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Psychedelics for Addictions

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Disclosures

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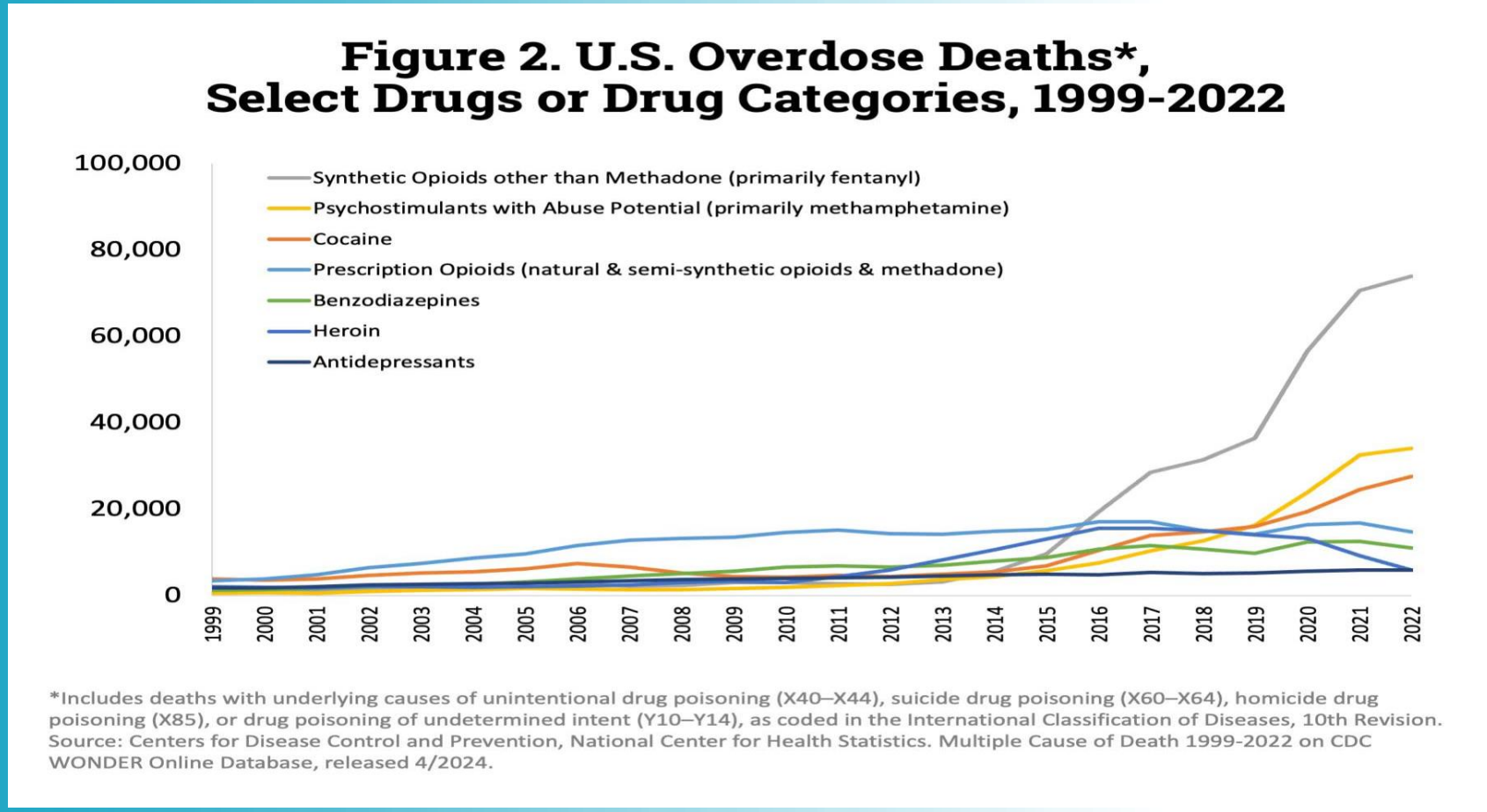
My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- I have received stock options in CB Therapeutics
- I have served as an advisor/consultant for CB Therapeutics, Cerebral, Compass Pathways, EBSCO Industries, Livanova, and Janssen Pharmaceuticals
- I have received research funding from Compass Pathways and MindMed

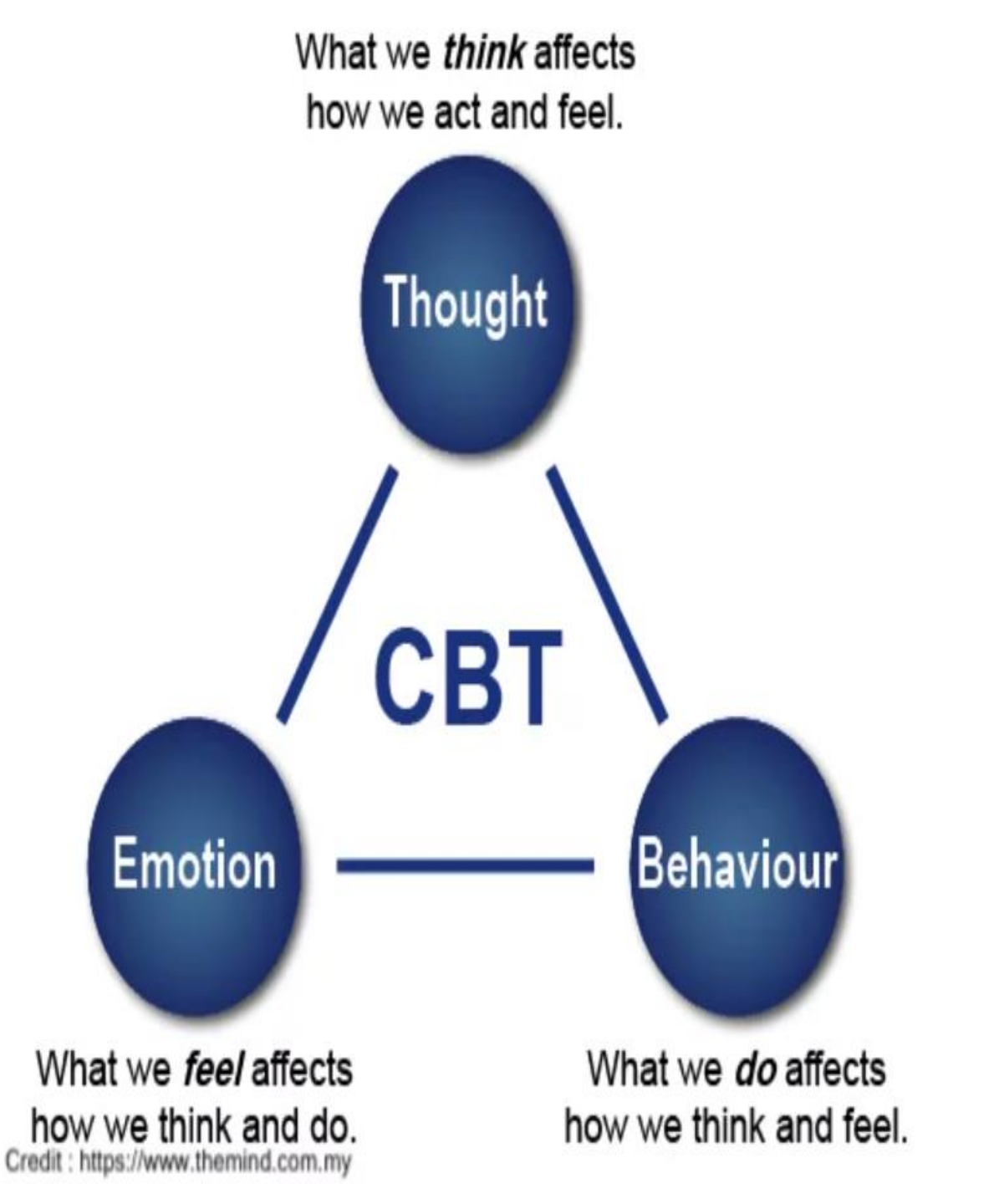
Outline

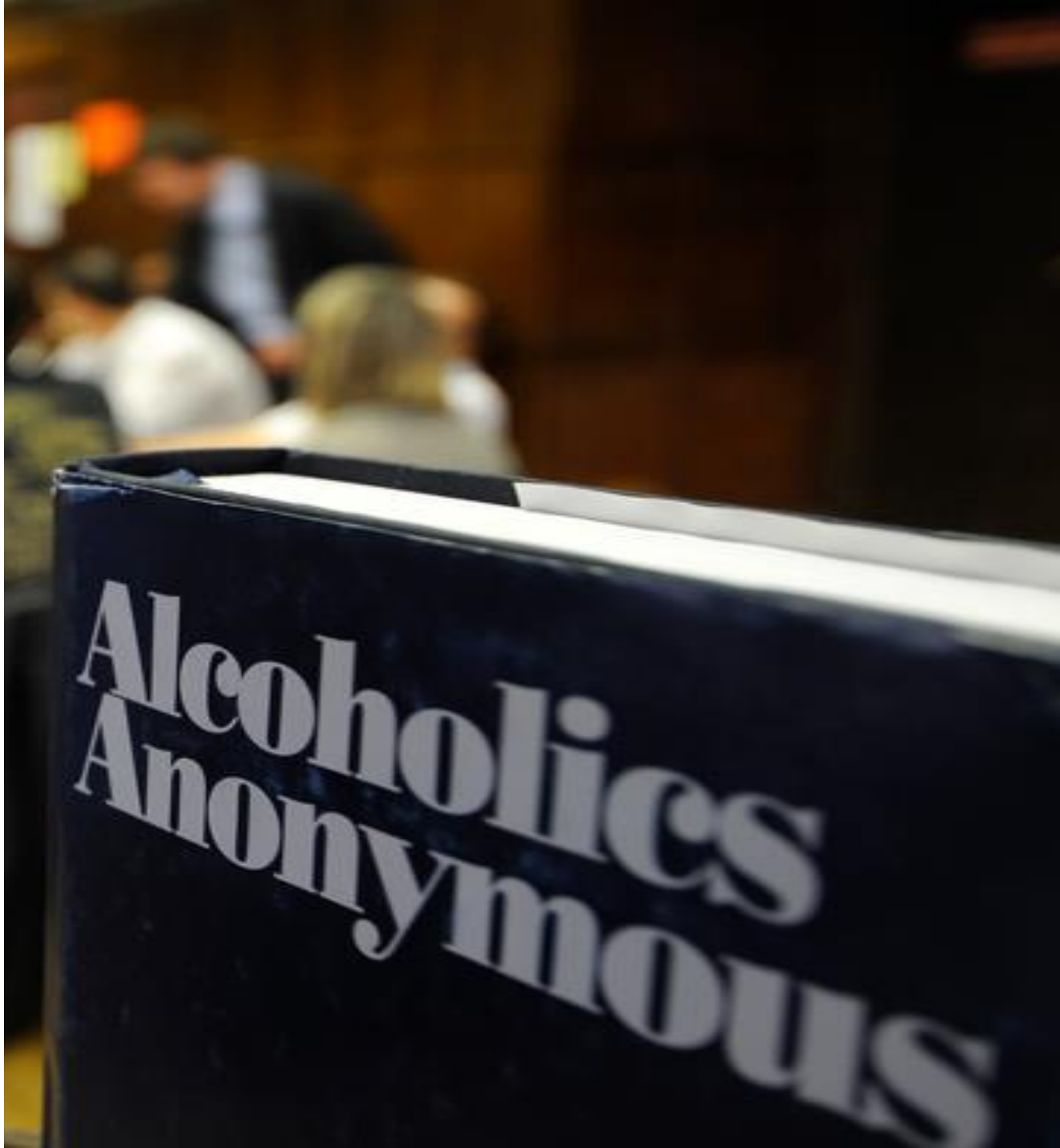
- Introduction
- Some history
- Addictive and anti-addictive potential of psychedelics
- Data from clinical studies
- Concluding remarks

Escalating overdose deaths



https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates


What we *think* affects how we act and feel.
Thought
CBT
Emotion
Behaviour
What we *feel* affects how we think and do.
What we *do* affects how we think and feel.
Credit : https://www.themind.com.my


Alcoholics Anonymous

Few pharmacological options

Psychedelic-assisted therapy?

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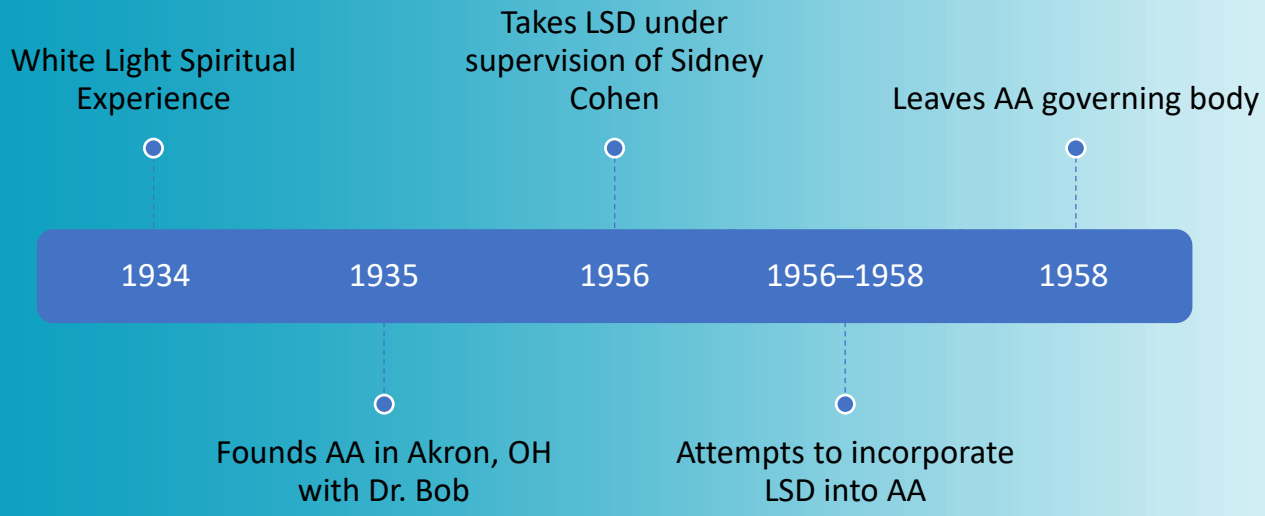
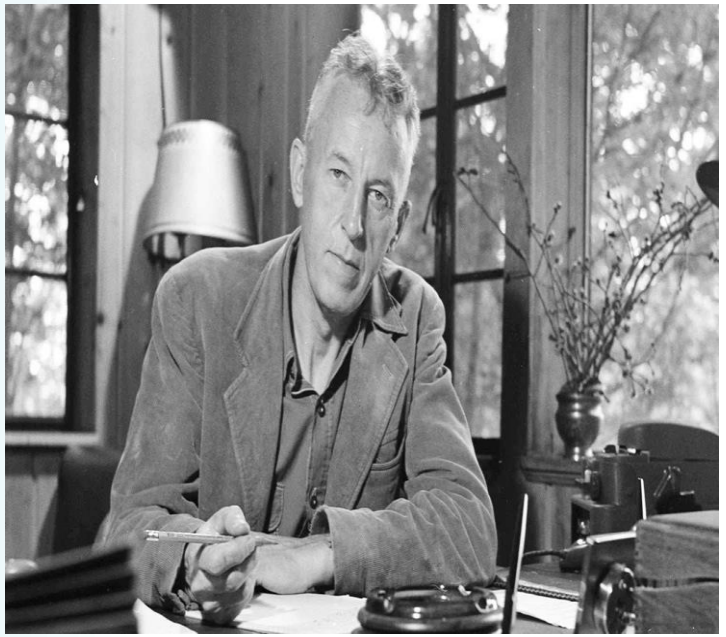
An intriguing chapter in psychedelic history

Bill W and LSD





LSD for Alcohol Use Disorder

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Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs[1,2] and Pål-Ørjan Johansen[1,2]

Psychopharm

Journal of Psychopharmacology
26(7) 994–1002

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jop.sagepub.com
SAGE

Abstract

Assessments of lysergic acid diethylamide (LSD) in the treatment of alcoholism have not been based on quantitative meta-analysis. Hence, we performed a meta-analysis of randomized controlled trials in order to evaluate the clinical efficacy of LSD in the treatment of alcoholism. Two reviewers independently extracted the data, pooling the effects using odds ratios (ORs) by a generic inverse variance, random effects model. We identified six eligible trials, including 536 participants. There was evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84; $p = 0.0003$). Between-trial heterogeneity for the treatment effects was negligible ($I^2 = 0\%$). Secondary outcomes, risk of bias and limitations are discussed. A single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.

Keywords

Alcoholism, alcohol-related disorders, hallucinogens, meta-analysis, psychedelics, substance-related disorders

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Addictive and anti-addictive potential of psychedelics

Hallucinogen use disorder (HUD)

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~5% of users will develop dependence

Past year and lifetime HUD prevalence: 0.05% and 0.60%

- Most prevalent among 18-20 yos (0.33% and 0.26%)

Of patients with lifetime HUD, prevalence of severities:

- Mild: 66.8%
- Moderate: 18.5%
- Severe: 14.6%

Bogenschutz & Ross, 2017; NSDUH, 2019; Shalit et al, 2019

HUD features and risk factors

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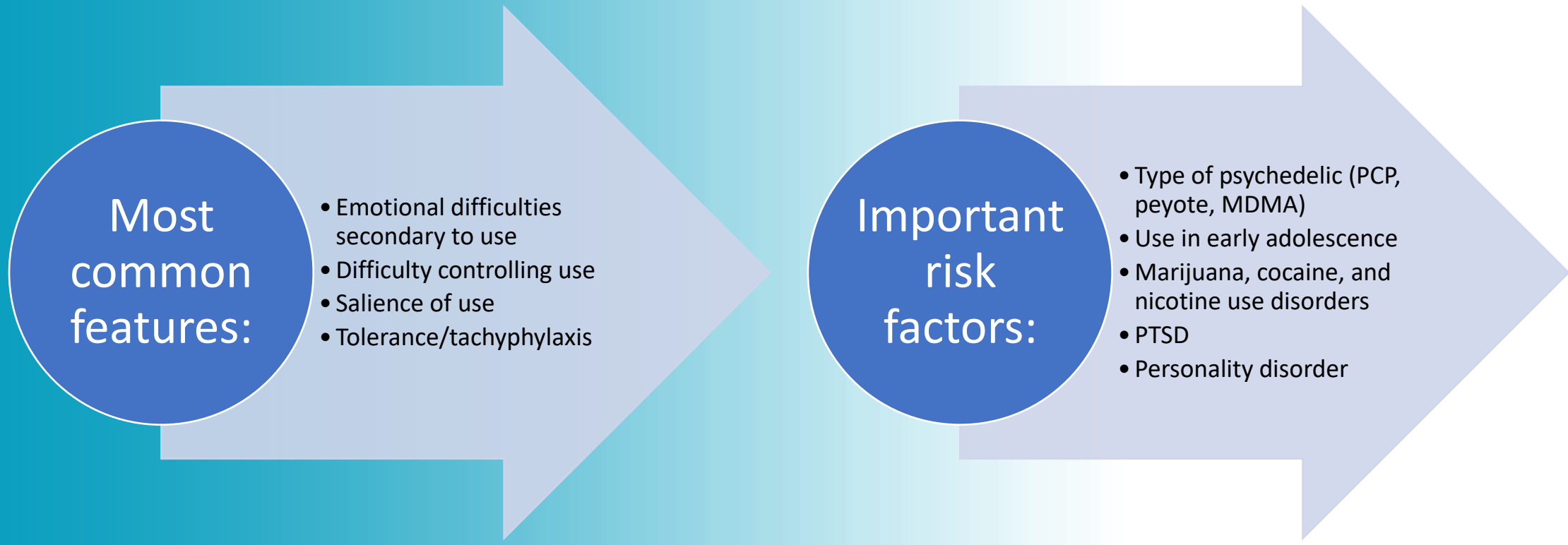

Stone et al, 2006; Shalit et al, 2019; Jones et al, 2023

Why aren't psychedelics more addictive?

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- Not reliably pleasurable
- Rapid tachyphylaxis
- Limited dopaminergic stimulation
- 5-HT2C receptor agonism- modulates dopamine activity in VTA-Nac reward pathway

Canal and Murnane, 2017

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Clinical study data on psychedelic treatments for SUDs

Alcohol use disorder

MDMA Therapy for AUD

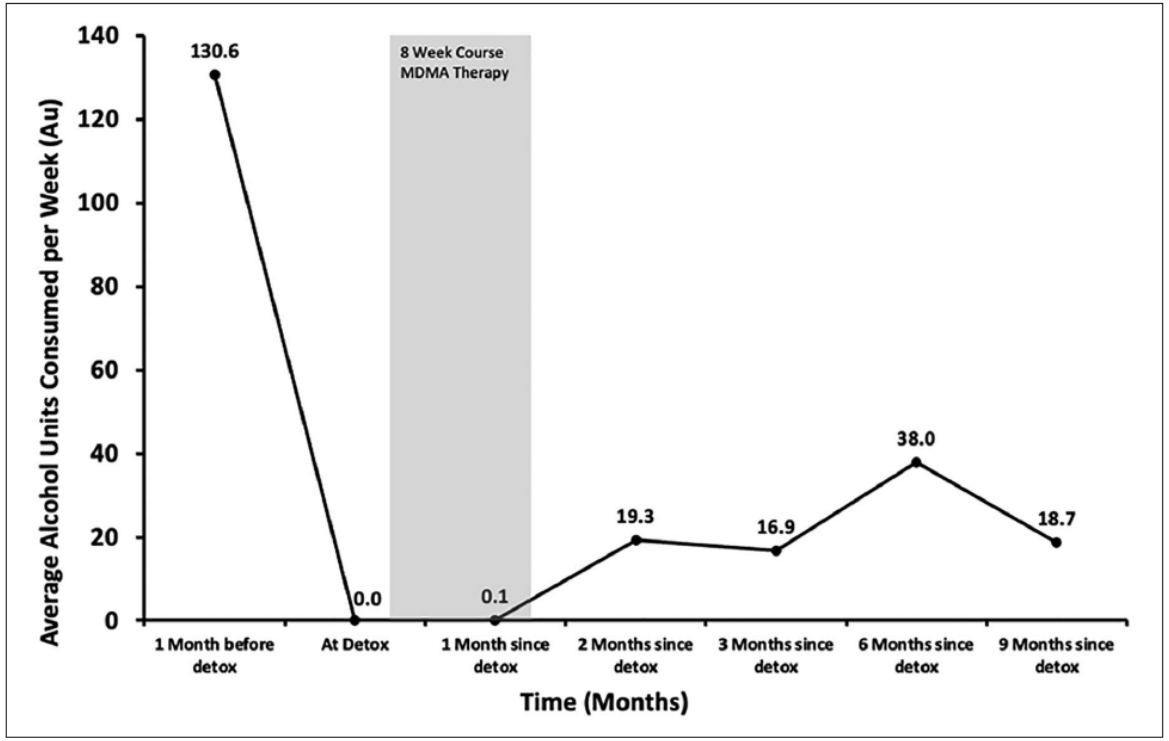

Figure 3. Timeline follow back (TLFB) assesses drinking behaviour prior to and following the study. Data are collected daily by self-reporting and reviewed at one month prior to detox, immediately following detox and at one, three, six and nine months follow-up. A full data set was not

Sessa et al, 2021

> JAMA Psychiatry. 2022 Aug 24. doi: 10.1001/jamapsychiatry.2022.2096. Online ahead of print.

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

- Inclusion criteria:
  - Aged 25 to 65 years
  - Diagnosis of alcohol dependence ascertained using the Structured Clinical Interview for *DSM-IV*
  - At least 4 heavy drinking days during the 30 days prior to screening (defined as ≥ 5 drinks in a day for men and ≥ 4 drinks in a day for a women)
- Exclusion criteria:
  - Major psychiatric and drug use disorders
  - Any hallucinogen use in the past year or more than 25 lifetime uses
  - Medical conditions that contraindicated either study medication
  - Use of exclusionary medications
  - Current treatment for AUD

Interventional design

95 participants randomized to 2 therapy sessions with either psilocybin or diphenhydramine at weeks 4 and 8

Psilocybin 25 mg/70 kg (1st session) and 25-40 mg/70 kg (2nd session)	Diphenhydramine, 50 mg (1st session) and 50-100 mg (2nd session)

All participants who completed double blind observation period (weeks 5-36) and still meeting safety criteria were offered open label trial at week 38

Therapeutic programming

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Participants received 12 non-dosing therapy sessions

4 prior to first dosing session	4 prior to second dosing session	4 in month after second dosing session

Therapeutic approaches included motivational interviewing and CBT

Primary outcome

- Percentage of heavy drinking days
  - Assessed using a timeline followback interview
  - Contrasted between groups over 32-week period following first administration of study medication
  - Analyzed using multivariate repeated-measures analysis of variance

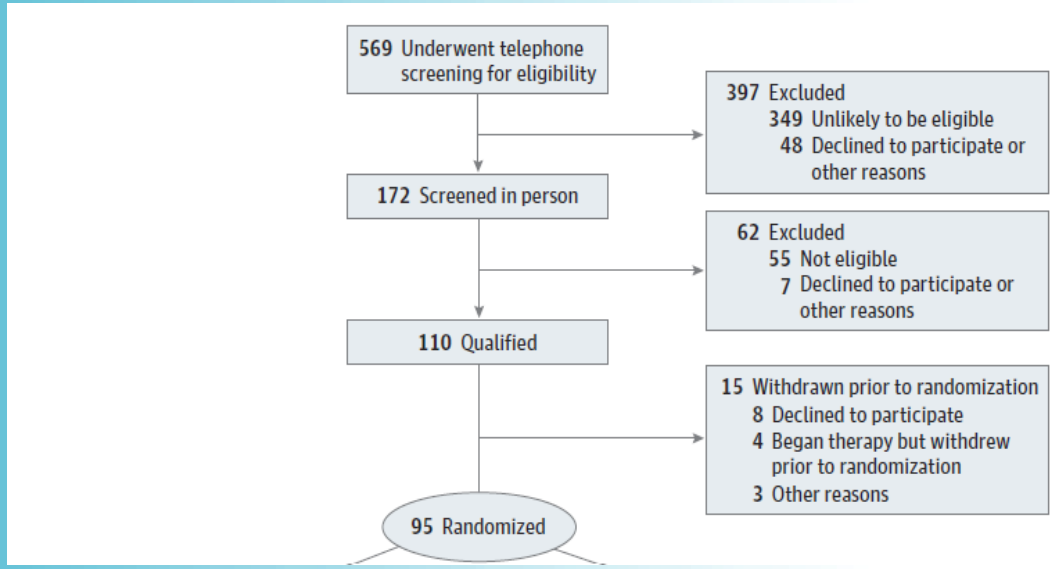
Participant demographics

Mean age: 46 ± 12 years

Gender: 44.2% female

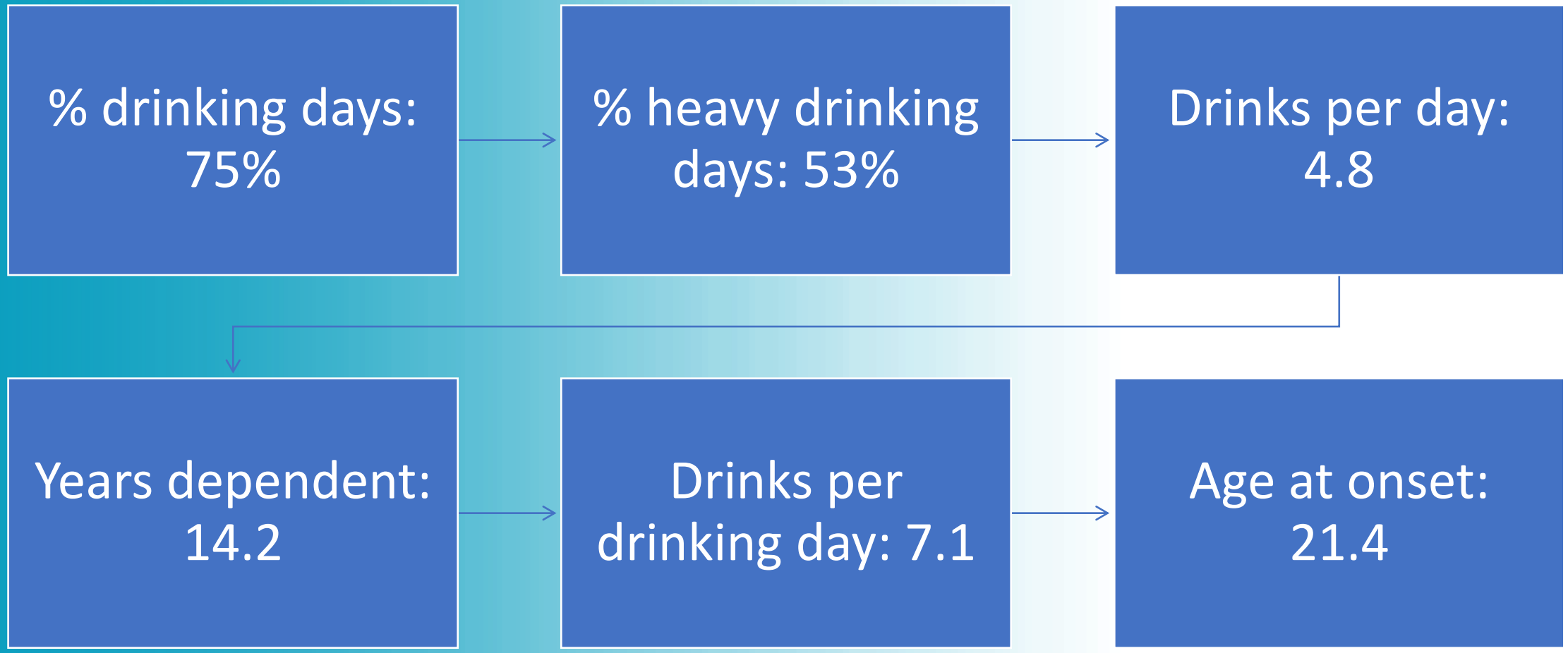
Race/ethnicity: 78.9% non-Hispanic White

93 received at least 1 dose of study medication

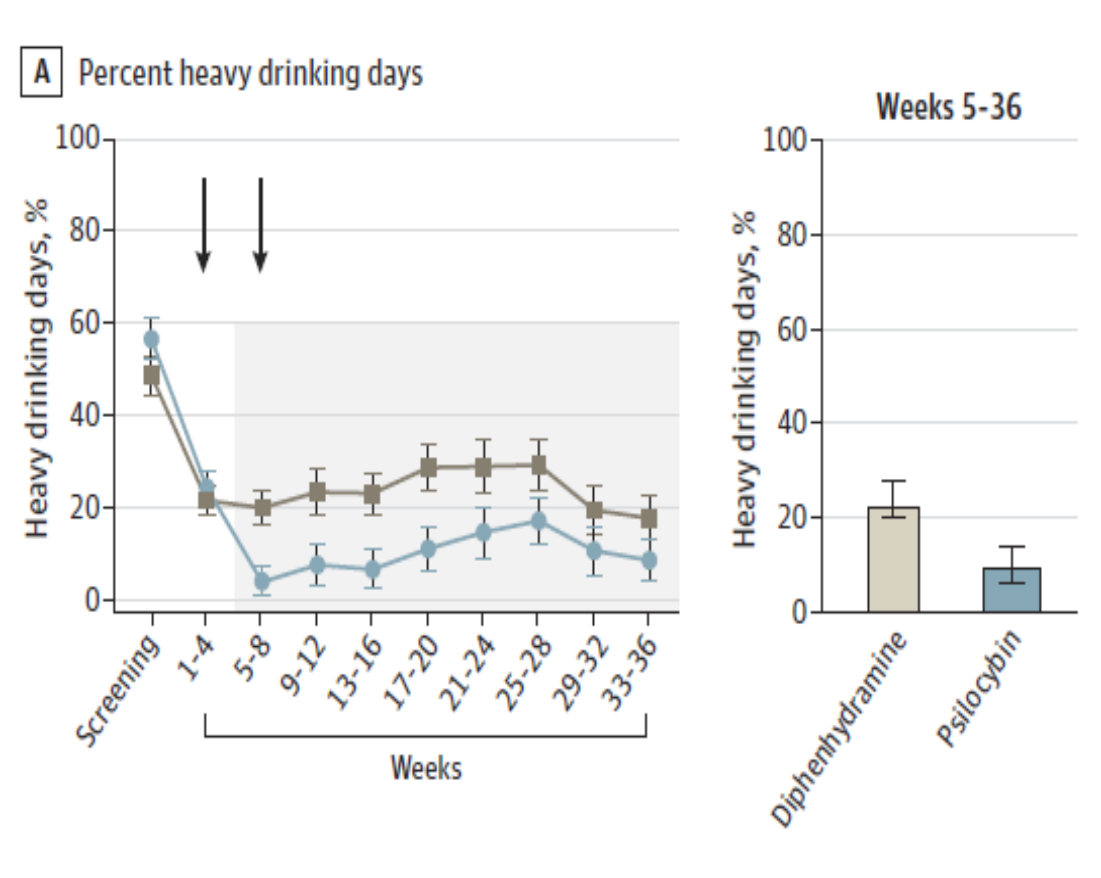


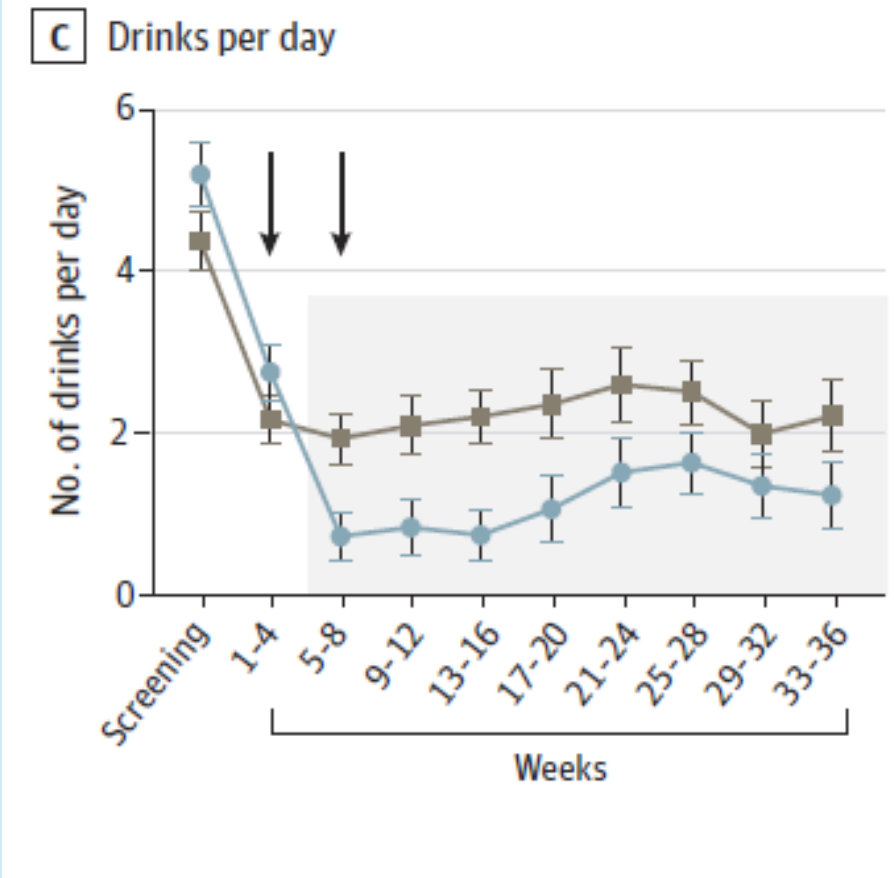
- 52% randomized to psilocybin
- 48% randomized to diphenhydramine

Baseline AUD severity



Outcomes


A Percent heavy drinking days
Heavy drinking days, %
100
80
60
40
20
0
Screening
1-4
5-8
9-12
13-16
17-20
21-24
25-28
29-32
33-36
Weeks
Weeks 5-36
Heavy drinking days, %
Diphenhydramine
Psilocybin


C Drinks per day
No. of drinks per day
6
4
2
0
Screening
1-4
5-8
9-12
13-16
17-20
21-24
25-28
29-32
33-36
Weeks

Cocaine use disorder

Psilocybin therapy for CUD

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Brief Summary:

The primary purpose of this study is to evaluate the feasibility and estimate the efficacy of psilocybin-facilitated treatment for cocaine use. We also will monitor the impact of psilocybin-facilitated treatment on the use of other drugs and outcomes relevant to cocaine involvement (e.g., criminal involvement).

MRI assessment is a unique aspect of this study. As a potential biological mechanism of psilocybin's effect includes changes in default mode network functional connectivity (Carhart-Harris et al., 2012), we will determine if psilocybin's therapeutic effects are mediated by such changes. Moreover, as Glx (a brain metabolite that reflects glutamate) abnormalities have been shown to play a role in cocaine addiction, we will determine if psilocybin impacts Glx in the anterior cingulate cortex and hippocampus.

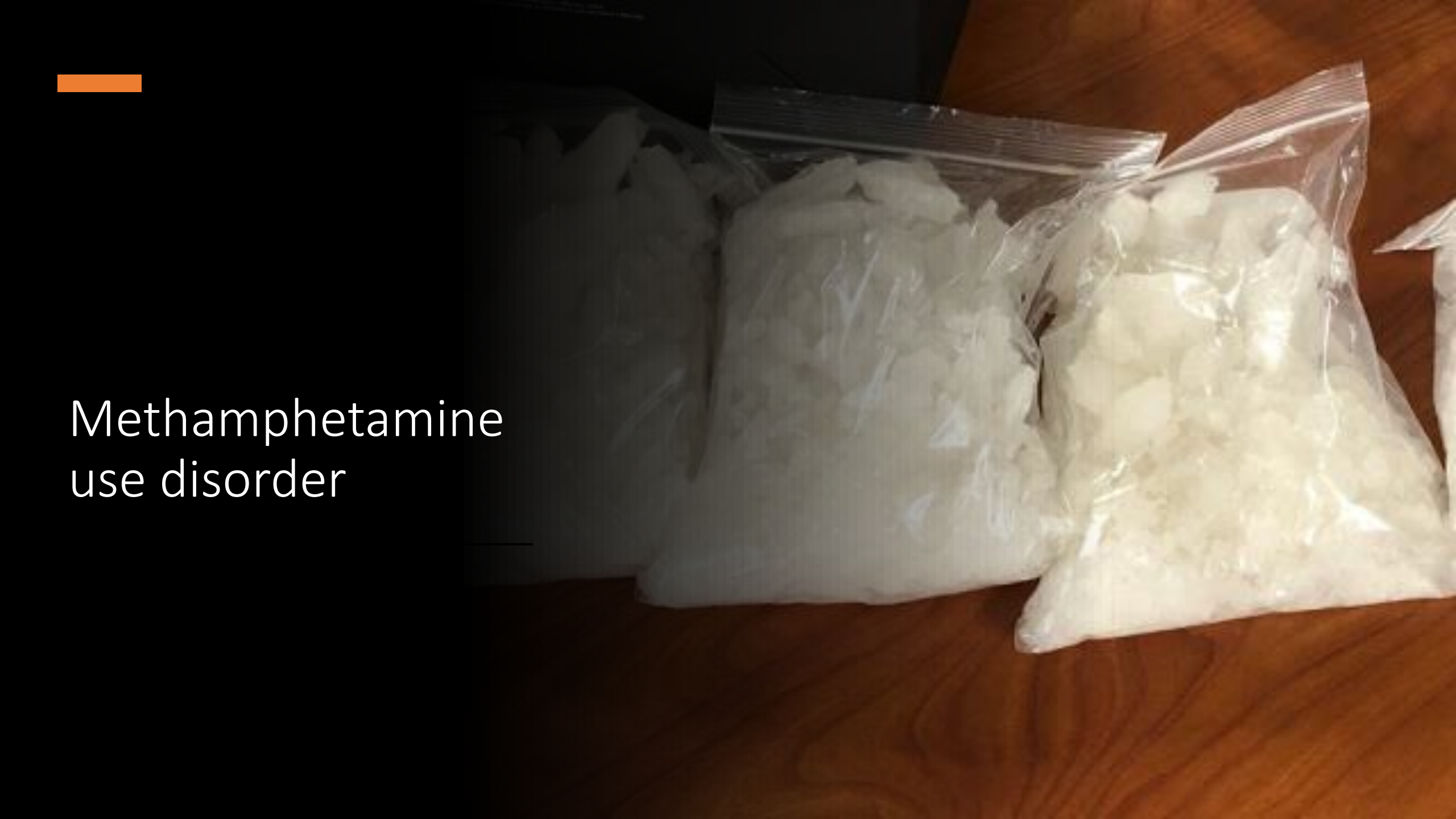
Condition or disease	Intervention/treatment	Phase
Cocaine-Related Disorders	Drug: Psilocybin Drug: Diphenhydramine	Phase 2

▸ Show detailed description

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	40 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Psilocybin-facilitated Treatment for Cocaine Use: A Pilot Study
Study Start Date :	May 2015
Estimated Primary Completion Date :	July 2023
Estimated Study Completion Date :	July 2023

Methamphetamine use disorder



Methamphetamine use disorder

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Opioid use disorder

Clinical Trial > Arch Gen Psychiatry. 1973 Jun;28(6):808-14.
doi: 10.1001/archpsyc.1973.01750360040005.

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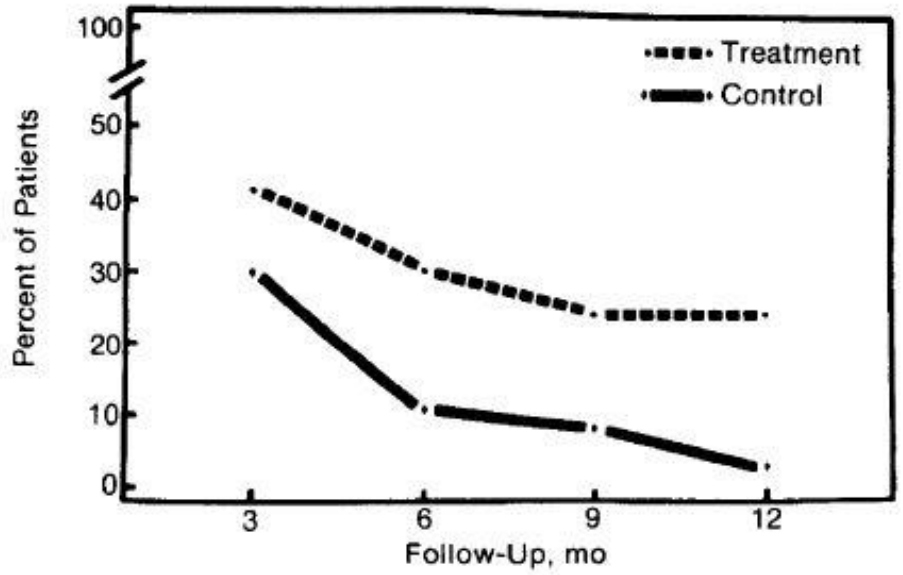
Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study

- Setting: Aftercare clinic for paroled people with OUD
- Design: 78 participants randomized to either outpatient group psychotherapy (control) or 4-6 week admission to halfway house with 1 LSD (300-450 µg) therapy session

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



Observational Study > Am J Drug Alcohol Abuse. 2018;44(1):37-46.
doi: 10.1080/00952990.2017.1310218. Epub 2017 Apr 12.

Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study

- 14 patients seeking treatment from ibogaine providers in New Zealand followed for 1 year
- Significant reduction in SOWS scores post acute treatment
- Abstinence rates post-treatment:
  - 57% at 3 months
  - 50% at 6 months
  - 55% at 12 months (n=11)

Noller et al, 2018

Limitations of ibogaine

- QTc prolongation
- 32 reported deaths from torsade de pointes (TdP)/ventricular arrythmia
  - Appears safe in research settings, though screening necessary
- 18-MC and noribogaine being considered as alternatives

Aćimović et al, 2021, Luz & Mash, 2021

Clinical trials of psychedelics for OUD

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- Psilocybin
  - Psilocybin for Opioid Use Disorder in Patients on Methadone Maintenance With Ongoing Opioid Use
  - Adjunctive Effects of Psilocybin and a Formulation of Buprenorphine
  - Standardized Natural Psilocybin-assisted Psychotherapy for Tapering of Opioid Medication
- Ibogaine
  - Preliminary Efficacy and Safety of Ibogaine in the Treatment of Methadone Detoxification
  - A Study of Oral Ibogaine in Opioid Withdrawal

Tobacco use disorder

Clinical Trial > J Psychopharmacol. 2014 Nov;28(11):983-92. doi: 10.1177/0269881114548296. Epub 2014 Sep 11.

Pilot study of the 5–HT2AR agonist psilocybin in the treatment of tobacco addiction

- Open label
- Psilocybin administered within 15-week smoking cessation program
- Primary outcome- biologically confirmed abstinence
- Target quit date set for 1st psilocybin session (week 5)
- High dose psilocybin then administered at week 7 and 13 (optional)
- Guided imagery during prep meetings and 1st psilocybin session
- Study staff met w/ participants weekly

Johnson et al, 2014

Pilot study of the psilocybin in the treatment of tobacco addiction

- Exclusion criteria
  - Family or personal history of bipolar disorder, psychotic disorders, and other substance use disorders within past 5 years
- Participants
  - 15 participants with nicotine dependence
  - 67% male
  - Mean age: 51 years
  - Mean smoking duration: 31 years
  - 6 previous quit attempts

Results

- 80% reported seven-day abstinence at 6 months
  - 92% had biologically verified abstinence
- 67% abstinent at 12 months
- 60% abstinent at 30 months

Johnson et al, 2014; 2017

Some hypothesized therapeutic mechanisms in SUDS

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- 5-HT2C receptor agonism
- Increased cognitive flexibility
- Enhancement of neuroplasticity/neurogenesis
  - Addiction associated with reduced neuroplasticity and BDNF levels
  - Psychedelics may temporarily increase BDNF levels
- Disruption of functional neural networks
  - Altered connectivity, including hyperconnectivity, has been demonstrated for some neural networks in SUDs.
  - Psychedelics may temporarily disrupt Default Mode Network, decreasing maladaptive hyperconnectivity.
  - Psychedelics can also modulate connectivity between thalamus and cortex, which is often dysregulated in SUDs.

Ivan Ezquerra-Romano et al, 2018; Corominas-Roso et al, 2013; Huang et al, 2008; Sonmez et al, 2016; Tolomeo et al, 2022 Shafiee et al, 2024

Questions to ponder

- How essential is psychotherapy? Does the type of psychotherapy matter?
- Which patients with SUDs are psychedelic treatments inappropriate for?
- Can we treat SUDs using psychedelics in group settings?
- What points in SUDs treatment spectrum would be best for incorporating psychedelics?
- Will psychedelics be accepted into current SUDs treatment paradigm?

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Thank you

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References

1. Aćimović T, Atanasijević T, Denić K, Lukić V, Popović V, Bogdanović M. Death due to consumption of ibogaine: case report. Forensic Sci Med Pathol. 2021 Mar;17(1):126-129. doi: 10.1007/s12024-020-00342-0. Epub 2021 Jan 12. PMID: 33433774.
2. Barnett BS, Beaussant Y, King F 4th, Doblin R. Psychedelic Knowledge and Opinions in Psychiatrists at Two Professional Conferences: An Exploratory Survey. J Psychoactive Drugs. 2021 Aug 19:1-9. doi: 10.1080/02791072.2021.1957183. Epub ahead of print. PMID: 34409921.
3. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015 Mar;29(3):289-99. doi: 10.1177/0269881114565144. Epub 2015 Jan 13. PMID: 25586396.
4. Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, Mennenga SE, O'Donnell K, Owens LT, Podrebarac S, Rotrosen J, Tonigan JS, Worth L. 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. JAMA Psychiatry. 2022 Aug 24. doi: 10.1001/jamapsychiatry.2022.2096. Epub ahead of print. PMID: 36001306.
5. Bogenschutz MP, Ross S. Hallucinogen-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 10th ed. Philadelphia, PA: Wolters Kluwer; 2017: 1312-1327.
6. Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev. 2014;7(3):157-164. doi:10.2174/1874473708666150107121331
7. Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, Johnson MW. Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol. 2019 Sep;33(9):1088-1101. doi: 10.1177/0269881119845793. Epub 2019 May 14. PMID: 31084460.
8. Jones G, Herrmann F, Wang E. Associations between individual hallucinogens and hallucinogen misuse among U.S. Adults who recently initiated hallucinogen use. Addict Behav Rep. 2023 Aug 12;18:100513. doi: 10.1016/j.abrep.2023.100513. PMID: 37649653; PMCID: PMC10462802.
9. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol*. 2014;28(11):983-992. doi:10.1177/0269881114548296
10. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017 Jan;43(1):55-60. doi: 10.3109/00952990.2016.1170135. Epub 2016 Jul 21. Erratum in: Am J Drug Alcohol Abuse. 2017 Jan;43(1):127. PMID: 27441452; PMCID: PMC5641975.
11. Johnson MW, Garcia-Romeu A, Johnson PS, Griffiths RR. An online survey of tobacco smoking cessation associated with naturalistic psychedelic use. J Psychopharmacol. 2017 Jul;31(7):841-850. doi: 10.1177/0269881116684335. Epub 2017 Jan 18. PMID: 28095732; PMCID: PMC6753943.

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References

1. Luz M, Mash DC. Evaluating the toxicity and therapeutic potential of ibogaine in the treatment of chronic opioid abuse. Expert Opin Drug Metab Toxicol. 2021 Sep;17(9):1019-1022. doi: 10.1080/17425255.2021.1944099. Epub 2021 Jun 24. PMID: 34139922.
2. Noller GE, Frampton CM, Yazar-Klosinski B. Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. Am J Drug Alcohol Abuse. 2018;44(1):37-46. doi: 10.1080/00952990.2017.1310218. Epub 2017 Apr 12. PMID: 28402682.
3. Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW. Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. J Psychopharmacol. 2018 Jul;32(7):756-769. doi: 10.1177/0269881118780612. Epub 2018 Jun 25. PMID: 29938565.
4. Oesterle TS, Thusius NJ, Rummans TA, Gold MS. Medication-Assisted Treatment for Opioid-Use Disorder. Mayo Clin Proc. 2019 Oct;94(10):2072-2086. doi: 10.1016/j.mayocp.2019.03.029. Epub 2019 Sep 19. PMID: 31543255.
5. Pisano VD, Putnam NP, Kramer HM, Franciotti KJ, Halpern JH, Holden SC. The association of psychedelic use and opioid use disorders among illicit users in the United States. J Psychopharmacol. 2017 May;31(5):606-613. doi: 10.1177/0269881117691453. Epub 2017 Feb 14. PMID: 28196428.
6. Sessa B, Higbed L, O'Brien S, Durant C, Sakal C, Titheradge D, Williams TM, Rose-Morris A, Brew-Girard E, Burrows S, Wiseman C, Wilson S, Rickard J, Nutt DJ. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. J Psychopharmacol. 2021 Apr;35(4):375-383. doi: 10.1177/0269881121991792. Epub 2021 Feb 18. PMID: 33601929.
7. Shafiee A, Arabzadeh Bahri R, Rafiei MA, Esmaeilpur Abianeh F, Razmara P, Jafarabady K, Amini MJ. The effect of psychedelics on the level of brain-derived neurotrophic factor: A systematic review and meta-analysis. J Psychopharmacol. 2024 May;38(5):425-431. doi: 10.1177/02698811241234247. Epub 2024 Feb 22. PMID: 38385351.
8. Shalit N, Rehm J, Lev-Ran S. Epidemiology of hallucinogen use in the U.S. results from the National epidemiologic survey on alcohol and related conditions III. Addict Behav. 2019 Feb;89:35-43. doi: 10.1016/j.addbeh.2018.09.020. Epub 2018 Sep 16. PMID: 30245407
9. SMITH CM. A new adjunct to the treatment of alcoholism: the hallucinogenic drugs. Q J Stud Alcohol. 1958 Sep;19(3):406-17. PMID: 13579169.
10. Stone AL, Storr CL, Anthony JC. Evidence for a hallucinogen dependence syndrome developing soon after onset of hallucinogen use during adolescence. Int J Methods Psychiatr Res. 2006;15(3):116-30. doi: 10.1002/mpr.188. PMID: 17019896; PMCID: PMC6878397.