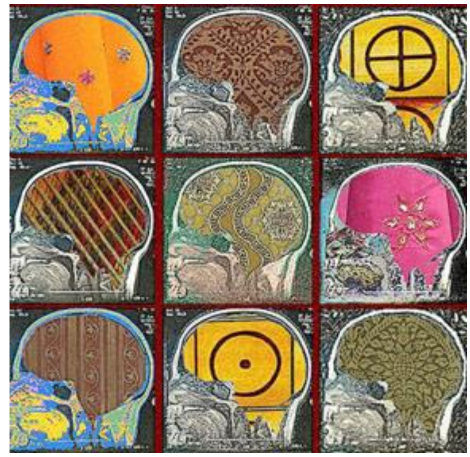
DRUG MECHANISM OF ACTION TARGETING ADDICTION & MOOD



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Minnesota Psychiatric Society. May 3, 2025

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DISCLOSURE DECLARATION – MARK A. FRYE 2025

Grant Support -
Assurex Health
Breakthrough Discoveries for Thriving with Bipolar Disorder
Baszucki Group

CME/Travel/Honoraria -
Carnot Laboratories
American Physician Institute

Financial Interest / Stock ownership / Royalties -
Chymia LLC.

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LEARNING OBJECTIVEs Mood

1. **Recognize**
   Appreciate new emerging treatments for depression with a narrower phenotype

2. **Understand**
   The risk benefit ratio of comprehensive rating scales for depression
   - regulatory standard for drug development
   - limited biomarker targeted drug development

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LEARNING OBJECTIVEs Addiction

1. **Recognize**
   The scope of the problem: co-occurrence of mood disorders and substance use disorders (SUD).

2. **Understand**
   Neurobiological substrates and drug mechanisms of action targeting mood and addiction.

3. **Review and Summarize**
   Current pharmacological treatments and novel therapies.

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BURDEN OF DEPRESSION

FDA approval 1987

- WHO 2020 – Depression ranks 2nd in DALYs
  - 121 million people worldwide & 850,000 suicides annually

DALYs=Disability Adjusted Life Years
Garmany & Terzic JAM 2024, Nassan et al., 2016, Olfsen M et al., JAMA Psychiatry 2014, Zhong et al,., Mayo Clinic Proceedings 2013

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BURDEN OF DEPRESSION & SUBSTANCE USE DISORDERS - GLOBAL

- WHO Global Health Observatory study (2024)
  - Increased lifespan ≠ longer healthy life
  - Healthspan years lived in good health
    - health-adjusted life expectancy = estimate of healthy longevity (years of life weighted by health status)
    - healthspan – lifespan **GAP** (life burdened with disease)
      - health-adjusted life 63 yrs vs. life expectancy 72.5 yrs
      - largest healthspan-lifespan gap was US
      - mental /substance use disorders, and musculoskeletal diseases, contributed most to years lived with disability in US

Garmany & Terzic JAMA 2024

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Burden of Depression - LOCAL

Improving health globally by studying health locally

Prevalence of Chronic Diseases Health Care Utilization

- ICD codes 1/1/14- 12/31/19 age- sex-specific prevalence rates
- 154,254 individuals included
  - Musculoskeletal disorders (42%)
  - Dermatological (40%)
  - Anxiety/depression/bipolar disorders (24%)
- Lower education and a higher area deprivation index score were associated with modifiable chronic diseases
- Effective diagnosis and management in health care delivery and more focused preventative efforts in disadvantaged communities are imperative

Salmons et al., Mayo Clinic Proceedings 2025

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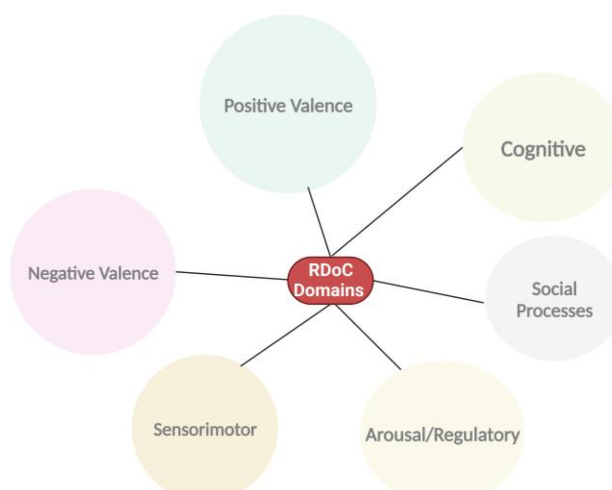
MAJOR DEPRESSION

- Significant morbidity & mortality
- Heterogenous disease
- RDoC— a research framework for investigating mental disorders.
  - ➢ 6 major functional domains
  - ➢ each domain – 3 to 6 constructs
- Anhedonia – Dysfunction in the positive valence system (constructs associated with reward- and motivation-related behavior)



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[Mapping depression rating scale phenotypes onto research domain criteria (RDoC) to inform biological research in mood disorders - PubMed]

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Mood Disorder Precision Medicine Consortium

RDoC Construct	Phenotype (Mayo & Emory)		HAMD-17 items
Loss	Core Depression (CD)	Symptoms	depressed mood #1 work and activities #7
		Criteria definition	score of 3 or 4 on both items #1 and #7
Potential Threat ("Anxiety")	Anxiety (ANX)	Symptoms	agitation #9 anxiety psychological #10 anxiety somatic #11 hypochondriasis #15
		Criteria definition	total score ≥6 from items #9, #10, #11, and #15
Sleep-Wakefulness	Neurovegetative Symptoms of Melancholia (NVSM)	Symptoms	late insomnia #6 somatic gastrointestinal #12
		Criteria definition	score of 1 or 2 on both items #6 and #12
Atypical RDoC Construct	**Phenotype (Mayo only)**		**QIDS-C16**
Sleep-Wakefulness	Neurovegetative Symptoms Atypical Depression (NVSAD)	Symptoms	Hypersomnia # 4 Appetite (Increased) # 7
		Criteria definition	score of 2 or 3 on both question 4 and 7

MAYO CLINIC

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[Acylcarnitine metabolomic profiles inform clinically-defined major depressive phenotypes - PubMed]

MAYO CLINIC

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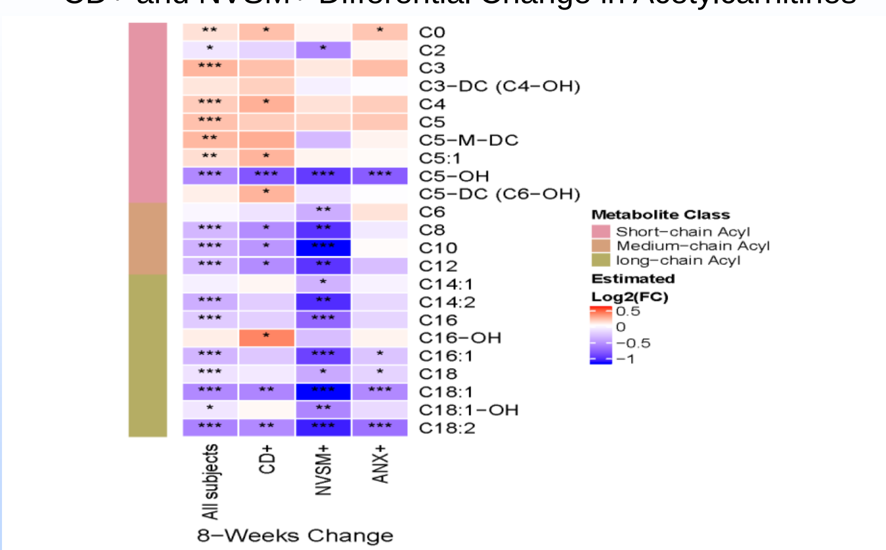
Metabolomic Signature After Eight Weeks Citalopram: CD+ and NVSM+ Differential Change in Acetylcarnitines



Ahmed eta l., 2019 under review

MAYO CLINIC

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Acetyl-carnitines & Depressive Phenotypes

- acetyl-carnitine (LAC) involved in mitochondrial energy regulation & synaptic plasticity
- preclinical models of depression associated with reduced LAC, dendritic plasticity, and hippocampal glutamate function
- preclinical LAC supplementation induces rapid and lasting antidepressant-like effects via epigenetic histone acetylation
- LAC levels decreased in 2 cohorts of patients with MDD
  - degree of LAC deficiency reflected both severity and AOO of MDD.
  - early onset trauma and female gender predicted LAC deficit

MAYO CLINIC

Nasca et al., 2018 Proc Natl Acad Sci USA

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ANHEDONIA

- Diminished interest of pleasure in nearly all activities
  - core symptom of depression
- Independent driver of morbidity and predictor of suicidal ideation
- Barrier to patients seeking and engaging in care
- Barrier to functional recovery and *<u>predictor of poor long-term outcomes</u>*
- Notable negative impact to the economy
  - Absenteeism and reduced productivity

Cao et al. Prog Neuropsychopharmacol Biol Psychiatry. 2019; Craske et al. Depress Anxiety. 2016; Khazanov et al. Br J Clin Psychol. 2022; Ballard et al. J Affect Disord. 2017

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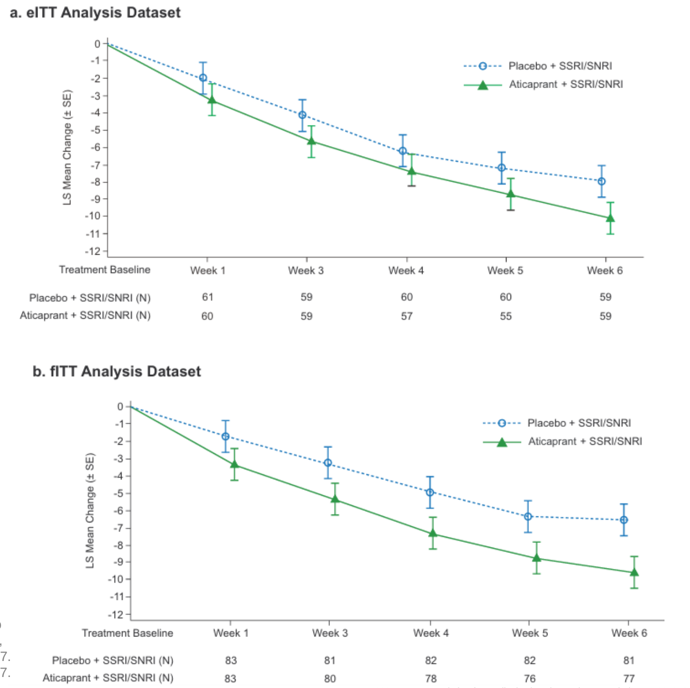
Phase 2 Study of Aticaprant, kappa receptor antagonist for depression

Significant baseline mean MADRS Change Aticaprant vs placebo

Between group differences significantly greater among participants with high vs low hedonic tone as measured by the Snaith-Hamilton Pleasure Scale (SHAPS)



Schmidt ME, et al. Efficacy and safety of aticaprant, a kappa receptor antagonist, adjunctive to oral SSRI/SNRI antidepressant in major depressive disorder: results of a phase 2 randomized, double-blind, placebo-controlled study. Neuropsychopharmacology. 2024 Aug;49(9):1437-1447. doi: 10.1038/s41386-024-01862-x. Epub 2024 Apr 22. PMID: 3864948; PMCID: PMC11251157.

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LEARNING OBJECTIVEs

Addiction

1. **Recognize**
   The scope of the problem: co-occurrence of mood disorders and substance use disorders (SUD).

2. **Understand**
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   Current pharmacological treatments and novel therapies.

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1. THE SCOPE OF THE PROBLEM

"In wine there is wisdom, in beer there is Freedom, in water there is bacteria." *Benjamin Franklin*

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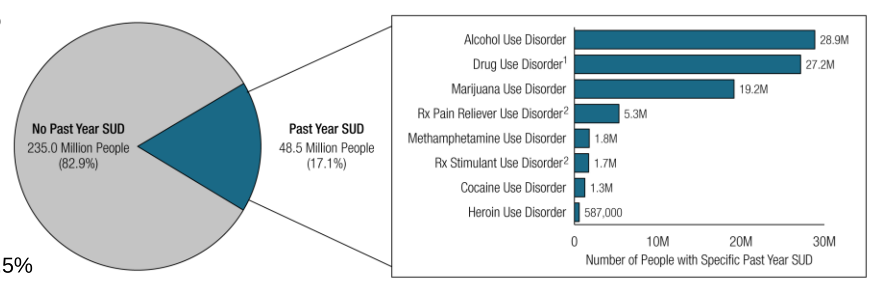
SUBSTANCE USE DISORDERS

- AUD 12-month prevalence 13.9%
- AUD lifetime prevalence 29.1%
- DUD 12-month prevalence 3.9%
- DUD 9.9% lifetime prevalence
- NTUD – 12-month prevalence 28.5%
- NTUD 27.9% lifetime



The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: Review and summary of findings. Social Psychiatry and Psychiatric Epidemiology, 50, 1609-1640. https://doi.org/10.1007/s00127-015-1088-0.
Substance Abuse and Mental Health Services Administration. (2024). Key substance use and mental health indicators in the United States: Results from the 2023 National Survey on Drug Use and Health (HHS Publication No. PEP24-07-021, NSDUH Series H-59). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2023-nsduh-annual-national-report

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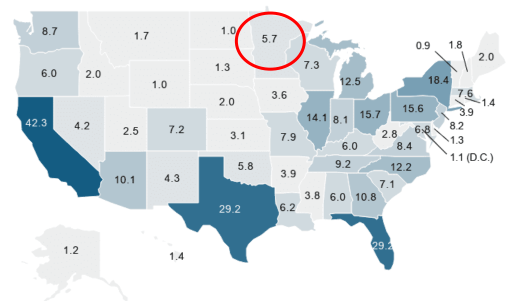
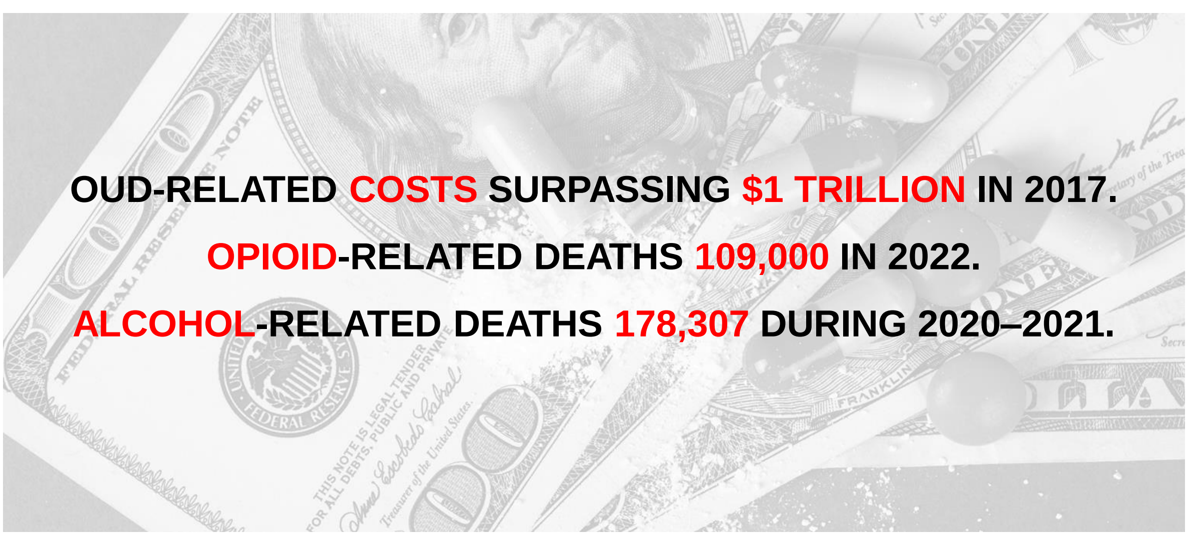
ALCOHOL USE DISORDER

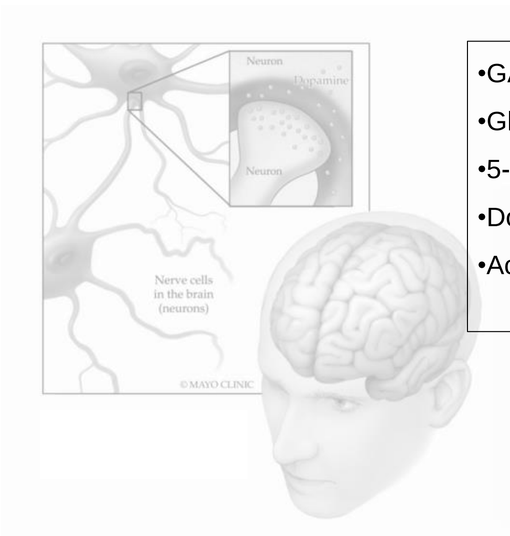
- One of the leading preventable causes of death in the United States.
- 178,000 deaths each year in the US.
- Alcohol is implicated in
  - 18.5% of emergency department visits
  - 20% of prescription opioid overdose fatalities
  - 25% deaths by suicide
- Alcohol-associated liver disease (ALD) is the most common cause of advanced liver disease and frequent indication for liver transplantation worldwide.





Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet. 2019;394(10208):1560-79.

NEUROBIOLOGICAL FINDINGS AND MOLECULAR TARGETS IN SUD



- GABA-A and glycine receptors
- Glutamatergic system (NDMA-receptors)
- 5-HT-1B agonist, 5-HT-2C agonist; 5-HT-3 antagonist
- Dopamine, opioid, endocannabinoid(CB1r) systems
- Acetylcholine nicotinic receptors

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3. PSYCHOPHARMACOLOGY:

"OLD" AND "NEW" AGENTS

(or not so new!)

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PHARMACOLOGICAL AGENTS

MOOD DISORDERS	SUBSTANCE USE DISORDERS

• Antidepressants
• Traditional Mood Stabilizers (e.g., lithium, AED)
• Antipsychotics
• NMDA-r Antagonists (e.g., ketamine, esketamine)
• "Novel agents" – psychedelics (e.g., psilocybin for TRD)
	• AUD
	  • Disulfiram
	  • Naltrexone
	  • Acamprosate
	• OUD
	  • Naltrexone
	  • Buprenorphine
	  • Methadone
	  • Lofexidine
	• NTUD
	  • Bupropion
	  • Varenicline
	  • NRT
	• OTHER SUD
	  • No FDA-approved medications to date.

OLANZAPINE-SAMIDORPHAN

- Evidence of opioid modulation in MDD - KOR agonism – dysphoria, MOR agonism - euphoria
- Samidorphan – KOR antagonist
- To mitigate weight gain and metabolic side effects
- Long-term safety and efficacy – 4 y open label study – more favorable metabolic profile
- FDA-approved in May 2021 for the treatment of SCZ and BD I
- Will this medication be more effective in BD-SUD patients due to effects on opioid system?
- Potential for precipitated opioid withdrawals (???MOR effects)

Drugs (2021) 81:1431–1436 https://doi.org/10.1007/s40265-021-01568-0.
J Clin Psychiatry 2025;86(1):24m15511
Neuropsychopharmacology (2015) 40, 1448–1455

BUPRENORPHINE-SAMIDORPHAN FOR MDD

- Multicenter, double-blind, placebo-controlled RCT
  - 2 mg/2 mg of buprenorphine/samidorphan (the 2/2 dosage group),
  - 8 mg/8 mg of buprenorphine/samidorphan (the 8/8 dosage group), or
  - placebo.
- Significantly greater improvements in the 2/2 dosage group across the three depression outcome measures (HAM-D, MADRS, and CGI).
- There was also evidence of improvement in the 8/8 dosage group, although it did not achieve statistical significance.
- Overall, the buprenorphine/samidorphan combinations were well tolerated, and there was no evidence of opioid withdrawal on treatment discontinuation.

PMID: 26869247 DOI: 10.1176/appi.ajp.2015.15070921

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SAFETY, TOLERABILITY, AND CLINICAL EFFECT OF LOW-DOSE BUPRENORPHINE FOR TREATMENT-RESISTANT DEPRESSION IN MID-LIFE AND OLDER ADULTS

- Open-label protocol, buprenorphine was prescribed for 15 adults age 50 and older with TRD
- The average dose of buprenorphine was 0.4 mg/day (average maximum dose = 0.7 mg/ day)
- There was a **sharp decline in depression severity** during the first three weeks of exposure.
- **Low-dose buprenorphine** may be a novel-mechanism medication that provides a **rapid and sustained improvement** for older adults with TRD.

J Clin Psychiatry. 2014 August ; 75(8): e785–e793. doi:10.4088/JCP.13m08725.

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KETAMINE

- Evidence suggests that ketamine's rapid antidepressant effect requires opioid system activation.
- Implications for patients receiving naltrexone for addictions treatment.

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

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BUPROPION-DEXTROMETHORPHAN

- FDA-approved for depression
- Randomized, double-blind, multicenter, parallel-group trial (dextromethorphan-bupropion, N43; bupropion, N37)
- Dextromethorphan-bupropion significantly improved depressive symptoms compared with bupropion monotherapy In patients with MDD and was generally well tolerated.
- Dextromethorphan-bupropion is an effective, fast-acting, and well tolerated option for depression treatment and produced remission in a large percentage of patients.
- Implications for patients with MDD-SUD – given dextromethorphan potential for abuse

(Clin Psychopharmacol Neurosci. 2023 Nov 30;21(4):609-616. DOI:10.9758/cpn.23.1081.)

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Off-label treatments for SUD

- **Nicotinic Agents (A4β2 partial agonist)**
  - Varenicline off-label for AUD
- **Serotonergic Agents for AUD**
  - SSRI's –disappointing results
  - Ondansetron
- **Noradrenergic Agents**
  - Prazosin
  - Dexmedetomidine
- **Other Opioid Antagonists**
  - Nalmefene (not available in US)

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TAKE HOME POINTS

- MOOD-SUD poorly understood, understudied, and underfunded.
- MOOD-SUD >>> therapeutic challenge and prognostic implications.
- Symptoms of AUD and SUD may obscure an underlying diagnosis of BD >>> diagnostic delays and negative impact on clinical outcomes.
- AUD-SUD remains underdiagnosed and undertreated in BD.
- There is a critical need for integrative care for individuals with co-occurring mood and SUD.
- Limited evidence of efficacy of existing pharmacological interventions, need for specific guidelines and novel therapies.

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QUESTIONS & ANSWERS

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