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Psychedelics

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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).

Otherwise I have no other relevant financial disclosures.

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

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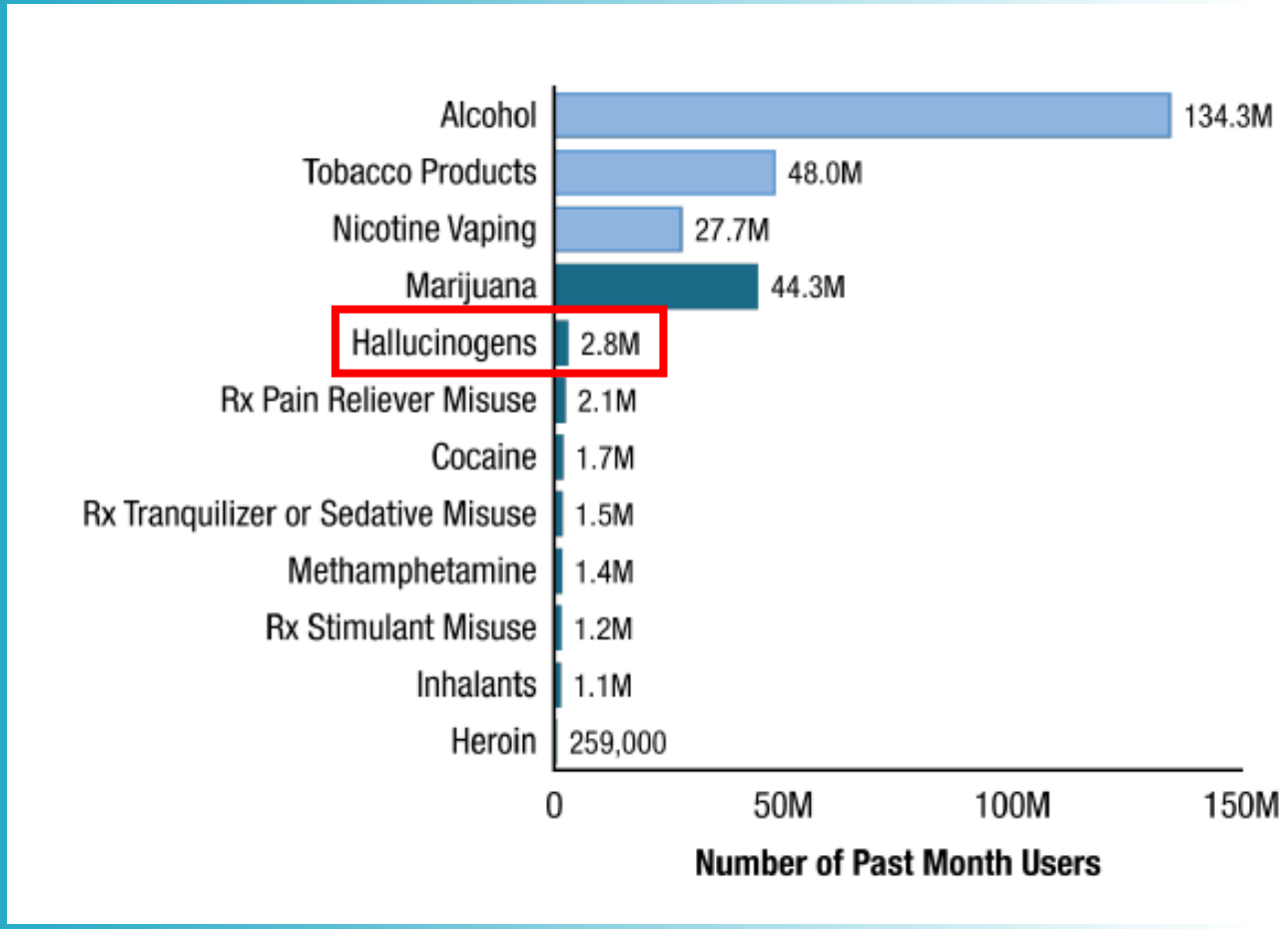

NSDUH 2025

What are psychedelics aka hallucinogens?

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"Classic" → serotonergic

- LSD, Psilocybin, Mescaline, 5-MeO-Dimethyl-tryptamine (5-MeO-DMT)

"Novel" → varied mechanisms

- Tryptamines/phenethylamines (2CI, NBOMe, etc) / Salvia Divinorum

Dissociative → NMDA antagonist

- Phencyclidine, Ketamine, Dextromethorphan

Deliriant → anticholinergic/cholinergic

- Belladonnna/Jimson weed/Datura (Atropine/scopolamine), Amanita (muscarine)

Empathogen → serotonergic/Noradrenergic

- MDMA, Cathinones/"bath salts", DOM/DOB

"Oneirogen" → Ibogaine (Iboga)

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

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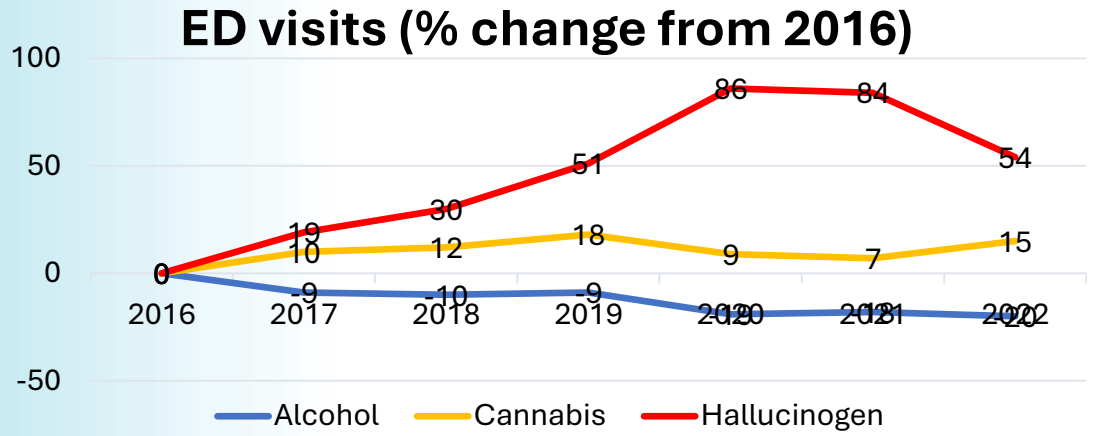
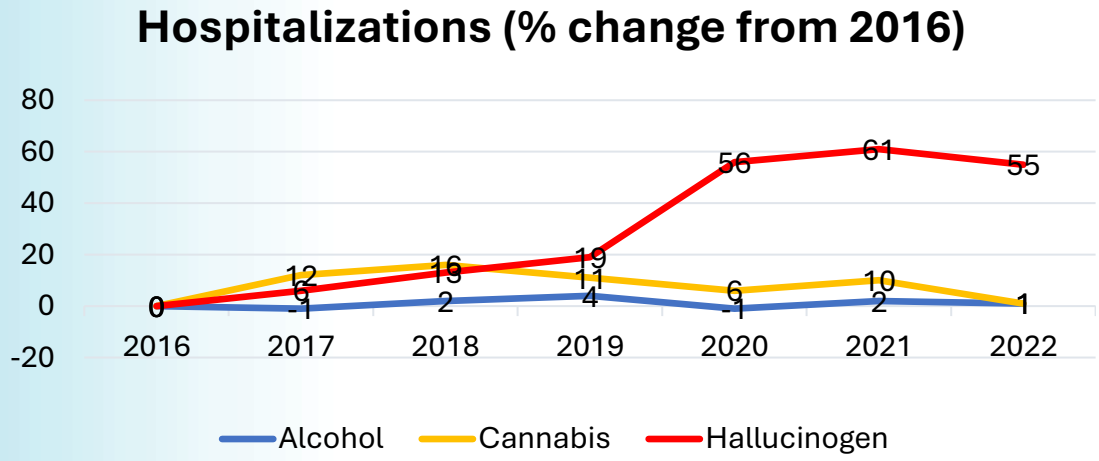
- Data from the California Department of Healthcare Access (HCAI)
- ICD-10 codes for hallucinogen-, cannabis-, and alcohol-related ED visits and hospitalizations

- **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)





Garel et al Addiction 2023

Hallucinogen Intoxication

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- Common reason for psychedelics to come to clinical attention in health care settings
- Characterized by self-limited panic reaction, anxiety, fears of "going insane"
  - Most patients can be discharged home once stable and back to baseline
  - Rare, but severe reactions such as violence, suicide attempt/completion can occur
- If we include MDMA, cathinones, and ketamine as psychedelics, then "overdoses" can occur, especially when combined with opioids or benzodiazepines
- Treatment of choice for most cases is the "talk through" or "talk down"
  - Dimmed lights, minimal distractions, ideally with a (non-intoxicated) sitter
  - Reassurance that experience is time-limited and drug-induced, therefore it will eventually resolve
- If "talk through" is not sufficient, or if patient is severely agitated, **benzodiazepines are treatment of choice**, but antipsychotics if needed for severe agitation/psychosis

Leonard et al 2018; Johnson et al 2020; Suzuki et al 2015

The New York Times

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.

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

Hallucinogen use disorder (HUD)

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- DSM has 2 categories: “PCP and related compounds” vs “Others”
- Tolerance develops rapidly to “classic” psychedelics and HUD difficult to develop, and withdrawal syndromes do not appear
- **Ketamine and PCP** are the most likely substances for HUD currently in the US. Ketamine addiction is endemic in many parts of the world, especially Asia (Hong Kong).
- Consider HUD when a patient reports regular use of hallucinogens despite knowledge of harm, or when the pattern of use appears to be out of control

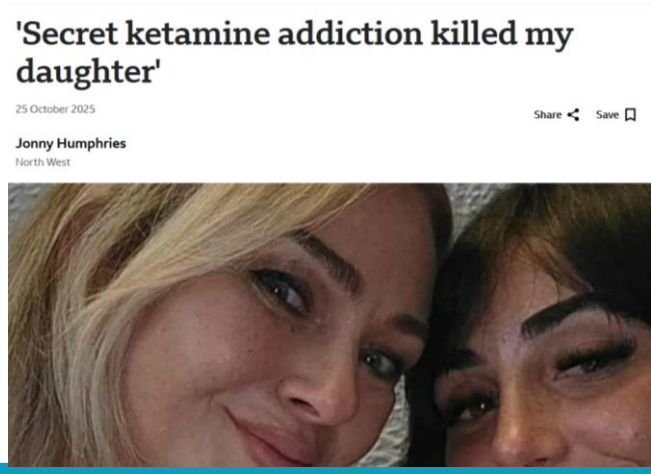

The New York Times

F.D.A. Issues Warning Over Misuse of Ketamine

Unsupervised treatment — fueled by telemedicine prescriptions — for various psychiatric problems poses a number of health risks, the agency said.

Share full article

Sandy Huffaker for The New York Times


BBC

Innovation Culture Arts Travel Earth Audio Video Live Documentari

'Secret ketamine addiction killed my daughter'

25 October 2025

Share Save

Jonny Humphries

North West

Johnson 2020; O’ Brien 2001

Hallucinogen persisting perceptual disorder (HPPD)

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- The reexperiencing of perceptual symptoms that were experienced while intoxicated with the hallucinogen following cessation of use of a hallucinogen, even after a single use.
- Often triggered by cannabis or anxiety
- Estimated 4% of those with history of using psychedelics (DSM5)
- Type I
  - Short, reversible and favorable disease course
  - Usually starts with "aura" and mild depersonalization/derealization
  - No significant discomfort associated, usually no treatment required
- Type II
  - Long, slowly reversible or irreversible course
  - Acute onset, sudden sense of detachment and severe symptoms
  - Can increase in intensity over time, high recurrence rates
- What has been reported to work in case reports: Antipsychotics (risperidone, olanzapine), clonidine, SSRI, benzos, lamotrigine, levetiracetam, naltrexone/naloxone, EMDR, tinted glasses/sunglasses

Skryabin et al 2018; Doyle et al 2022; Ford et al 2022

Hallucinogen-induced psychotic disorder

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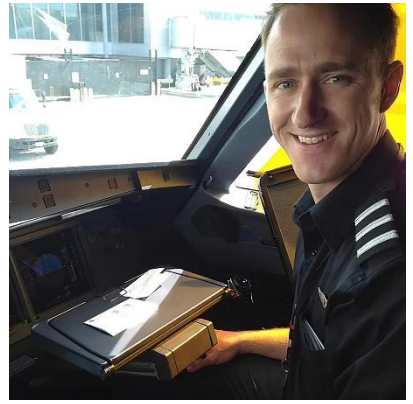
- The emergence of prominent psychotic symptoms that develop during or soon after substance intoxication or withdrawal, where the substance is capable of producing these symptoms, but they persist BEYOND the drug effects.
- Alcohol is the substance most commonly associated with substance-induced psychotic disorder, more than cannabis and stimulants
- Individuals with psychotic disorder are at greatest risk
- Treat as in the case of hallucinogen intoxication, and search for underlying etiologies, but no evidence-based treatments.
- Based on a meta-analysis and systematic review, 25% will eventually receive formal psychotic disorder diagnosis, therefore early evaluation by psychiatry strongly recommended



Joseph Emerson is a 44-year-old Alaskan Airline pilot. He took psilocybin for the first time with friends 48 hours prior to taking a flight back home. He was not able to sleep at all since then, believed he was dreaming, and experienced paranoia, hallucinations, and anxiety. He wondered “Am I dead? Am I in hell?”

He boarded the flight and was seated in the cockpit (allowed as an off-duty pilot) and tried cutting off the engine because he thought crashing the plane would wake him up from the dream. The pilot wrestled with him to avoid a crash.

Murrie et al Schizophrenia Bulletin 2020

Ongoing challenging experiences very common following psychedelic use

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RESEARCH ARTICLE

Extended difficulties following the use of psychedelic drugs: A mixed methods study

Jules Evans[1], Oliver C. Robinson[2]*, Eirini Ketzitzidou Argyri[3], Shayam Suseelan[2], Ashleigh Murphy-Beiner[4], Rosalind McAlpine[5], David Luke[2], Katrina Michelle[6], Ed Prideaux[7]

- Mixed-methods study of 608 individuals who reported extended difficulties **following** psychedelic experience.
- Aimed to describe the types of difficulties, prevalence, context, causality to psychedelics, current attitudes.
- Qualitative study to describe the difficulty in narrative form to identify themes.

Results:

- Problems most commonly associated with LSD and psilocybin
- Feelings to **anxiety, fear, existential struggle, social disconnection, depersonalization, and derealization**
- For **33%, problems persisted > 1 year, for 17% had > 3 years**

Conclusion:

- Persistent difficulties may be common, **particularly anxiety**.
- Reports of persistent issues even among trial participants, although more common in non-medical settings
- However, most felt the benefits outweighed the risks → challenging does not always mean they are AEs

Evans et al PLOS One 2023

NIDA has specifically identified psychedelics for addiction treatment as a research priority

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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

Volkow and Blanco 2023 American Journal of Psychiatry

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

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CHARLES B. TOWNS HOSPITAL

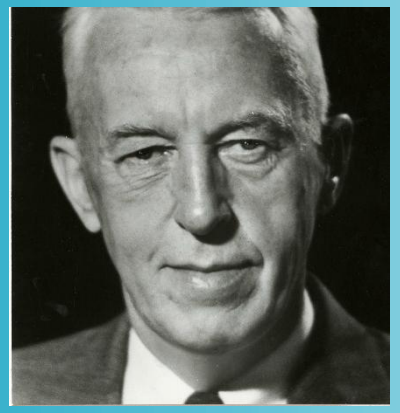
293 Central Park West New York, New York

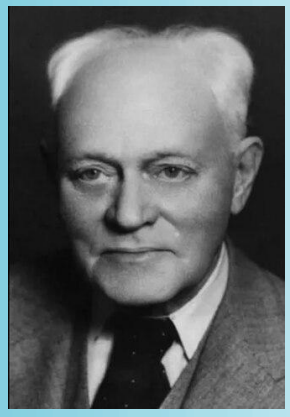
For ALCOHOLISM and DRUG ADDICTION

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





Further pioneered by Canadian treatment centers for AUD

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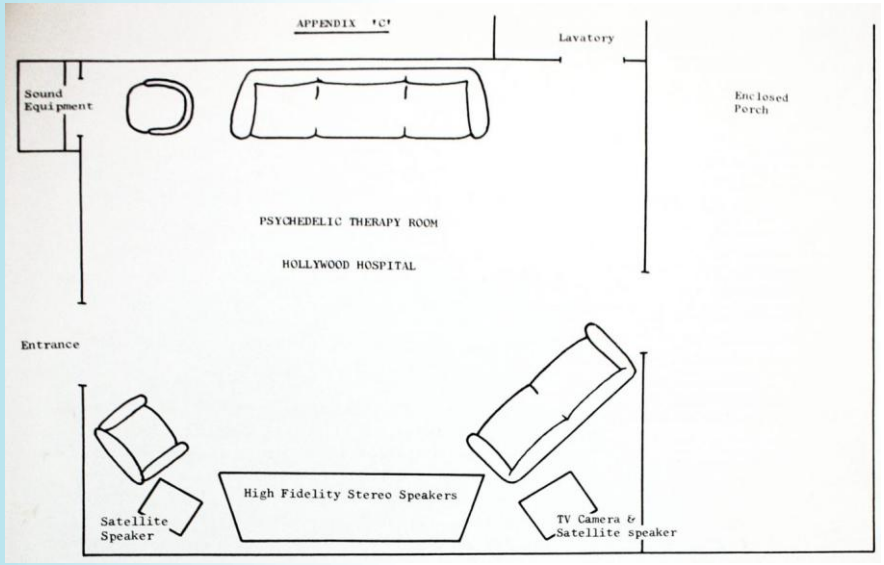

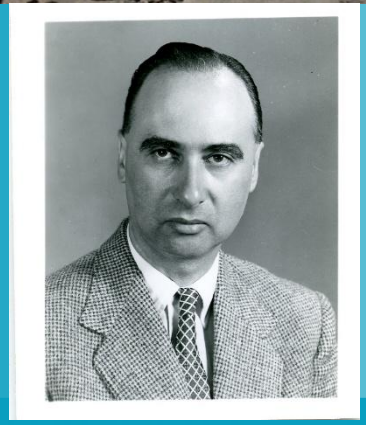

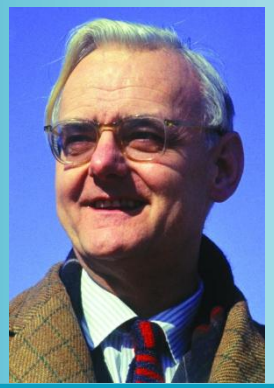

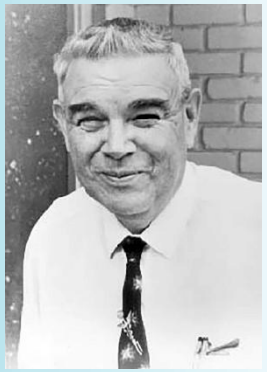

Randomized controlled trials from 1960s showed LSD to have short-term impact on AUD outcomes

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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)

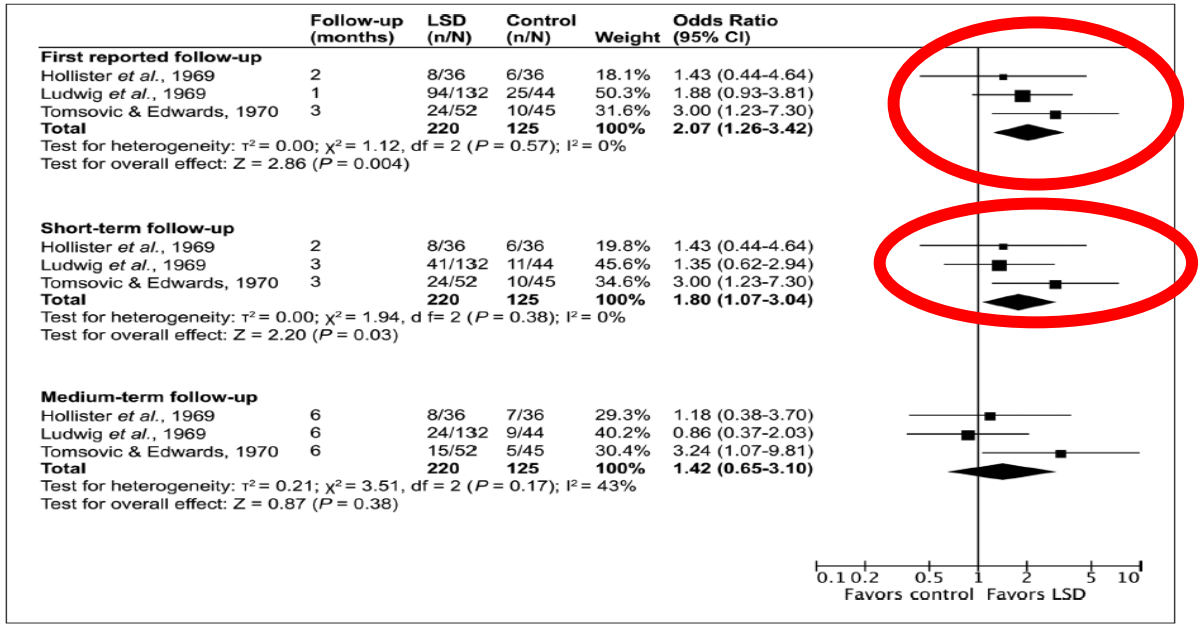

Figure 4. Maintained abstinence from alcohol after LSD versus control treatments.

Conclusion:

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

Krebs and Johansen 2012

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.

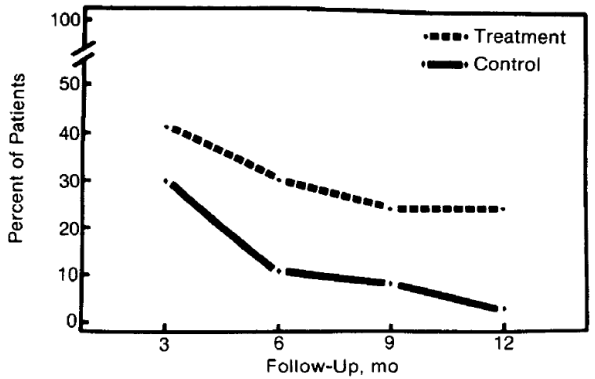
- 78 prisoners (with at least 18 months sentence remaining), and condition for release was to be in the study, with **daily urine toxicology**.
- Relapsed resulted in re-incarceration.
- Followed for up to 12-months

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

Savage and McCabe 1973

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

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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.

Kim and Suzuki Am J Addiction 2023; Prostko et al JAM 2025; Szpak et al ASCP 2024; Szpalk et al Psychedelic Medicine 2025

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

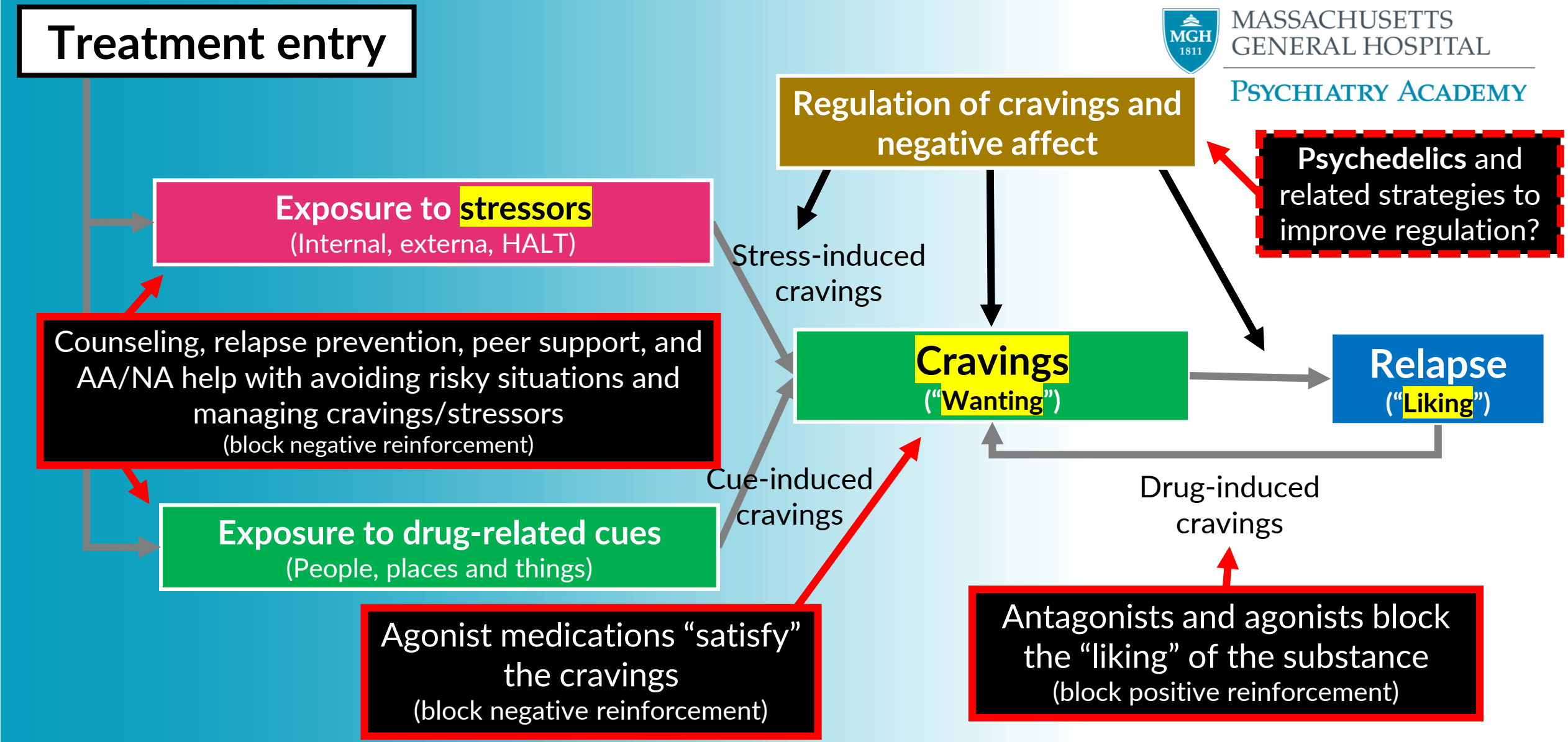
- "Craving"
- "Wanting"

Pre-occupation/ Anticipation

Impaired regulation

- Poor inhibitory control
- Risk taking

Loss of control


Treatment entry
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Regulation of cravings and negative affect
Psychedelics and related strategies to improve regulation?
Exposure to stressors
(Internal, externa, HALT)
Stress-induced cravings
Counseling, relapse prevention, peer support, and AA/NA help with avoiding risky situations and managing cravings/stressors
(block negative reinforcement)
Cravings
("Wanting")
Relapse
("Liking")
Cue-induced cravings
Drug-induced cravings
Exposure to drug-related cues
(People, places and things)
Agonist medications "satisfy" the cravings
(block negative reinforcement)
Antagonists and agonists block the "liking" of the substance
(block positive reinforcement)

Psilocybin disrupts the default mode network (DMN)

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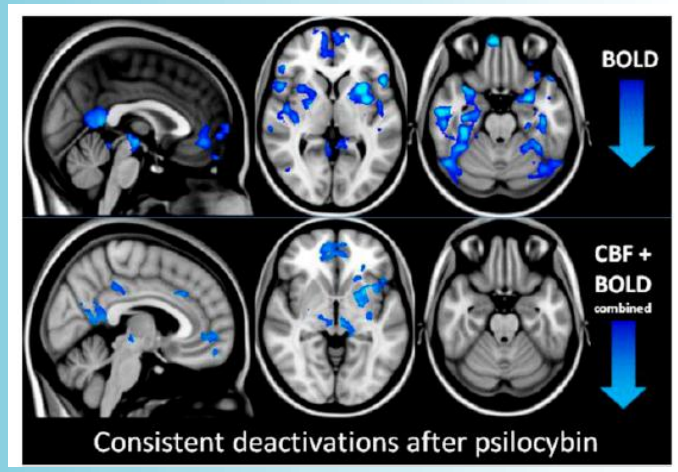
Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin

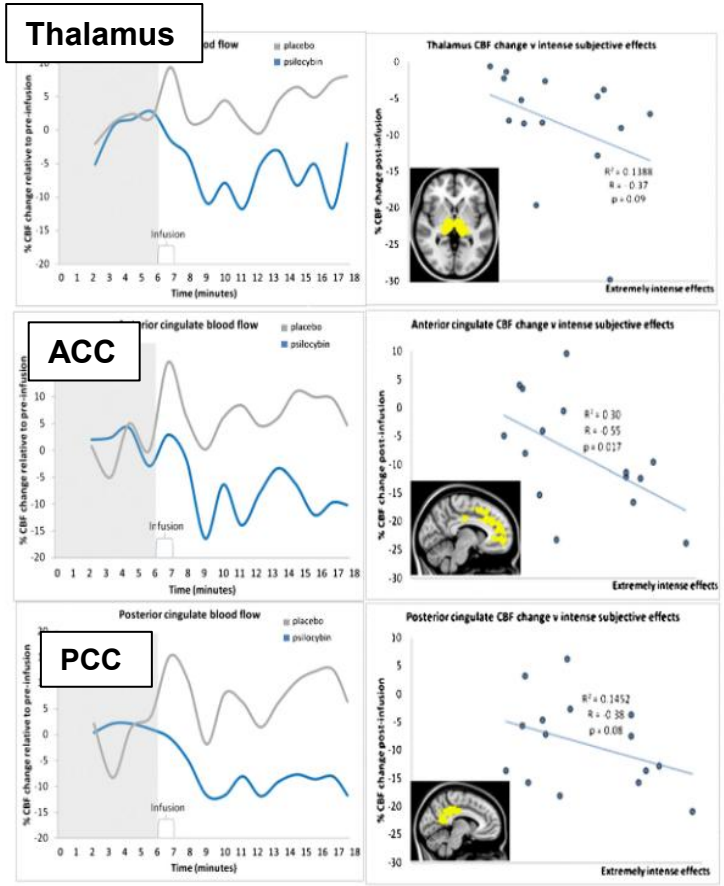
Robin L. Carhart-Harris[a,b], David Erritzoe[a,c], Tim Williams[b], James M. Stone[a], Laurence J. Reed[a], Alessandro Colasanti[a], Robin J. Tyacke[a], Robert Leech[d], Andrea L. Malizia[b], Kevin Murphy[e], Peter Hobden[e], John Evans[e], Amanda Feilding[f], Richard G. Wise[e], and David J. Nutt[a,b,1]

[a]Neuropsychopharmacology Unit, [d]Imperial College London, London W12 0NN, United Kingdom; [b]Academic Unit of Psychiatry, University of Bristol, Bristol BS8 2BN, United Kingdom; [c]Brain Research Imaging Centre, Cardiff University, Cardiff CF10 3AT, United Kingdom; [f]The Beckley Foundation, Beckley Park, Oxford OX3 9SY, United Kingdom; and [e]Neurobiology Research Unit, Rigshospitalet, and Center for Integrated Molecular Brain Imaging, University of Copenhagen, DK-2100 Copenhagen, Denmark

- 15 healthy volunteers (5F/10M) scanned during psilocybin IV infusion (2mg over 60s)
- ASL and BOLD fMRI

- **Results**:
  - NO increase an CBF/BOLD
  - Only decrease noted, maximal in hub regions such as thalamus, ACC, mPFC, PCC
  - Decreased coupling between mPFC and PCC
  - Magnitude of decrease correlated with intensity of the subjective effects





Carhart-Harris et al *PNAS* 2012

Psychedelics help to increase neuroplasticity

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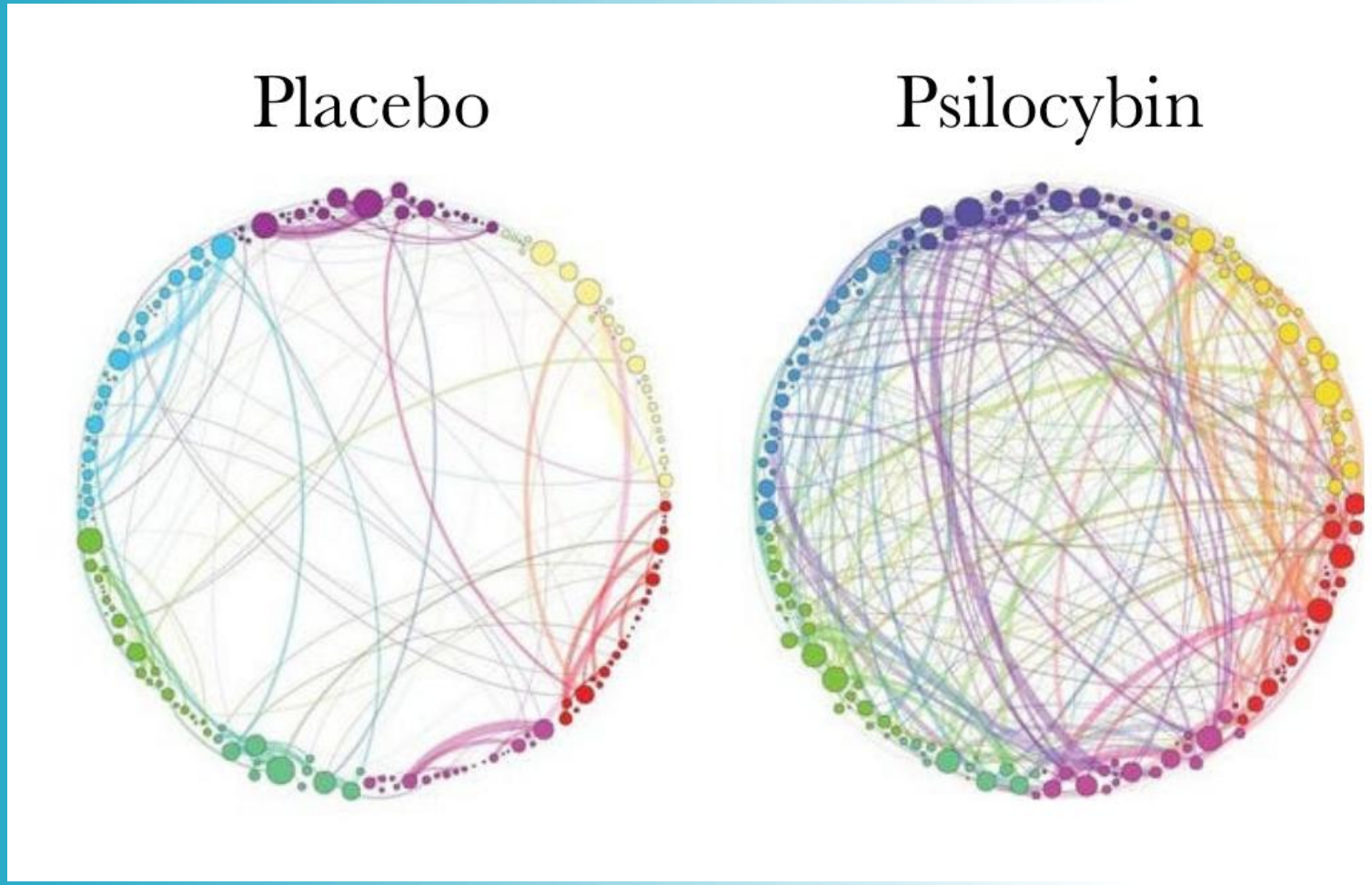

Petri et al 2014 Journal of the Royal Society

Psychedelics might reopen “critical period”

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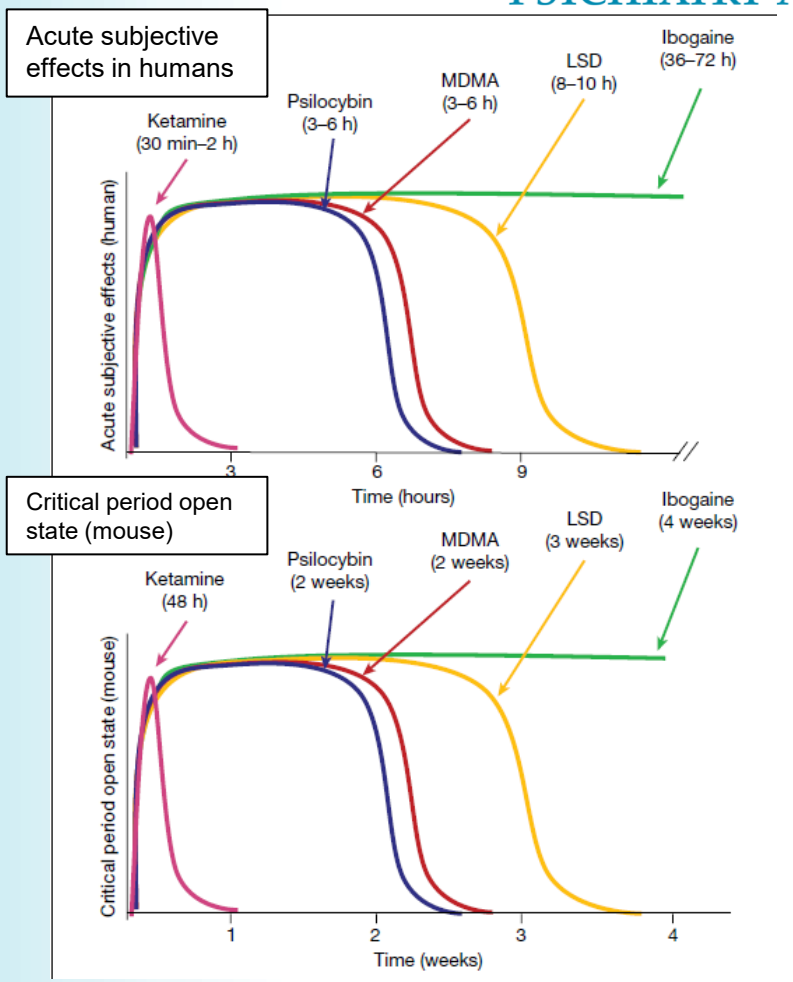
Article

Psychedelics reopen the social reward learning critical period

https://doi.org/10.1038/s41586-023-06204-3
Received: 31 August 2021
Accepted: 11 May 2023

Romain Nardou[1,2], Edward Sawyer[1,2], Young Jun Song[1,2], Makenzie Wilkinson[1,2], Yasmin Padovan-Hernandez[1], Júnia Lara de Deus[1,2], Noelle Wright[1,2], Carine Lama[1,2], Sehr Faltin[1,2], Loyal A. Goff[1,3,4], Genevieve L. Stein-O'Brien[1,2,5] & Gül Dölen[1,2,5,6,7,8]



- **Critical period**: During early brain development, heightened sensitivity to permit synaptic, circuit, and behavioral modifications. These are periods marked by high levels of neuroplasticity. Classic example is imprinting.
- In mice, psychedelics appear to reopen the social learning critical period that is oxytocin and context dependent.
- Re-organization of the extracellular matrix may underlie the mechanism for this effect.

Nardou et a Nature 2023

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:

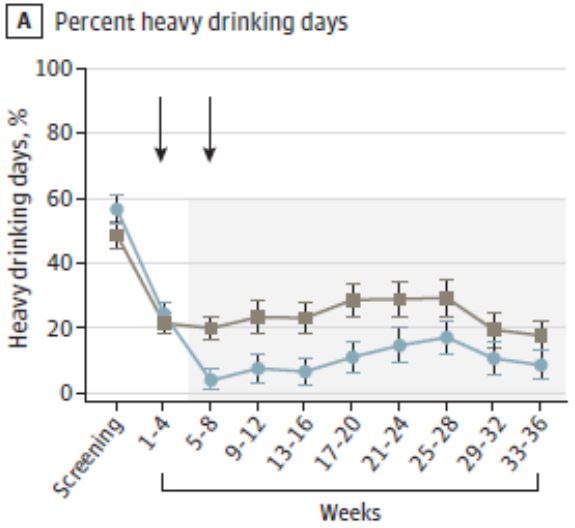
- 95 individuals with AUD randomly assigned to receive two sessions of psilocybin 25mg or diphenhydramine. All received 12 weeks of manualized psychotherapy.

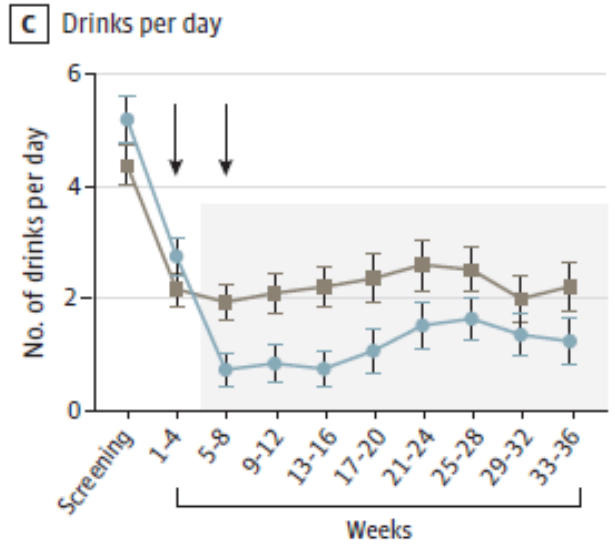
Primary outcomes:

- 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





Conclusion:

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

Bogenschutz et al JAMA 2022

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 Rossgoderer,[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]

[a]Department of Adult Psychiatry and Psychotherapy, Psychiatric University Clinic Zurich and University of Zurich, Lenggstrasse 31, Zurich 8032, Switzerland

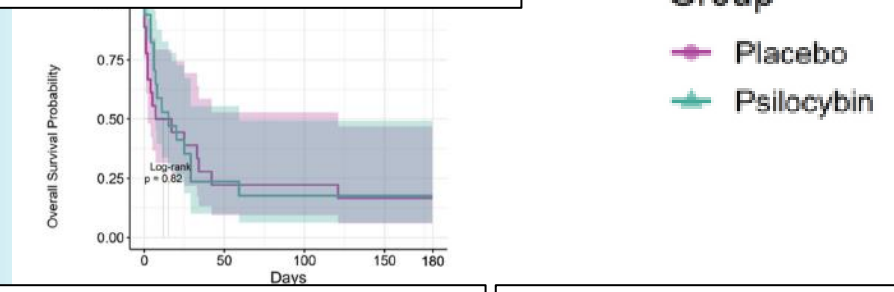
Design:
- Double-blind, placebo-controlled randomized trial

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.

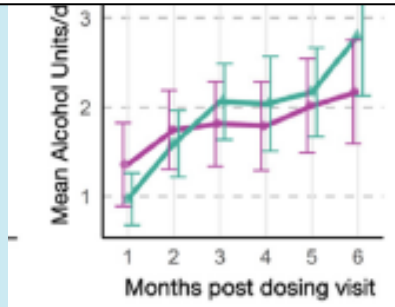
Primary outcomes:
- Abstinence
- Mean alcohol use at 4 weeks in drinks per day

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)

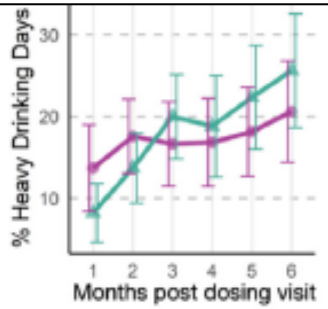
Abstinence at 6 months



Mean alcohol use at 6 months



% HDD at 6 months



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

Rieser et al 2025

A single infusion of ketamine helped reduce relapse to cocaine

MASSACHUSETTS GENERAL HOSPITAL

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.

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

Design:

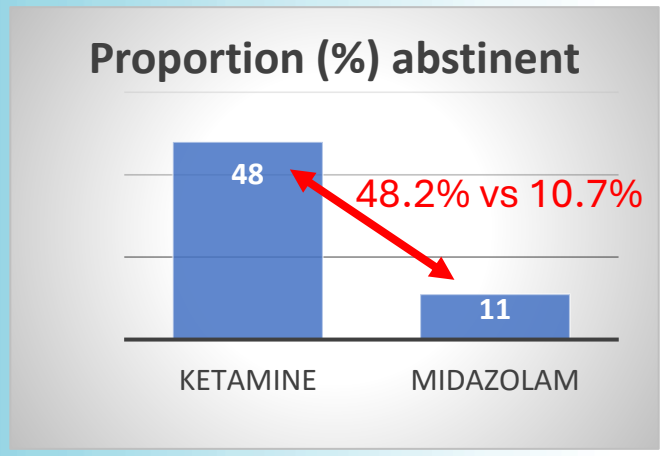
- Double-blind randomized clinical trial

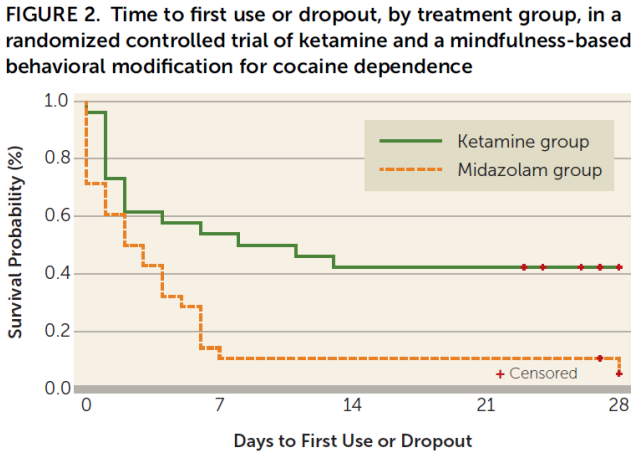
Method:

- 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





Conclusion:

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

Dakwar et al 2019

A single infusion of ketamine helped reduce relapse to alcohol

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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.

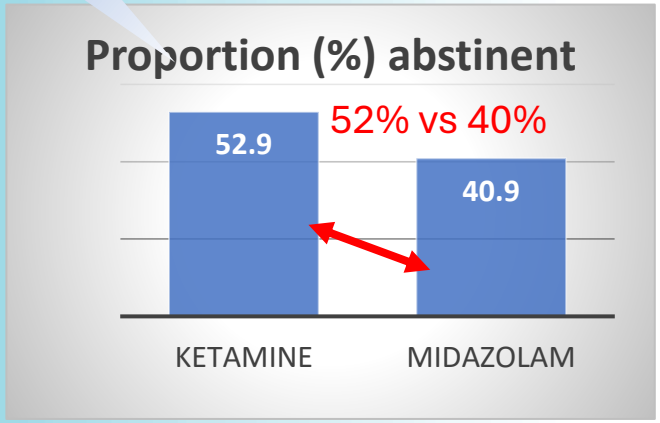
Design:
- Double-blind randomized clinical trial

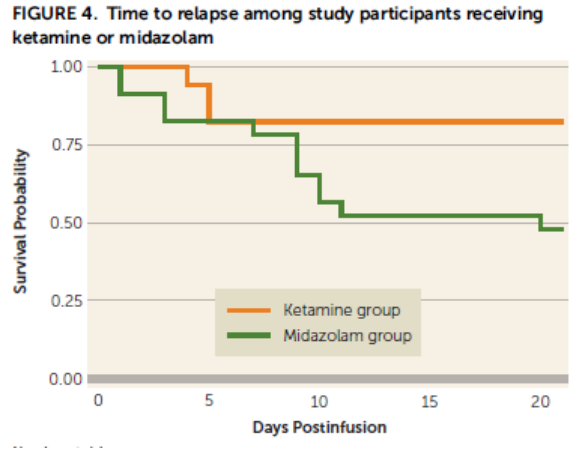
Method:
- 40 individuals with AUD randomly assigned to receive either single infusion of ketamine 0.71mg/kg or midazolam. All received manualized psychotherapy.

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





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

Dakwar et al 2020

Ketamine with psychotherapy helped increase abstinence from alcohol

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PSYCHIATRY ACADEMY

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 Mollaahmetoglu, M.Sc., H. Valerie Curran, D.Clin.Psych., Brigitta Brandner, M.D.

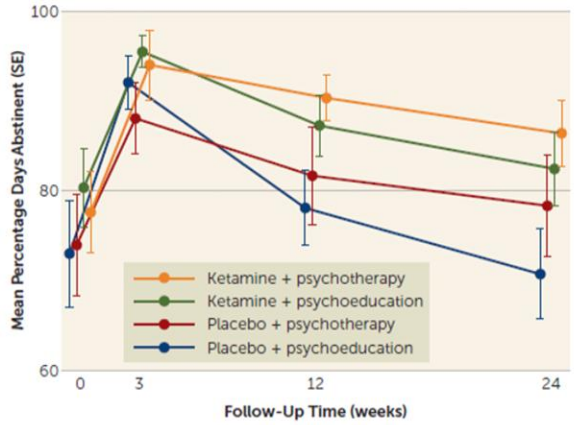
Design:
- Double-blind, placebo-controlled, phase 2, randomized clinical trial

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**

Grabski et al 2021

Ketamine may be helpful for OUD

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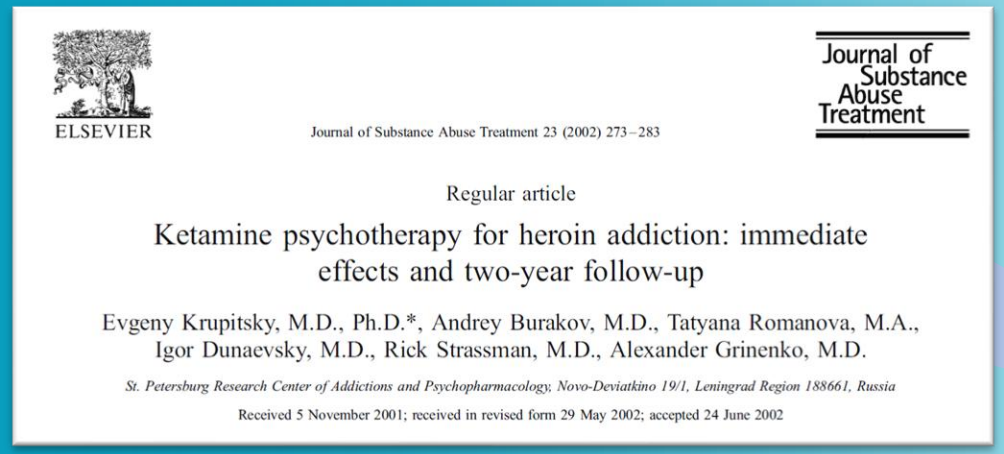


ELSEVIER

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-Deviatkino 19/1, Leningrad Region 188661, Russia

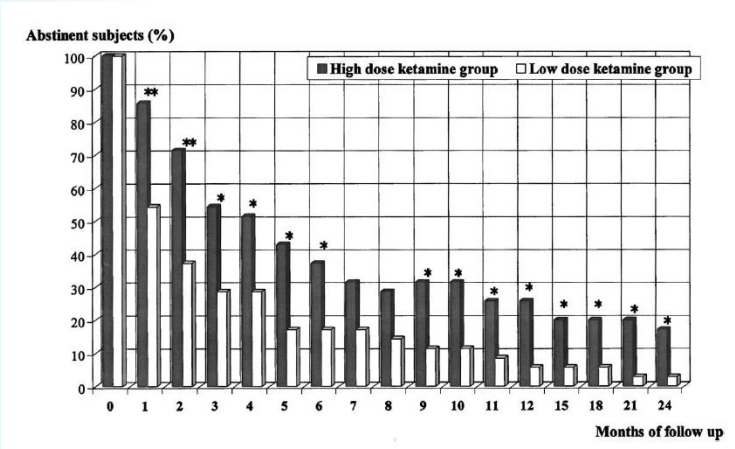
Received 5 November 2001; received in revised form 29 May 2002; accepted 24 June 2002

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

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?



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

Krupitsky et al JSAT 2002

Ketamine may be helpful for OUD

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

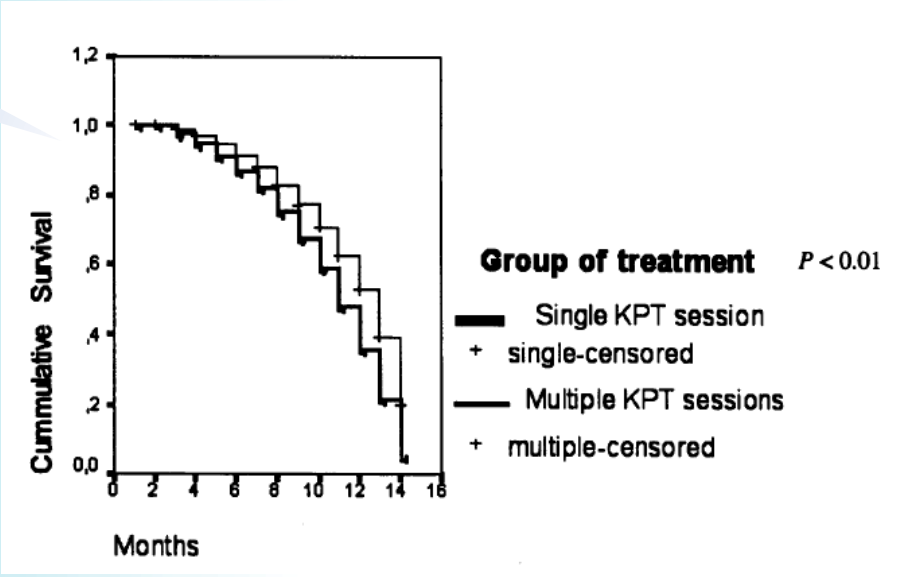
Evgeny M. Krupitsky, M.D., Ph.D.*; Andrei M. Burakov, M.D., Ph.D.**;
Igor V. Dunaevsky, M.D., Ph.D.***; Tatyana N. Romanova, M.S.****;
Tatyana Y. Slavina, M.D., Ph.D.***** & Alexander Y. Grinenko M.D., Ph.D.******

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

Krupitsky et al JSAT 2002

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

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

Patrick Köck [a,*], Katharina Froelich [a], Marc Walter [a], Undine Lang [a], Kenneth M. Dürsteler [a,b]

[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=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

Kock et al 2022 Journal of Substance Abuse Treatment

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**: **Two RCTs** 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**: **One pilot RCT** 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**: **Two pilot RCTs**, 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 arrythmias concerns remain
MDMA	Alcohol	**Poor**: One open-label study only

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

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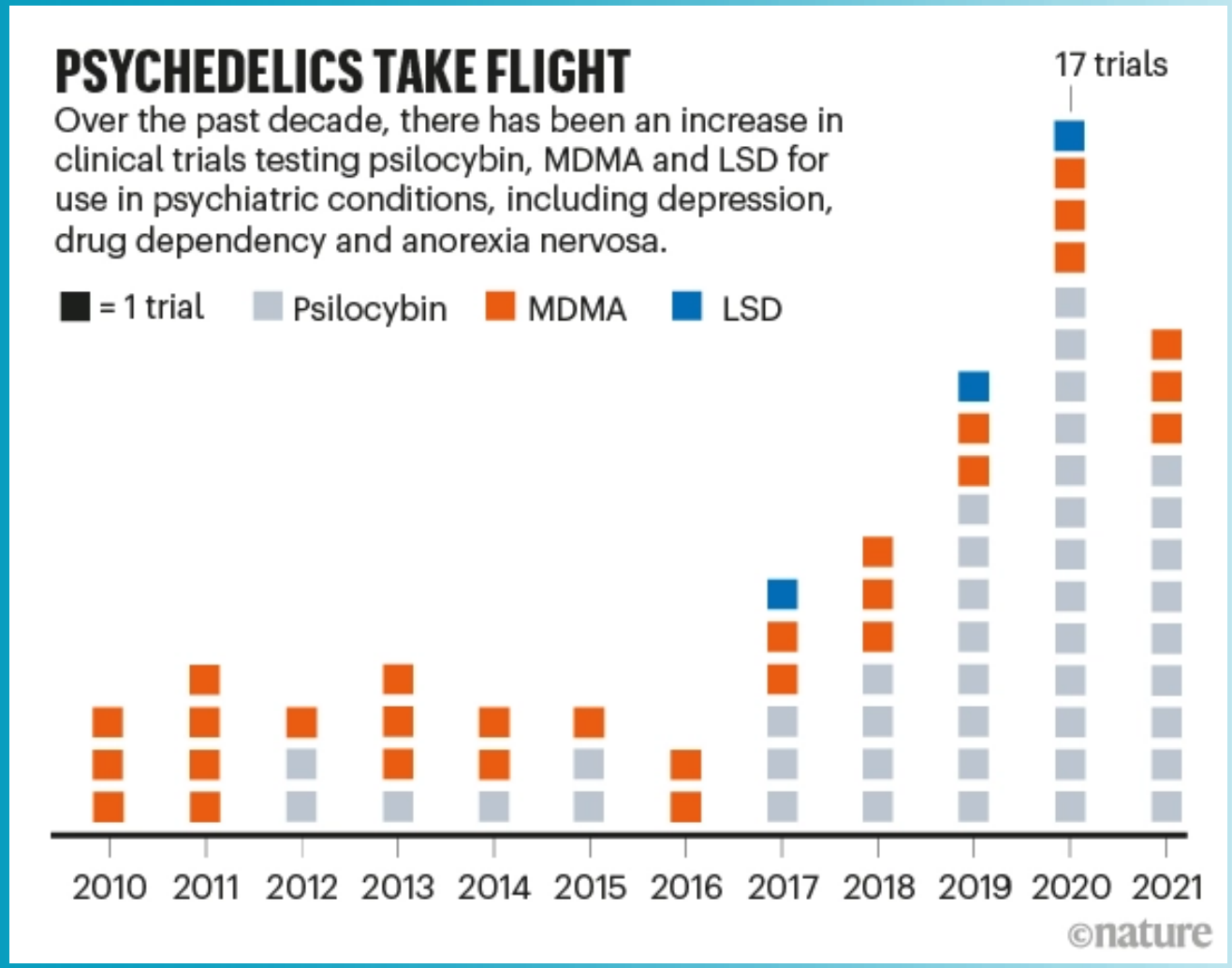

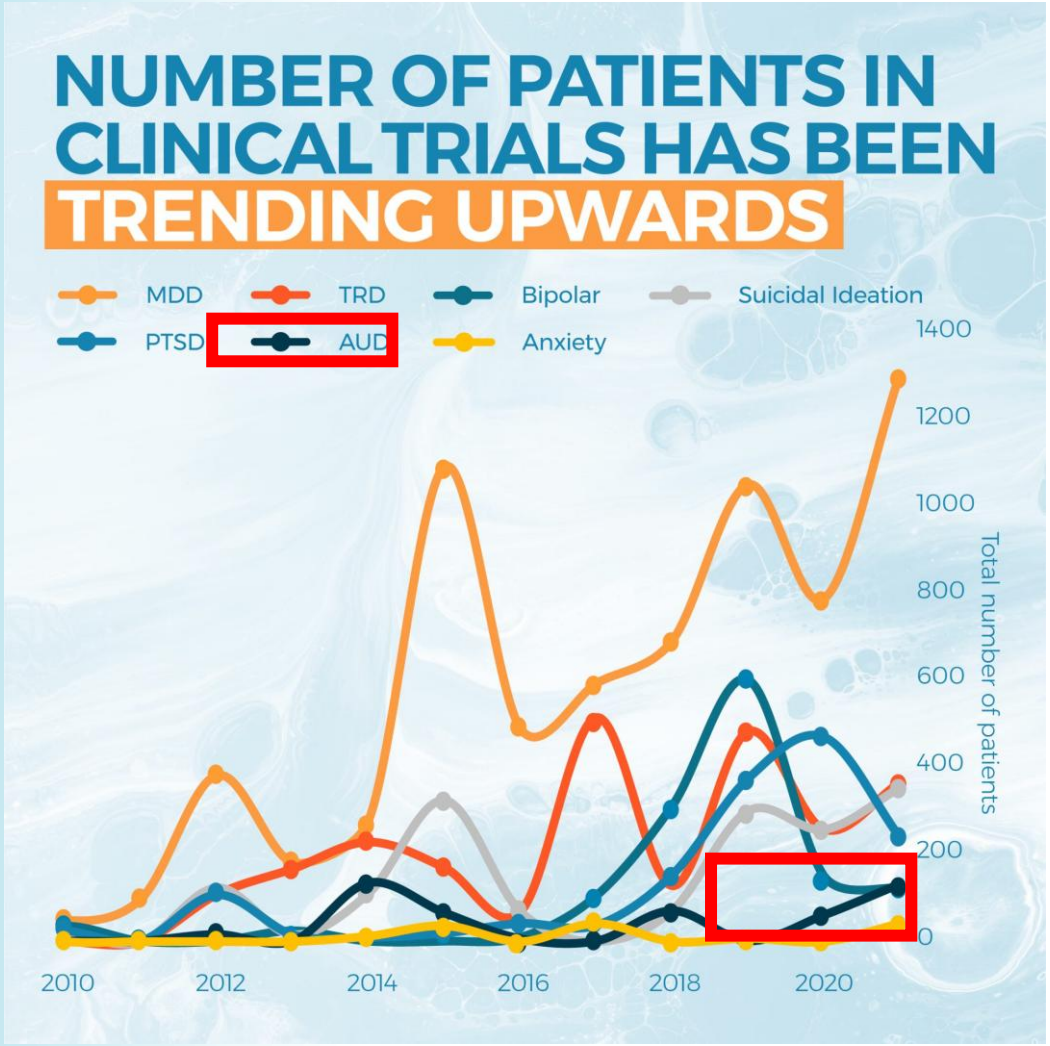

Psychedelic Drug Development Chart as of Q3 2025

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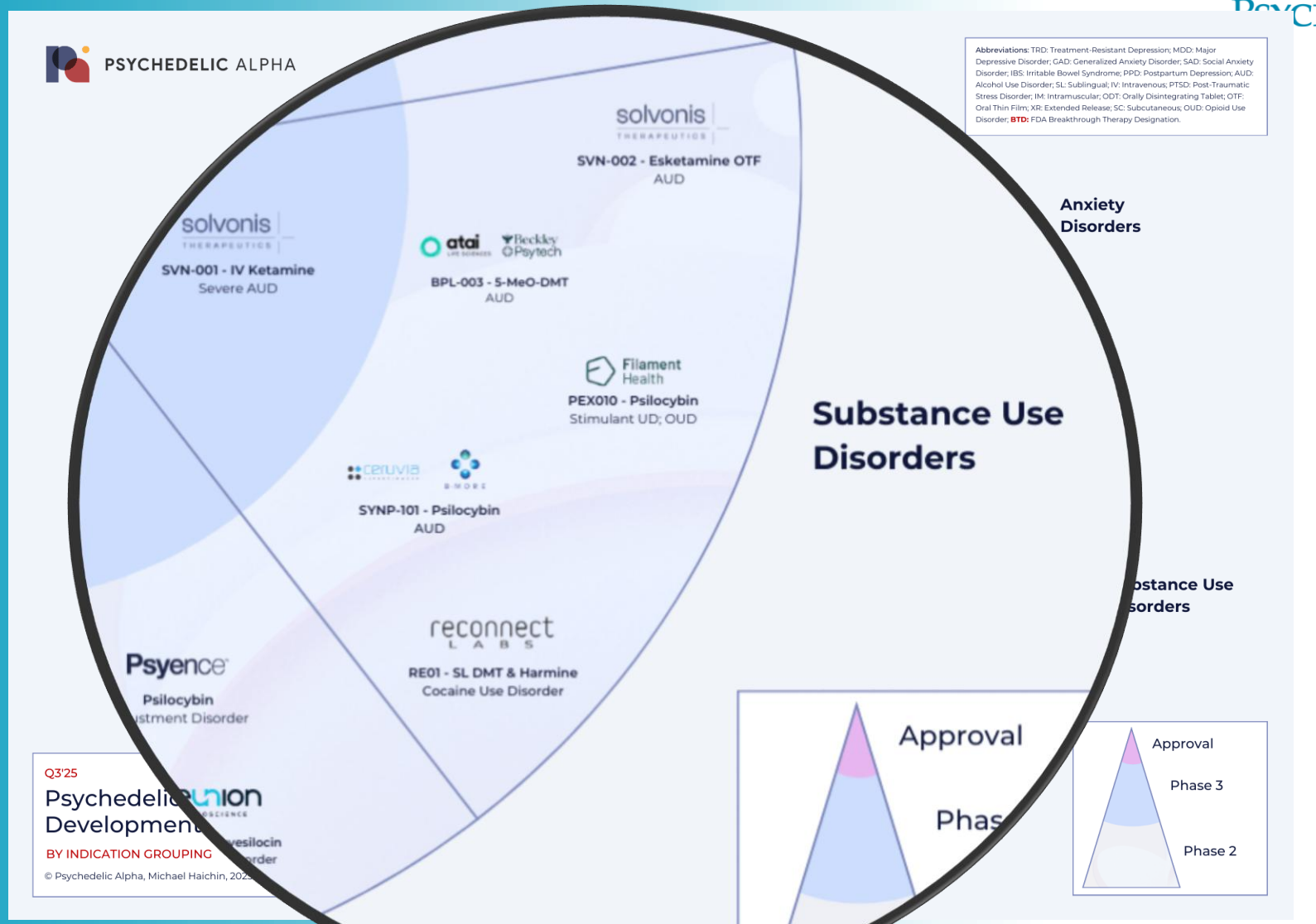

Source: https://psychedelicalpha.com/news/q325-psychedelic-drug-development-pipeline-bullseye-charts

Conclusions

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- 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
- Psychedelics can lead to significant harms including use disorder.
- Psychedelics are a focus of intensive research as novel therapeutics.
- Psilocybin and ketamine with the most promising early results but **efficacy is still not established!!**