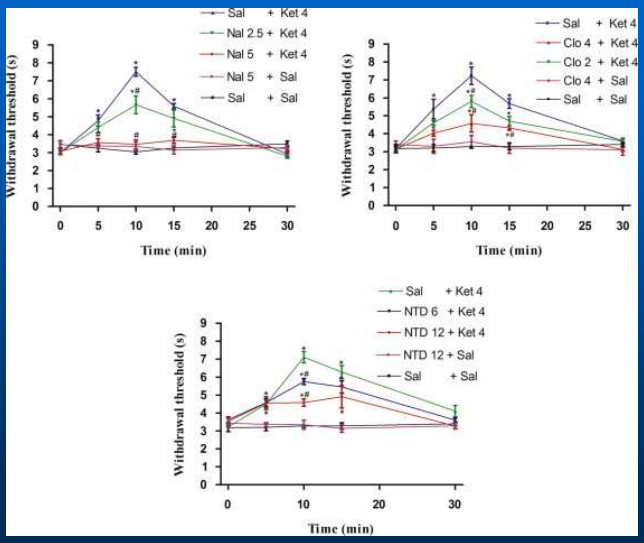
*p=0.020

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

Ketamine and Morphine in OCD

- IV ketamine significantly more effective than placebo in refracratory 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).

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.

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.

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.

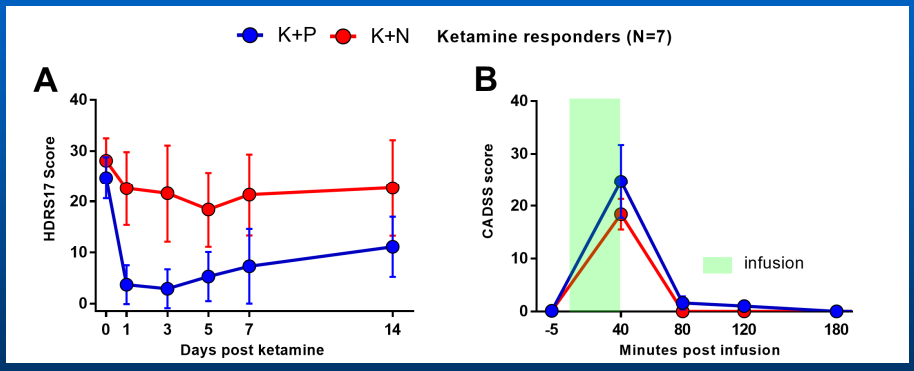
Method: In a proposed double-blind crossover study of 30 adults with treatment-resistant depression, the authors performed a planned interim analysis after studying 14 participants, 12 of whom completed both conditions in randomized order: placebo or 50 mg of naltrexone preceding intravenous infusion 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

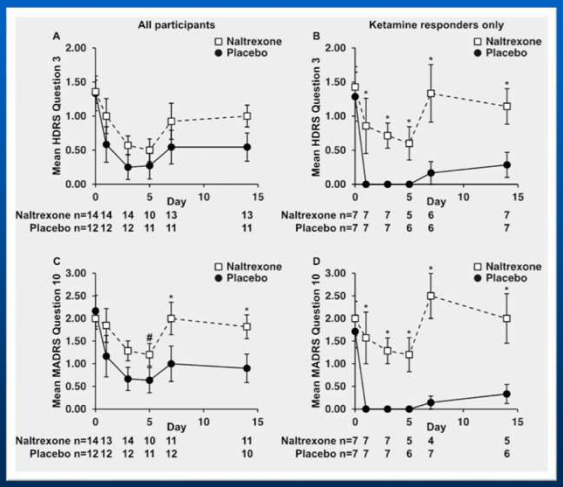
Naltrexone Pretreatment Blocks Ketamine's Antidepressant Effects but not Dissociative Symptoms



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.

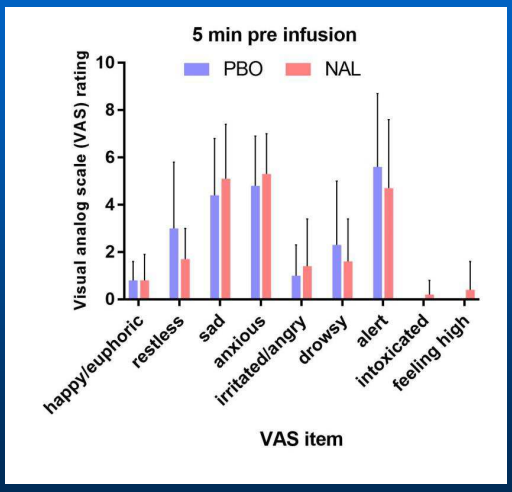
Anti-suicide Effects of Ketamine Are Blocked by Naltrexone



Heifets B et al, Molecular Psychiatry, in press.

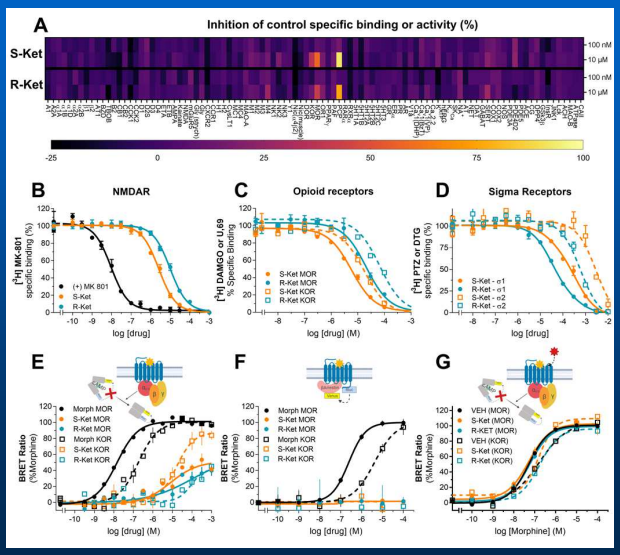
#p<0.10, *p<0.05 after Bonferroni correction for multiple comparisons

VAS Item Scores After Placebo vs. Naltrexone



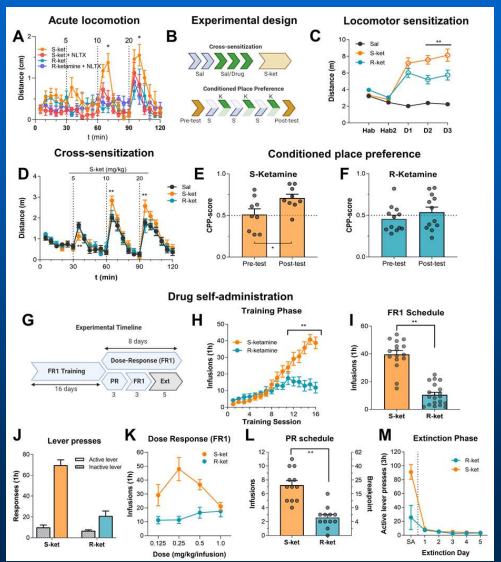
Williams N, Heifets B et al, Am J Psychiatry, e-pub, Aug 28, 2018.

Divergent pharmacodynamics of ketamine enantiomers



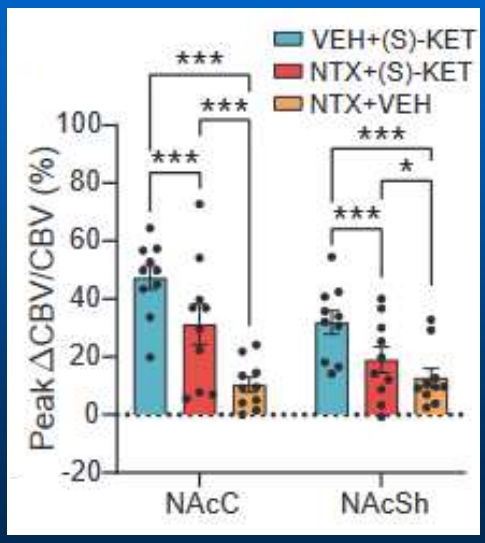
Bonaventura J et al, Mol Psych 2021.

Functional brain imaging reveals regional differences in the effects of ketamine enantiomers



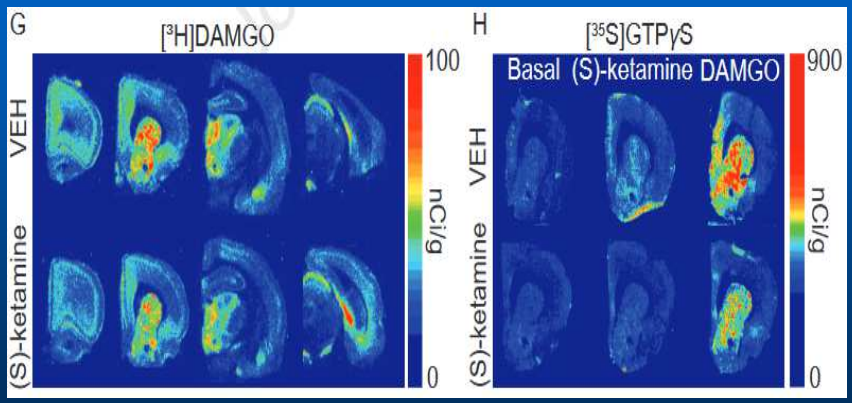
Bonaventura J et al, Mol Psych 2021.

Naltrexone Blocks S-ketamine in Nucleus Accumbens



Levinstein et al. Biol Psych, posted online December 2022.

S-ketamine Binds to Mu-opioid Receptors PET Results

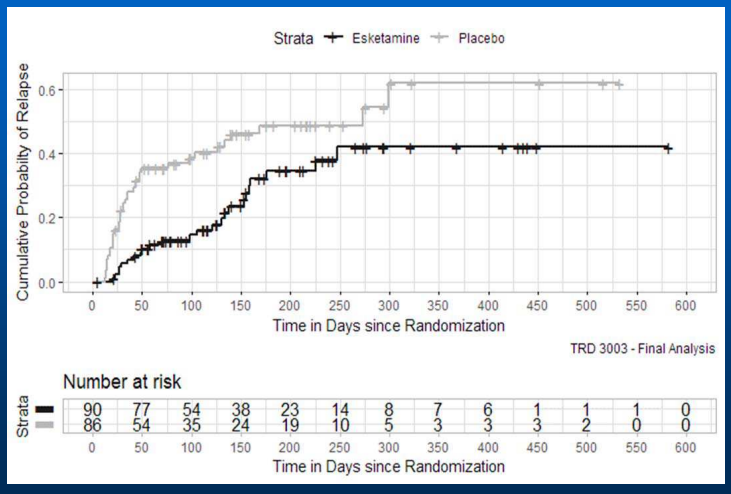


Levinstein et al. Biol Psych, posted online December 2022.

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, Psychopharmacology 2022
- Jiang and Pittenger, SoBP poster 2021
- Levinstein et al, Biol Psych on line 2022

Discontinuation from Esketamine in Stable Remitters



FDA Briefing Document, February 12, 2019.

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.

Deaths, Serious Adverse Events, Adverse Events Leading to Study Withdrawal (cont'd)

"The patient who committed suicide 4 days after last dose was enrolled in an ongoing study; that patient's Columbia Suicide Severity Rating Scale (C-SSRS) score was not available. The other two patients had scores of 0, both at baseline and at the visit prior to their deaths. 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."

FDA Briefing Document, February 12, 2019.

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 2022) but two Phase III trials as monotherapy or add-on failed (Remalda press release 2022)

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