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PSYCHIATRY ACADEMY

Psychedelics for the Treatment of Substance Use Disorders

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Disclosures



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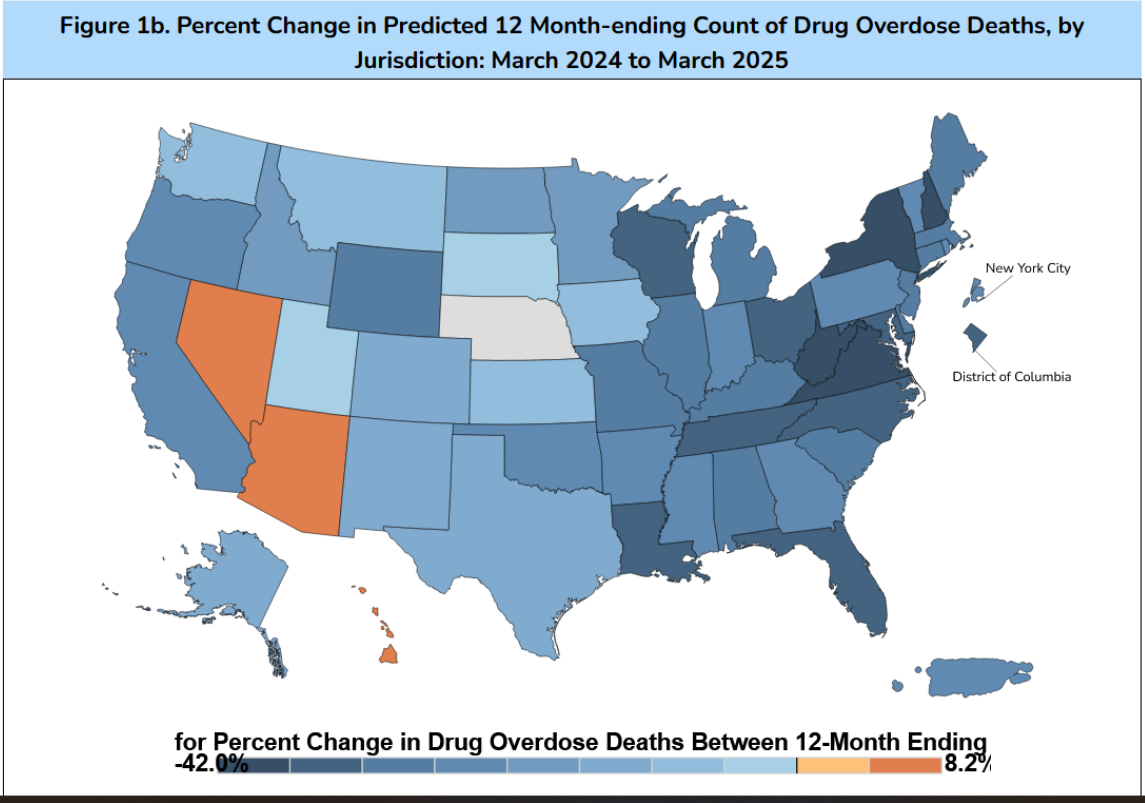
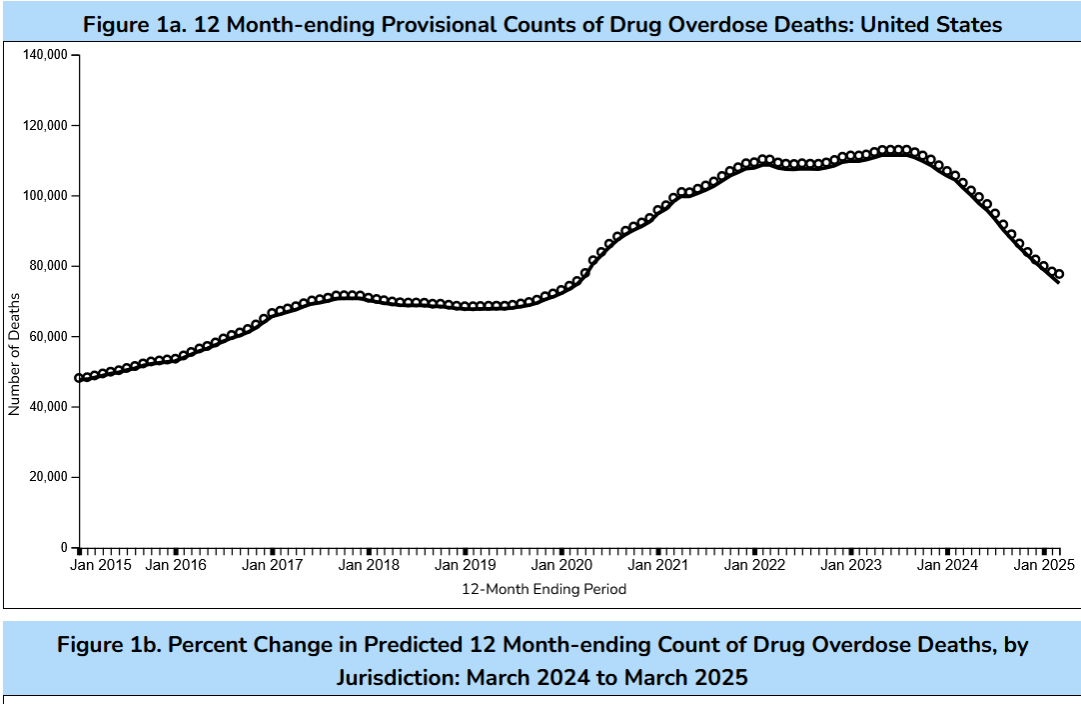
I have the following relevant financial relationship with a commercial interest to disclose:

I receive in-kind support from Braeburn to receive Brixadi injections to conduct a NIH-funded trial (R21DA060411).

Drug overdose deaths in the US are declining, but remain unacceptably high



Based on data available for analysis on: August 3, 2025



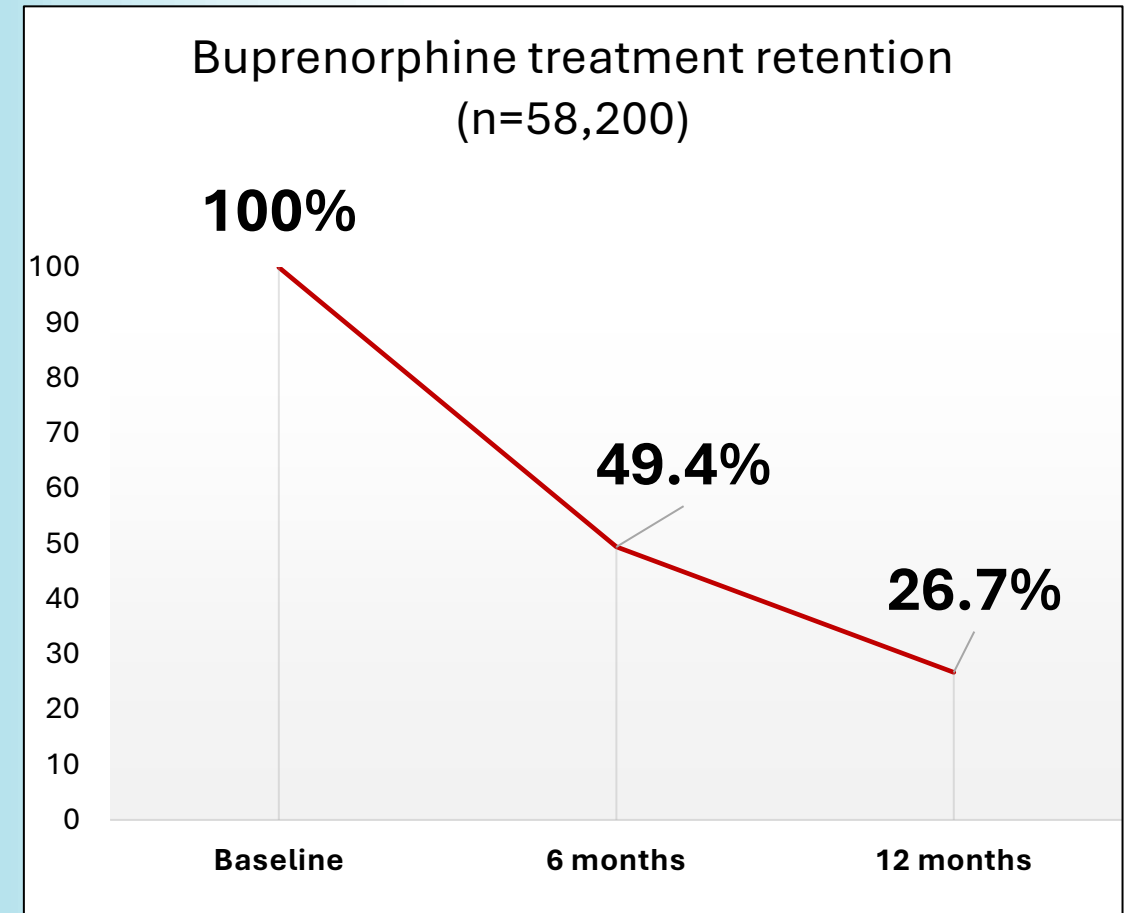
Buprenorphine with robust evidence-base for efficacy, but outcomes remain sub-optimal



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70%

reduction in mortality and overdoses



NIDA has specifically identified psychedelics as addiction treatment as research priorities



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NIDA

NATIONAL INSTITUTE
ON DRUG ABUSE

Research Gap

Research on psychedelics, such as
psilocybin, ketamine, ibogaine

Goal

Expand treatment
options for OUD

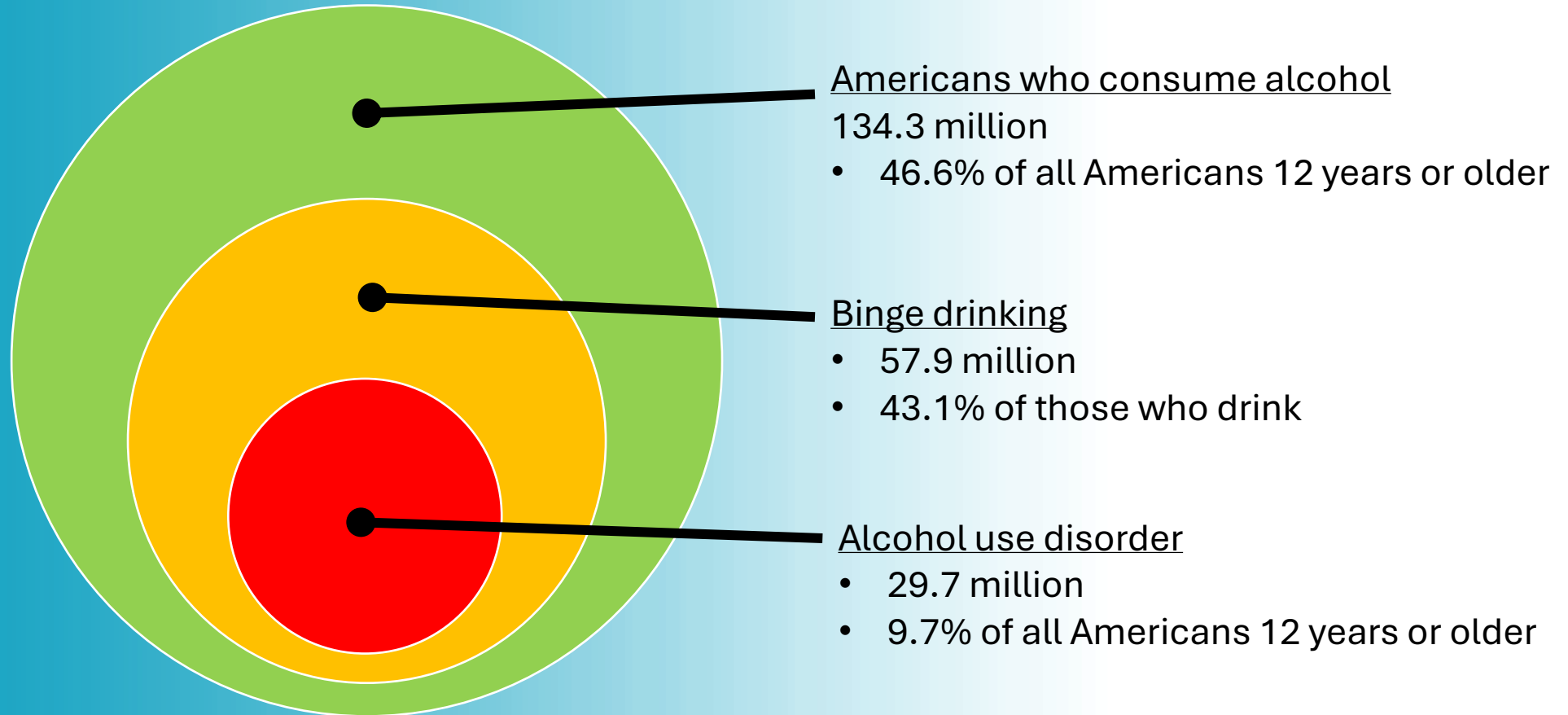


Prevalence of unhealthy alcohol use also remains high



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www.cdc.gov/alcohol

**Number of people who die each year
from excessive alcohol use in the US***

*Based on deaths per year during 2020-2021.

National Institute on Alcohol Abuse and Alcoholism Strategic Plan:

Fiscal Years 2024–2028

Advancing Alcohol Research to Promote Health and Well-Being



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Goal 1: Elucidate the biological mechanisms and consequences of alcohol misuse



Goal 2: Identify patterns, trends, and public health impact of alcohol misuse



Goal 3: Prevent and reduce alcohol misuse, alcohol use disorder, and associated consequences



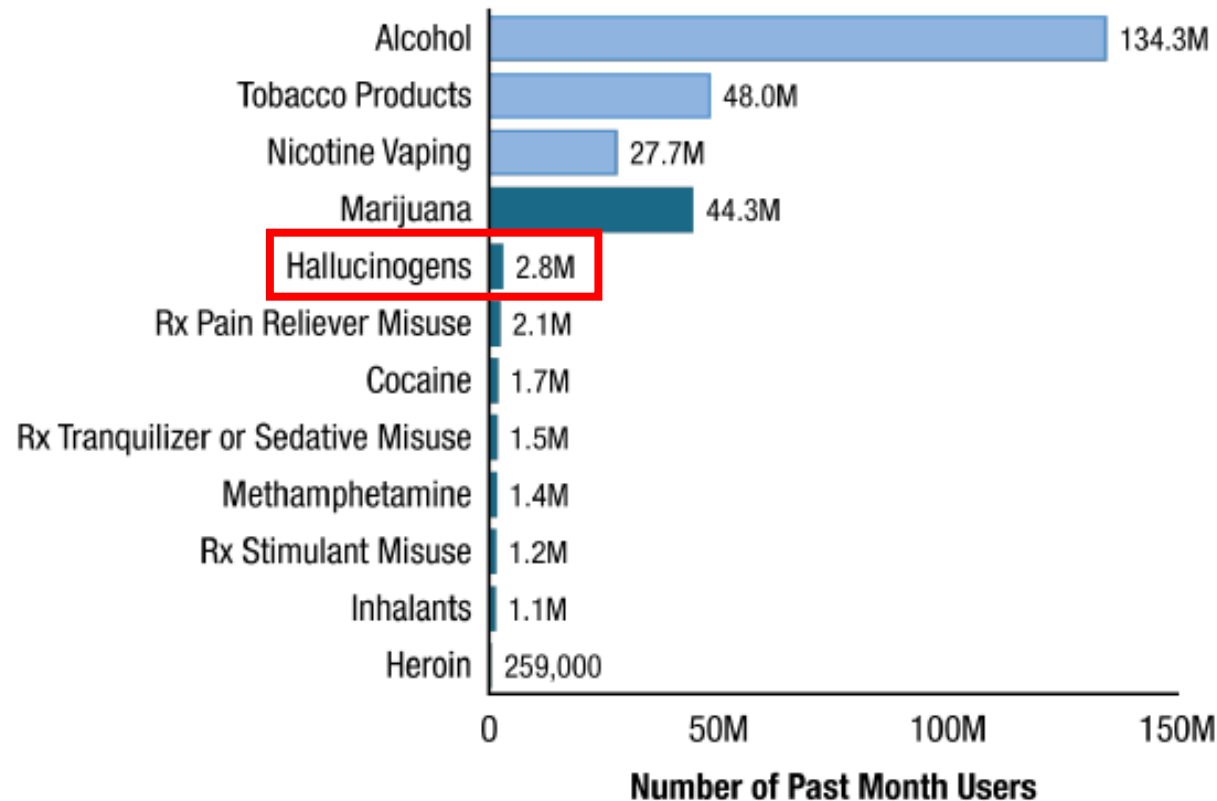
Goal 4: Improve diagnosis and **expand treatment of alcohol use disorder** and alcohol-related conditions

Psychedelics the 2nd most used class of drugs in the general population



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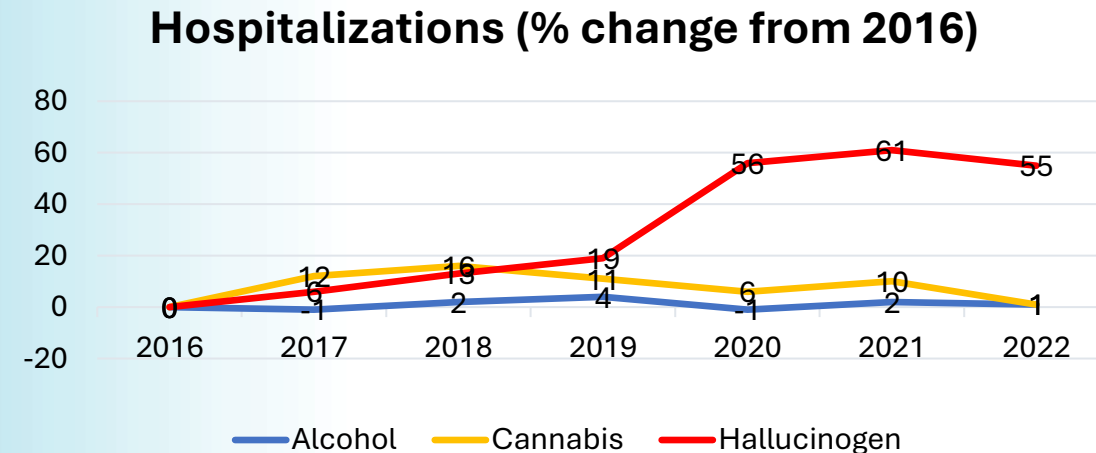
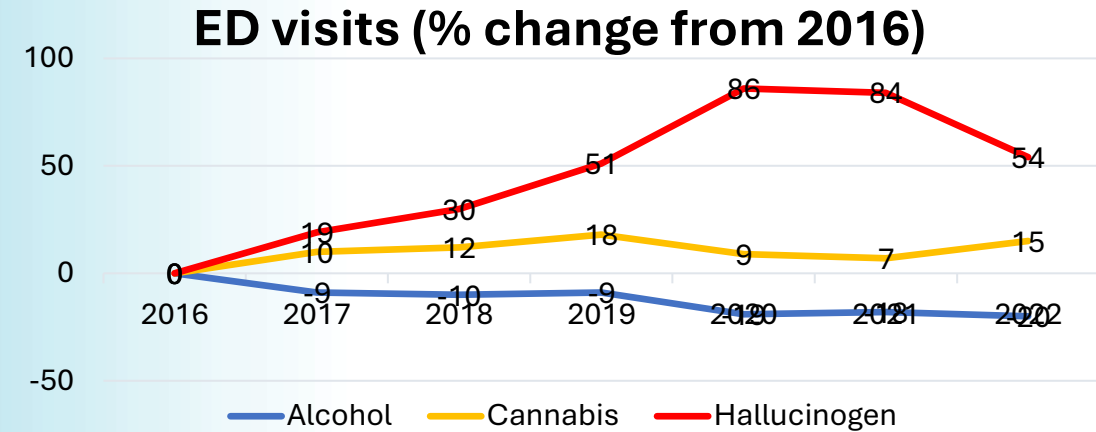
Increasing ED visits and hospitalizations related to psychedelics, but overall numbers remain low



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- Data from the California Department of Healthcare Access (HCAI)
- ICD-10 codes for hallucinogen-, cannabis-, and alcohol-related ED visits and hospitalizations
- **Results:**
 - 54% increase in ED visits from hallucinogens
 - 55% increase in hospitalizations from hallucinogens
 - Significantly different from alcohol and cannabis
 - BUT the **absolute numbers are significantly lower** for hallucinogens compared to alcohol and cannabis (e.g. 2016: Alcohol 326,550, Cannabis 121,267, Hallucinogens 2,260)



Matthew Perry Died of 'Acute Effects of Ketamine,' Autopsy Says

The medical examiner said drowning, coronary artery disease and the effects of an opioid also contributed to the death of the “Friends” actor, who was found in a hot tub in October.

 Share full article    585



The coroner's office said Matthew Perry had ketamine and the opioid buprenorphine



The earliest attempts at psychedelic treatment for SUD in the US was in NYC



CHARLES B. TOWNS HOSPITAL

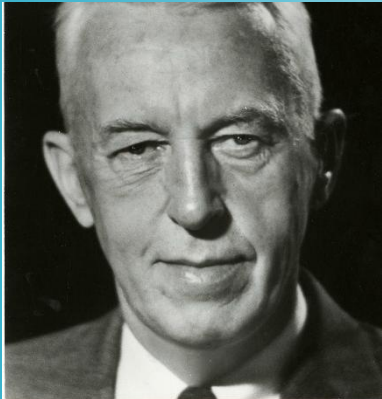
293 Central Park West New York, New York

For ALCOHOLISM and DRUG ADDICTION

ANY PHYSICIAN having an addict problem is invited to write for Hospital literature.

This institution has specialized in addictions for over 30 years. Its method of treatment has been fully described in THE JOURNAL A. M. A.; in The Handbook of Therapy, from the A. M. A. Press; and in other scientific literature. The treatment is a regular hospital procedure, and provides a definite means for eliminating the toxic products of alcohol and drugs from the tissues. A complete Department of Physical Therapy, with gymnasium and other facilities for physical rebuilding, is maintained. Operated as an "open" institution. Physicians are not only invited but urged to accompany and stay with their patients.

Located Directly
Across from Central Park



Spirituality and 12-steps of Alcoholics Anonymous



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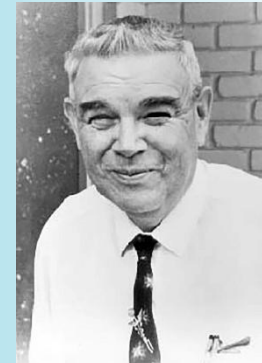
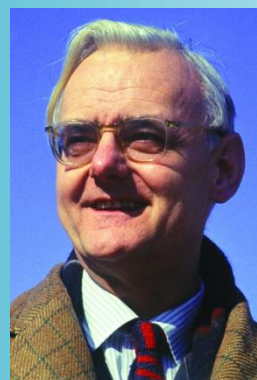
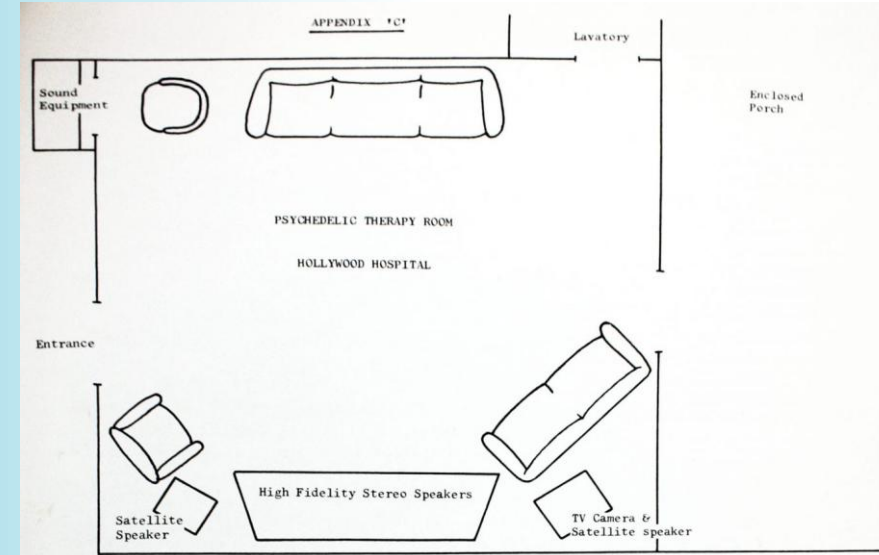
1. We admitted we were powerless over alcohol - that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics and to practice these principles in all our affairs.

Further pioneered by Canadian treatment centers for AUD



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Randomized controlled trials from 1960s showed LSD to have short-term impact on AUD outcomes



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Objective:

- To assess the evidence-base of LSD-assisted psychotherapy in treating AUD

Methods:

- Systematic review and meta-analysis of RCTs in which LSD was given to those with AUD with psychotherapy
- Outcome: “responder” = improvement in drinking

Results:

- Six double-blind, placebo-controlled RCTs (1966-1970)
- Total of 536 treatment seekers for AUD
- 61% receiving single dose of LSD (median=500mcg)
- Control group (ephedrine, amphetamine, low dose LSD)
- LSD associated with increased odds of being a “responder” compared to controls in the short-term (OR 1.96, 95%CI 1.36-2.84)

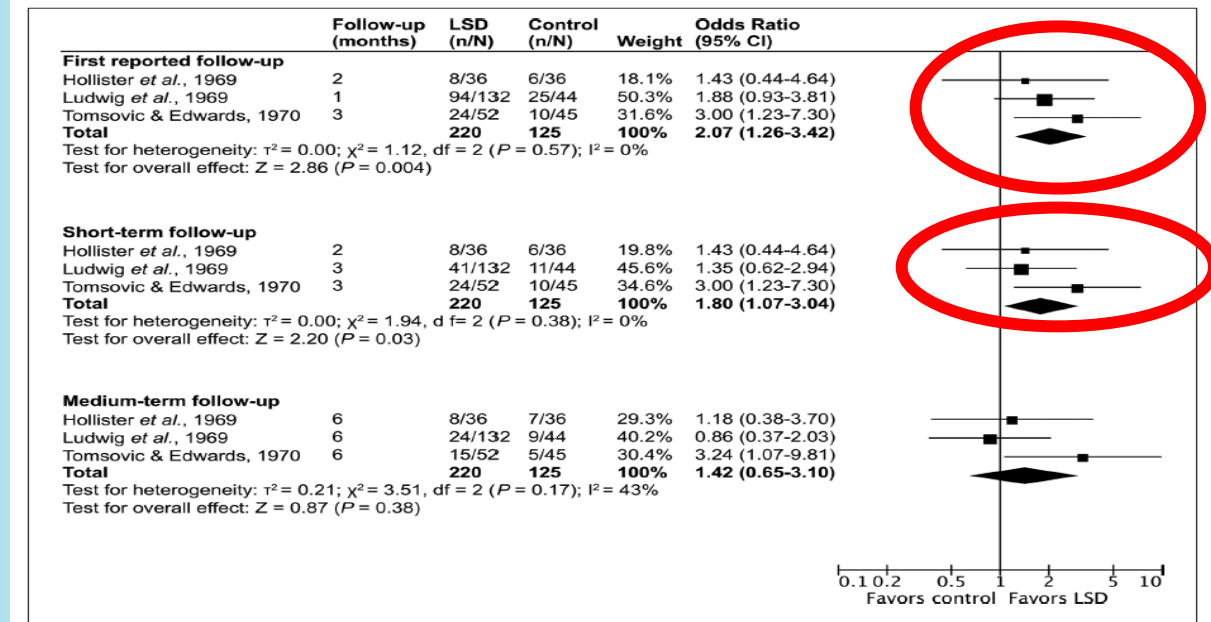


Figure 4. Maintained abstinence from alcohol after LSD versus control treatments.

Conclusion:

- Despite limitations, included studies were relatively rigorous for the time
- Single LSD treatment led to reduction in alcohol use in the short-term

A single trial showing LSD may facilitate abstinence from opioids



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Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

Charles Savage, MD, O. Lee McCabe, PhD, Baltimore

Objective:

- Conduct a trial of LSD-assisted psychotherapy on OUD-related outcomes

Methods: Open label RCT of single high dose LSD.

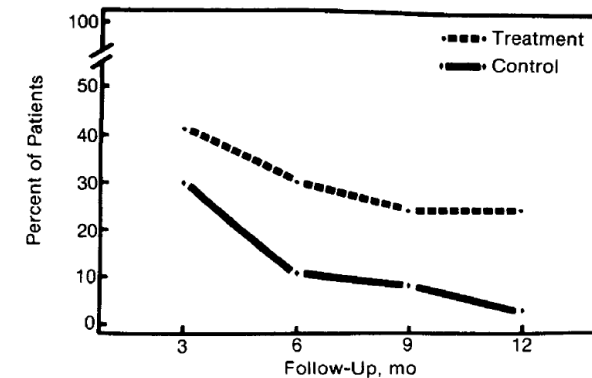
- 78 prisoners (with at least 18 months sentence remaining), and condition for release was to be in the study, with **daily urine toxicology**.
- Relapsed resulted in re-incarceration.
- Followed for up to 12-months

Outcome: Abstinence at 6 and 12 months

Results:

- **25% (LSD) vs 5% (TAU) maintained abstinence at 12 months**
- Additional 8% in LSD arm had brief relapse
- Total: 33% in LSD arm attained abstinence at 12 months
- Those who had a “psychedelic peak experience” appeared to be doing better than those who did not.
- Authors note many were “unmotivated” and only participated in hopes of being favorably considered for early release,

Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.



Conclusion:

- LSD assisted psychotherapy may be effective as a treatment for OUD but results should be interpreted with caution

Neurobiologic model of substance use disorders



Disrupted self-processing

- Maladaptive self-referential thoughts
- Default mode network

Self-referential
rumination



Operant Conditioning

- "Liking"
- Positive and Negative reinforcement

Binge/
intoxication



Opponent-process

- Reward vs anti-reward

Withdrawal/
Negative affect



Incentive sensitization

- "Craving"
- "Wanting"

Pre-occupation/
Anticipation



Impaired regulation

- Poor inhibitory control
- Risk taking

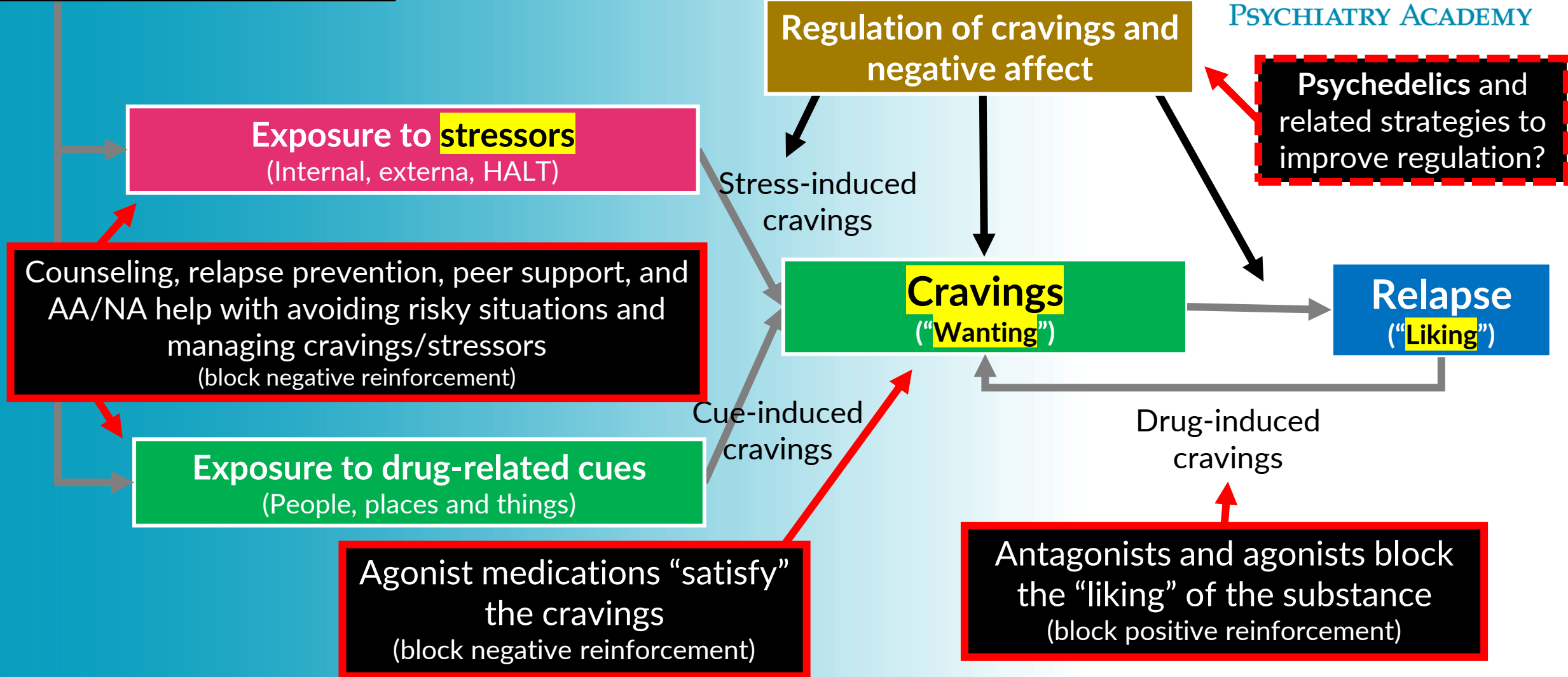
Loss of control

Treatment entry



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Psilocybin improved drinking outcomes in the first DBRCT



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Research

JAMA Psychiatry | Original Investigation

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder A Randomized Clinical Trial

Michael P. Bogenschutz, MD; Stephen Ross, MD; Snehal Bhatt, MD; Tara Baron, MA; Alyssa A. Forcehimes, PhD; Eugene Laska, PhD; Sarah E. Mennenga, PhD; Kelley O'Donnell, MD, PhD; Lindsey T. Owens, MA; Samantha Podrebarac, MA; John Rotrosen, MD; J. Scott Tonigan, PhD; Lindsay Worth, MA

Design:

- Double-blind randomized clinical trial

Methods:

- 95 individuals with AUD randomly assigned to receive two sessions of psilocybin 25mg or diphenhydramine. All received 12 weeks of manualized psychotherapy.

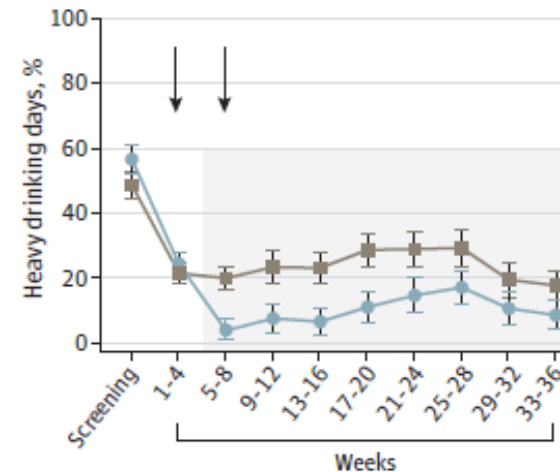
Primary outcomes:

- Percent heavy drinking days (%HDD) over the 32-week follow-up
- % drinking days (%DD); Drinks/drinking days (DDD)

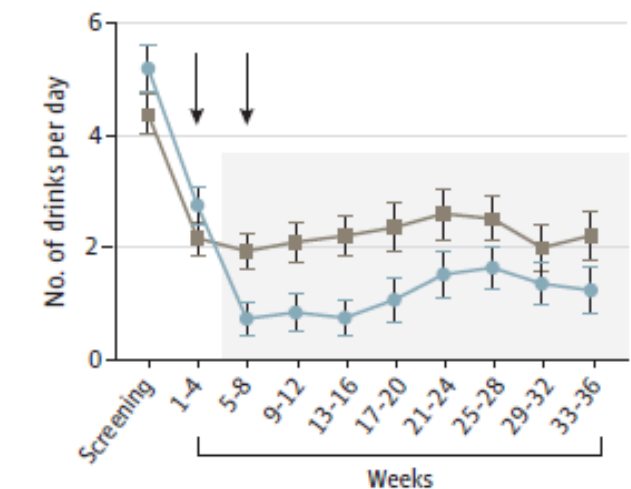
Results:

- During follow-up, **%HDD was 9.7% vs 23.6%** ($p=0.01$)
- Lower %DD and DDD in psilocybin
- No serious AEs
- Blinding NOT successful

A Percent heavy drinking days



C Drinks per day



Conclusion:

- Psilocybin compared to control led to greater reduction in drinking and heavy drinking

Psilocybin did NOT improve drinking outcomes in the second DBRCT



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Psilocybin-assisted therapy for relapse prevention in alcohol use disorder: a phase 2 randomized clinical trial

Nathalie M. Rieser,^{a,*} Raoul Bitar,^a Simon Halm,^a Christina Rossigoderer,^a Ladina P. Gubser,^a Maeva Thévenaz,^a Yara Kreis,^a Robin von Rotz,^a Carlos Nordt,^a Monika Visentini,^a Flora Moujaes,^a Etna J. E. Engeli,^a Andres Ort,^a Erich Seifritz,^a Franz X. Vollenweider,^a Marcus Herdener,^{a,b} and Katrin H. Preller^{a,b}

^aDepartment of Adult Psychiatry and Psychotherapy, Psychiatric University Clinic Zurich and University of Zurich, Lengstrasse 31, Zurich 8032, Switzerland



Design:

- Double-blind, placebo-controlled randomized trial

Methods:

- 37 individuals with AUD who recently completed withdrawal (i.e., “detox”) treatment were randomly assigned to receive one session of either psilocybin 25mg or placebo along with a 5-session manualized psychotherapy.

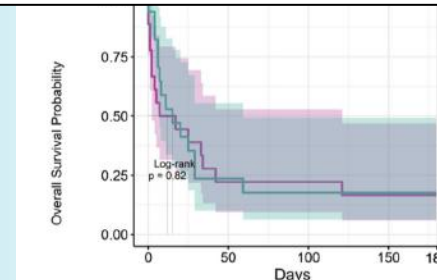
Primary outcomes:

- Abstinence
- Mean alcohol use at 4 weeks in drinks per day

Results:

- No difference in abstinence duration (16.8 vs 13.8 days)
- No difference in mean drinks per day at 4 weeks (0.51 vs 0.48)

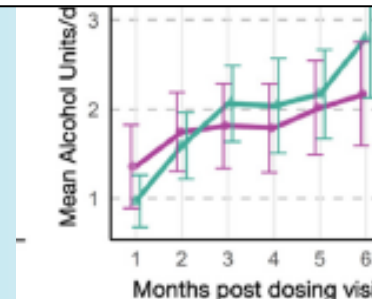
Abstinence at 6 months



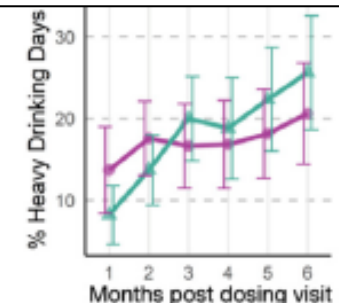
Group

- Placebo
- Psilocybin

Mean alcohol use at 6 months



% HDD at 6 months



Conclusion:

- Single-session of 25mg psilocybin with psychotherapy might not be sufficient for those with AUD recently completing inpatient treatment

A single infusion of ketamine helped reduce relapse to cocaine



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A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial

Elias Dakwar, M.D., Edward V. Nunes, M.D., Carl L. Hart, Ph.D., Richard W. Foltin, Ph.D., Sanjay J. Mathew, M.D., Kenneth M. Carpenter, Ph.D., C.J. "Jean" Choi, M.S., Cale N. Basaraba, M.P.H., Martina Pavlicova, Ph.D., Frances R. Levin, M.D.

Design:

- Double-blind randomized clinical trial

Method:

- 55 cocaine dependent patients randomly assigned to receive either single infusion of ketamine 0.5mg/kg or midazolam. All received manualized psychotherapy.

Primary outcomes:

- Abstinence from cocaine at 2 weeks
- Time to relapse

Results:

- At 2-weeks, ketamine (48.2%) vs midazolam (10.7%) abstinent
 - At 6-months, ketamine (44.0%) vs midazolam (0%) abstinent*
 - Relapse risk 53% lower in ketamine group
- * by self-report only, not biochemically confirmed
- **Cravings lower in ketamine group throughout trial**, and well tolerated with no adverse effects or dropout from adverse effects

Proportion (%) abstinent

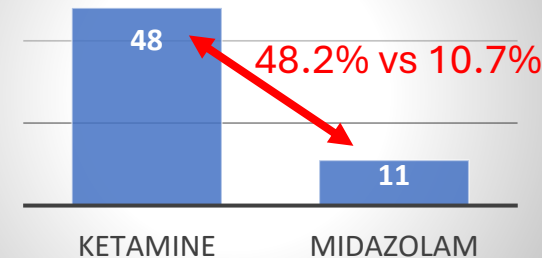
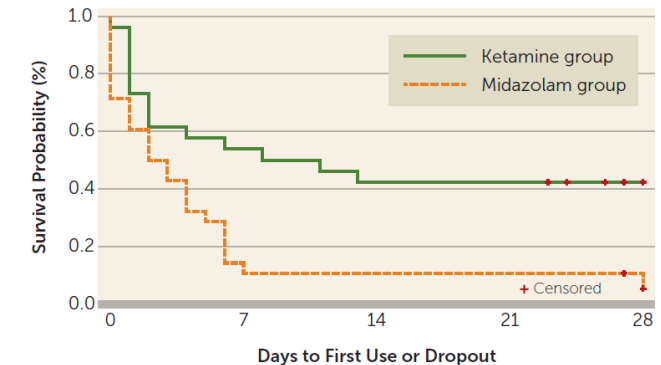


FIGURE 2. Time to first use or dropout, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence



Conclusion:

- Ketamine combined with psychotherapy significantly **reduced risk of cocaine relapse**

A single infusion of ketamine helped reduce relapse to alcohol



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A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial

Elias Dakwar, M.D., Frances Levin, M.D., Carl L. Hart, Ph.D., Cale Basaraba, M.P.H., Jean Choi, M.S., Martina Pavlicova, Ph.D., Edward V. Nunes, M.D.

Design:

- Double-blind randomized clinical trial

Method:

- 40 individuals with AUD randomly assigned to receive either single infusion of ketamine 0.71mg/kg or midazolam. All received manualized psychotherapy.

Primary outcomes:

- Abstinence from alcohol during 3-week f/u
- Time to relapse

Results:

- Ketamine (52%) vs midazolam (40%) abstinent during f/u
- Regression model significant for time by treatment interaction
- Ketamine group with significantly longer delay to relapse
- Cravings no different in the two groups

Proportion (%) abstinent

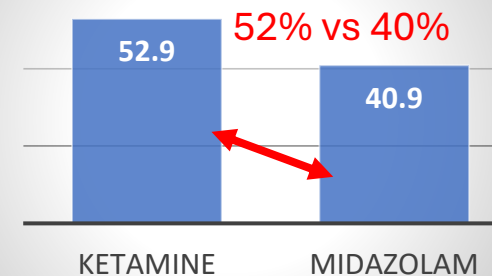
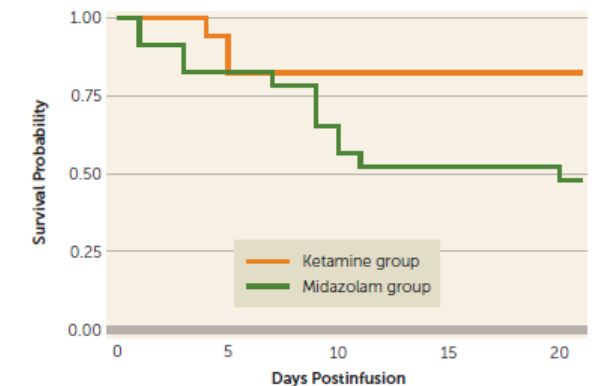


FIGURE 4. Time to relapse among study participants receiving ketamine or midazolam



Conclusion:

- Single infusion of ketamine combined with psychotherapy significantly **reduced risk of alcohol relapse**

Ketamine with psychotherapy helped increase abstinence from alcohol



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Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder

Meryem Grabski, Ph.D., Amy McAndrew, Ph.D., Will Lawn, Ph.D., Beth Marsh, B.Sc., Laura Raymen, M.Sc., Tobias Stevens, Ph.D., Lorna Hardy, Ph.D., Fiona Warren, Ph.D., Michael Bloomfield, Ph.D., Anya Borissova, M.D., Emily Maschauer, M.Sc., Rupert Broomby, M.D., Robert Price, M.D., Rachel Coathup, M.D., David Gilhooly, M.D., Edward Palmer, M.D., Richard Gordon-Williams, M.D., Robert Hill, Ph.D., Jen Harris, D.Clin.Psych., O. Merve Mollaahmetoğlu, M.Sc., H. Valerie Curran, D.Clin.Psych., Brianna Brandner, M.D.

Design:

- Double-blind, placebo-controlled, phase 2, randomized clinical trial

Method:

- 96 individuals with AUD randomly assigned to receive either three infusions of ketamine 0.8mg/kg or saline, with either mindfulness-based therapy vs alcohol education

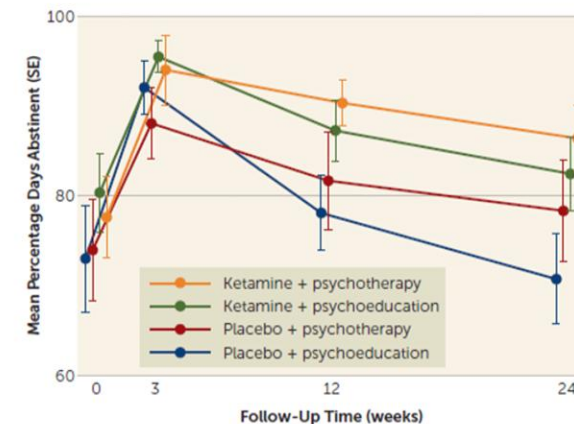
Primary outcomes:

- Percent days abstinent from alcohol at 6 months
- Relapse to alcohol at 6 months

Results:

- **More days abstinent** among those receiving ketamine vs placebo
- Greater difference for those also receiving psychotherapy
- **No significant difference in relapse rate**

FIGURE 3. Percentage days abstinent across the four treatment conditions in a study of ketamine and psychological therapy in the treatment of alcohol use disorder^a



Conclusion:

- Three infusions of ketamine combined with psychotherapy significantly **increased proportion of days of being abstinent compared to placebo**

Ketamine may be helpful for OUD



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Journal of Substance Abuse Treatment 23 (2002) 273–283

Journal of
Substance
Abuse
Treatment

Regular article

Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up

Evgeny Krupitsky, M.D., Ph.D.*, Andrey Burakov, M.D., Tatyana Romanova, M.A.,
Igor Dunaevsky, M.D., Rick Strassman, M.D., Alexander Grinenko, M.D.

St. Petersburg Research Center of Addictions and Psychopharmacology, Novo-Deviatkins 19/1, Leningrad Region 188661, Russia

Received 5 November 2001; received in revised form 29 May 2002; accepted 24 June 2002

Results:

- High dose, compared to Low dose, produced significantly more intense experience, led to greater % of abstinence over course of follow-up
 - At 6 months: approximately 36% vs 16%
 - At 12 months: approx. 25% vs 5%
 - At 24 months: approx. 16% vs 3%
- Less opioid craving for High dose vs Low dose
- Did not follow ITT principles—drop-outs were not accounted for?

Design:

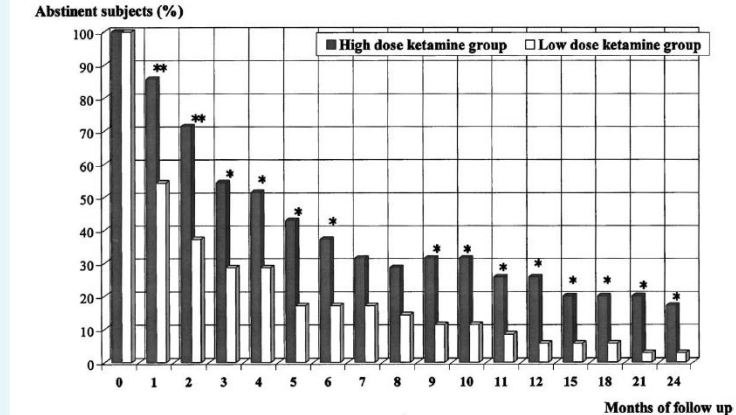
- RCT for individuals with OUD

Method:

- 70 individuals recruited from an inpatient unit in Russia, randomized to High (2mg/kg) vs Low (0.2mg/kg) IM ketamine with psychotherapy. Outcomes evaluated out to 24 months.

Outcomes:

- Abstinence from opioids, self-report and urine toxicology
- Cravings, mood, MMPI, attitudes, purpose in life, spirituality
- HRS



Conclusion:

- Ketamine may be safe for OUD, but results remains preliminary.

Ketamine may be helpful for OUD



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Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence[†]

Evgeny M. Krupitsky, M.D., Ph.D.*; Andrei M. Burakov, M.D., Ph.D.**;
Igor V. Dunaevsky, M.D., Ph.D.***; Tatyana N. Romanova, M.S.****;
Tatyana Y. Slavina, M.D., Ph.D.***** & Alexander Y. Grinenko M.D., Ph.D.*****

Design:

- RCT for individuals with OUD

Method:

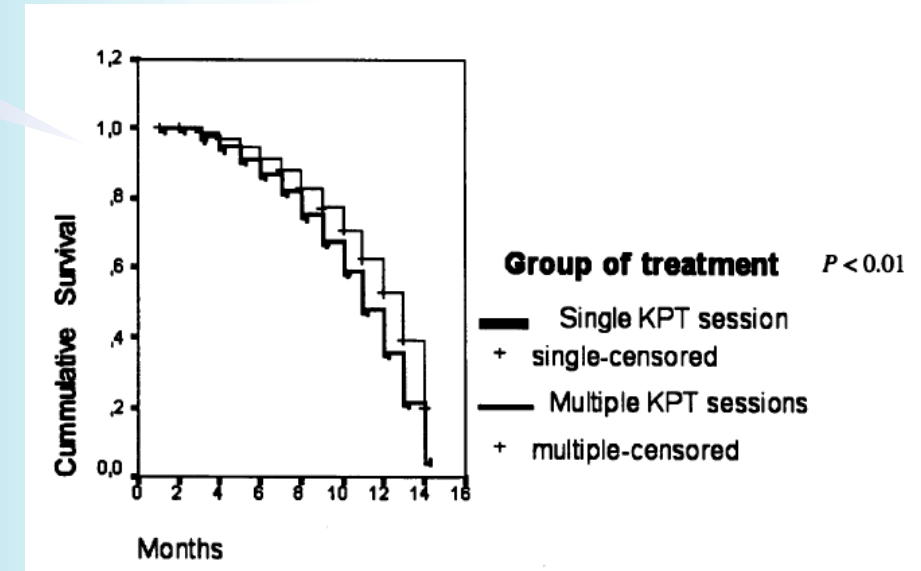
- 53 individuals recruited from an inpatient unit in Russia, randomized to Single (n=27) vs Multiple (n=26) IM ketamine (2mg/kg) treatments with psychotherapy. Outcomes evaluated out to 24 months.

Outcomes:

- Abstinence from opioids, self-report and urine toxicology
- Cravings, mood, MMPI, attitudes, purpose in life

Results:

- Multiple dosing, compared to single dosing, led to greater % of abstinence over course of follow-up
 - At 12 months: 50% vs 22.2%
- Again, did not follow ITT principles



Conclusion: Multiple ketamine treatments may be superior to single dosing for OUD

Ibogaine may improve OUD-related outcomes, but available evidence of poor quality. Rigorous research needed.



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journal homepage: www.elsevier.com/locate/jSAT



A systematic literature review of clinical trials and therapeutic applications of ibogaine

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^a University of Basel Psychiatric Clinics, Wilhelm Klein-Strasse 27, 4002 Basel, Switzerland

^b Department for Psychiatry, Psychotherapy and Psychosomatic, Psychiatric Hospital, University of Zurich, Zurich, Switzerland

Design

- Systematic review to assess the evidence-base for ibogaine as a treatment for SUDs focusing on clinical data and therapeutic interventions in humans.

Method:

- PRISMA review of publications up to December 2020
- Included case reports, case series, retrospective and observational studies, open-label clinical trials, and randomized trials

Results:

- Total of 743 records, narrowed down to 24 publications
 - Case report/series (n=7, 49 individuals)
 - Retrospective/observation (n=8, 325 individuals)
 - Open-label clinical trials (n=6, 280 individuals)
 - RCTs (n=3, 52 individuals)
- Dose:
 - 0.28mg/kg – 55mg/kg
- Outcome:
 - 2 RCTs were for safety of noribogaine, 1 for CUD
 - Most showed improvement in opioid withdrawal
 - Sustained reduction in opioid use, but by self-report
 - Reduction in PTSD symptoms
- Fatalities:
 - 2 deaths, both in treatment settings
 - Additional 38 deaths and 20 emergencies
 - 34.5% with other drug use
 - 70.7% had sought treatment for OUD

Conclusion:

- Accumulating anecdotal evidence of ibogaine's potential benefits but also harms

Current state of evidence for psychedelics as treatments for SUD



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Psychedelic	SUD	Quality of evidence
LSD	Alcohol	Fair: Methodological issues even though RCTs
	Opioid	Fair: Study of parolees, but daily urines a strength
Psilocybin	Alcohol	Mixed: <u>Two RCTs</u> with one positive and one negative results
	Tobacco	Poor: Open-label (waiting for phase 2 results; NIDA funding for phase 3)
	Opioids	Poor: Several trials ongoing; NIDA funding a multi-site trial for MMT
Ketamine	Cocaine	Fair: <u>One pilot RCT</u> with promising short-term benefit
	Opioids	Fair: 3 RCTs but not as adjunct to MOUD and questionable methods; may be useful for opioid withdrawal especially precipitated withdrawal
	Alcohol	Promising: <u>Two pilot RCTs</u> , three uncontrolled studies, too early to tell
	Cannabis	Poor: One open-label study
	Benzodiazepines	Poor: On open-label study
Ibogaine	Opioid	Poor: Uncontrolled observational studies only; cardiac arrhythmias concerns remain
MDMA	Alcohol	Poor: One open-label study only

Despite the tremendous interest, research of psychedelics for SUD has lagged other indications



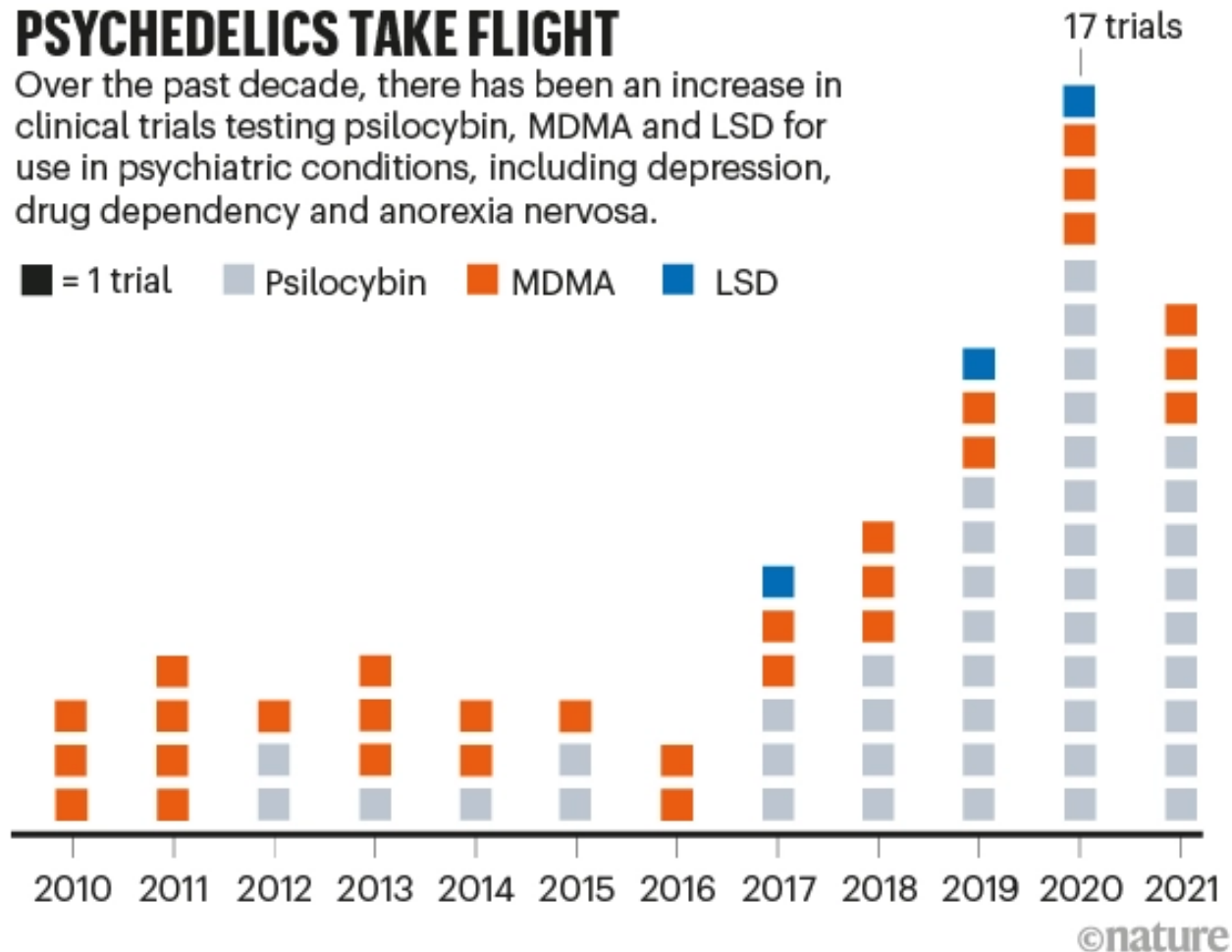
MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

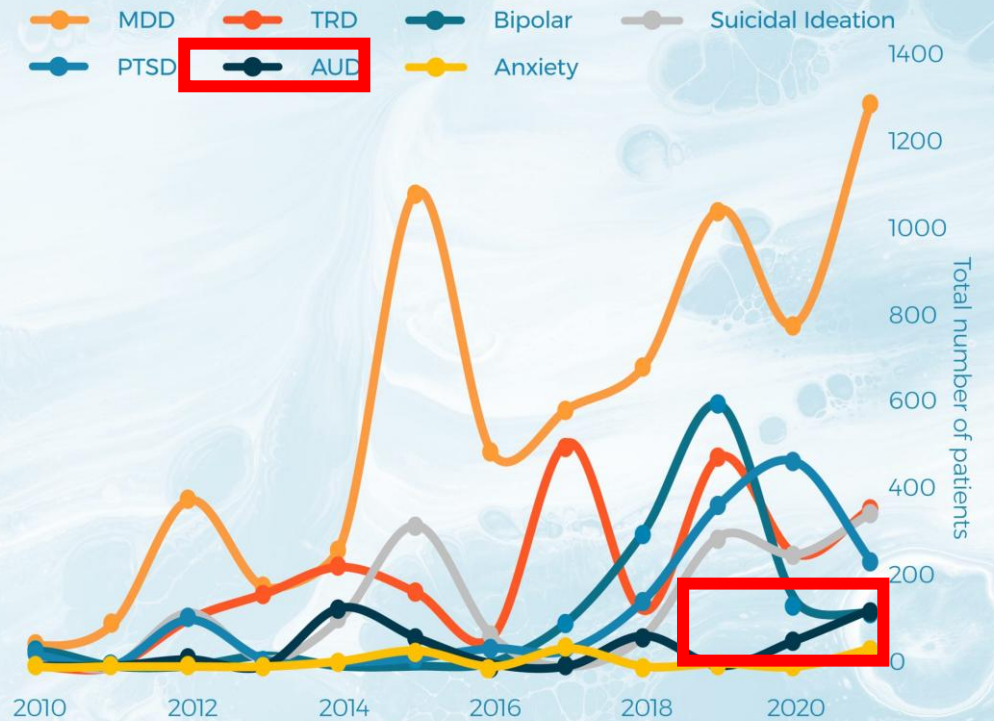
PSYCHEDELICS TAKE FLIGHT

Over the past decade, there has been an increase in clinical trials testing psilocybin, MDMA and LSD for use in psychiatric conditions, including depression, drug dependency and anorexia nervosa.

■ = 1 trial ■ Psilocybin ■ MDMA ■ LSD



NUMBER OF PATIENTS IN CLINICAL TRIALS HAS BEEN TRENDING UPWARDS

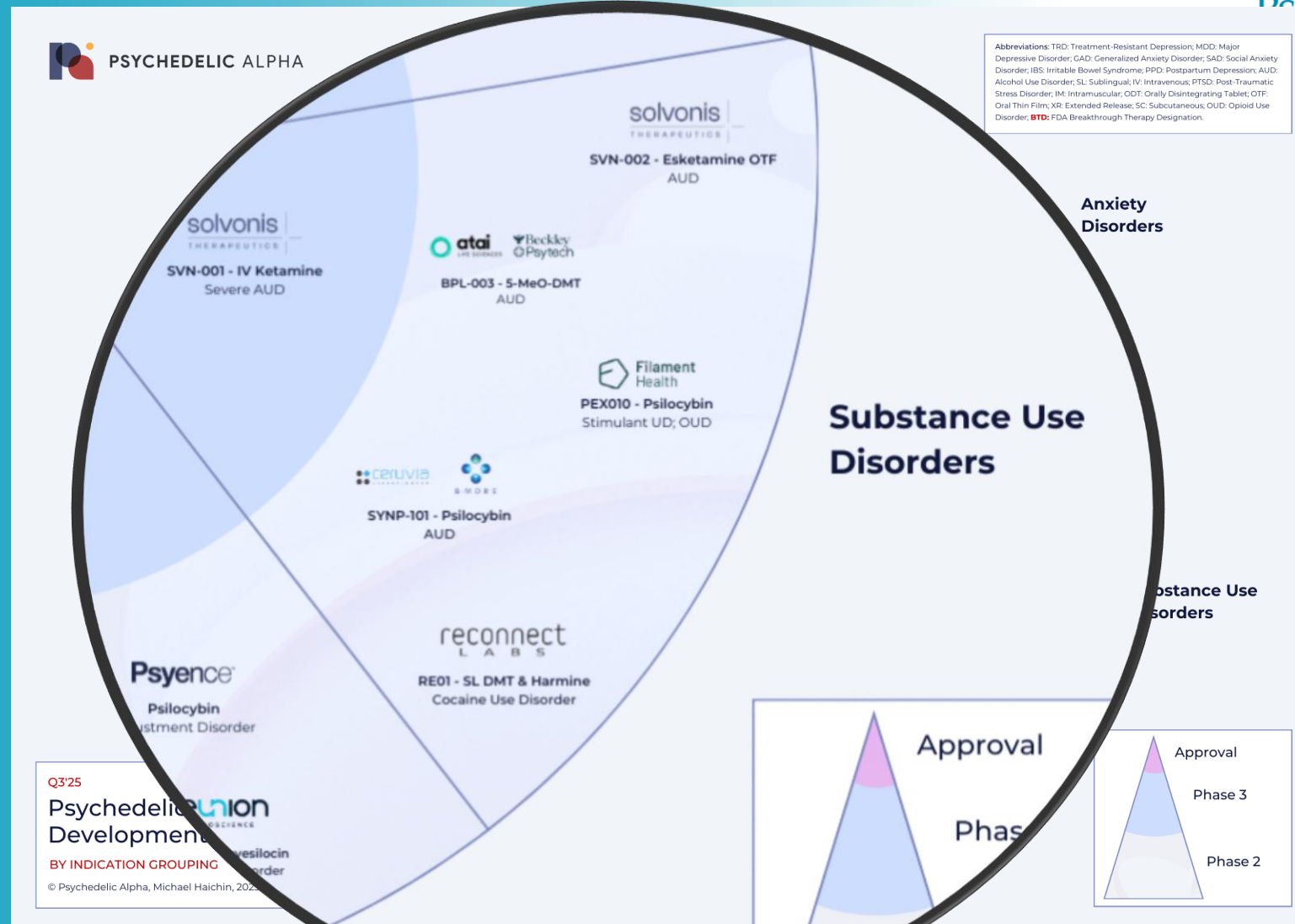


Psychedelic Drug Development Chart as of Q3 2025



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Do our colleagues, patients, and peer support specialists support the use of psychedelics as treatments for SUD?



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Addiction specialists' attitudes toward psychedelics: A National Survey

Amanda Kim MD, JD^{1,2}  | Joji Suzuki MD^{1,2} 

Attitudes Toward Psychedelic Treatments by Individuals With Histories of Substance Use or Psychiatric Disorders: A Survey Study

*Sara Prostko, BA, Alexander Wu, BA, Samuel Maddams, BS, Veronica Szpak, MSc,
Naomi Rosenblum, BA, Lori M. Hilt, PhD, and Joji Suzuki, MD*

Survey of Massachusetts peer recovery coaches' attitudes toward the use of psychedelics to treat substance use disorders



Veronica Szpak¹, Amanda Kim^{1,2}, Zachary Sager^{2,3} and Joji Suzuki^{1,2*}

Views on Psychedelic-Assisted Therapy for Substance Use Disorders from Individuals with Opioid Use Disorder and a History of Injection-Related Infections: A Qualitative Study

Veronica Szpak¹, Samuel Maddams¹, Amanda Kim^{1,2}, Zachary Sager^{2,3} and Joji Suzuki^{1,2,*}

Addiction specialists:

- 75% supported legal access
- 38% voiced safety concerns including potential for addiction and other harms.

Individuals with SUD:

- 72% believed psychedelics could help SUD
- 70% would personally try if available

Peer recovery coaches:

- 68% willing to support someone using psychedelics
- 84% agreed coaches should obtain training
- Less support (43%) for legal access, and concerns for potential for harm (57.5%)

Those with OUD who have survived serious infections:

- Overall support especially if standard therapies have not been effective. Some raising safety concerns.

Conclusions



- Psychedelics are used commonly in the general population, yet overall, relatively few ED visits confirming their relative safety compared to other substances such as opioids and alcohol
- Historically, psychedelic research has targeted SUD but less so in the modern era
- Psilocybin and ketamine with the most promising early results but **efficacy is still not established!!**
- Addiction treatment providers, peer recovery coaches, and patients with SUD are all generally supportive, but concerns for harms remain a concern.