Psychedelics for Addictions

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Disclosures

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

– I have received stock options from CB Therapeutics for advisory board service
– I own personal stock in Compass Pathways
– I have received monetary compensation for work as a topic editor on substance use disorders for DynaMed Plus (EBSCO Industries, Inc)
Outline

• Introduction
• Some history
• Addictive and anti-addictive potential of psychedelics
• Contemporary data
  – Surveys assessing naturalistic psychedelic use and possible effects on substance use
  – Clinical trials assessing psychedelic treatments for SUDs
• Concluding remarks
Overdose deaths

U.S. Drug Overdose Deaths Rose Nearly 30% in 2020

93,331 people died from drug overdoses in the U.S. in 2020

Source: Centers for Disease Control and Prevention
Bill W
Bill W and LSD

• 1934-Experiences White Light Spiritual Experience via belladonna treatment
• 1935- Founds AA in Akron, OH w/ Dr. Bob
• 1956- Under supervision of Dr. Sidney Cohen, takes LSD at Los Angeles VA
• 1956-1958- Attempts to incorporate LSD into AA
• 1958-Leaves AA governing body
Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs1,2 and Pål-Ørjan Johansen1,2

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 (I² = 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
Abuse of psilocybin mushrooms could also lead to poisoning if one of the many varieties of poisonous mushrooms is incorrectly identified as a psilocybin mushroom.

**Which drugs cause similar effects?**
Psilocybin effects are similar to other hallucinogens, such as mescaline and peyote.

**What is its legal status in the United States?**
Psilocybin is a Schedule I substance under the Controlled Substances Act, meaning that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.
Psychedelics’ addictive potential

Psychiatrists’ concerns about addictive potential predict opposition to medical legalization

Barnett et al, 2021
Hallucinogen use disorder (HUD)

- ~5% of people with h/o hallucinogen use will develop dependence
- 2019- past year rates of hallucinogen abuse and dependence of 0.08% and 0.05%
  - Most prevalent among 18-20 yos (0.33% and 0.26%)
- Of patients with HUD, past year/lifetime prevalence of severities are:
  - Mild: 79.9% and 66.8%
  - Moderate: 13.1% and 18.5%
  - Severe: 7.0% and 14.6%

Bogenschutz & Ross, 2017; NSDUH, 2019; Shalit et al, 2019
HUD risk factors and features

• Most common features:
  – Emotional difficulties secondary to use
  – Difficulty controlling use
  – Salience of use
  – Tolerance

• Important risk factors:
  – Type of psychedelic (MDMA, mescaline)
  – Use in early adolescence
  – Marijuana, cocaine, and nicotine use disorders
  – PTSD
  – Personality disorder

(Stone et al, 2006 and Shalit et al, 2019)
Why aren’t psychedelics more addictive?

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

Canal and Murnane, 2017
What do surveys about psychedelic use show?
Reduction/cessation in alcohol use following psychedelic experience

- 343 respondents w/ seven years problematic alcohol use pre-psychedelic
  - 72% met retrospective criteria for severe AUD
  - 83% no longer met AUD criteria post-psychedelic
  - Greater use reduction associated with:
    - Higher dose
    - Higher insightfulness
    - Mystical-type effects
    - Higher personal meaning assigned to experience

Garcia-Romeu et al 2019
Reduction/cessation in tobacco use following psychedelic experience

- Survey of 358 respondents who smoked 14 cigarettes/day for 8 years on avg
  - 5 quit attempts pre-psychedelic
- 38% reported continuous cessation post-use
- 28% reported persisting reduction
- 34% reported temp reduction w/ mode time to relapse of 3-6 mos
- Relapsers had psychedelic experiences lower in personal meaning/spiritual significance

Johnson et al, 2017
What do contemporary trials show?
Alcohol Use Disorder
Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

• Large correlations between acute effect intensity/mystical experience and:
  – Change in drinking behavior
  – Changes in craving and self-efficacy in some participants
A double blind trial of psilocybin-assisted treatment of alcohol dependence

Study Design

- **Study Type**: Interventional (Clinical Trial)
- **Actual Enrollment**: 135 participants
- **Allocation**: Randomized
- **Intervention Model**: Parallel Assignment
- **Masking**: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
- **Primary Purpose**: Treatment
- **Official Title**: A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence
- **Study Start Date**: June 2014
- **Estimated Primary Completion Date**: July 2021
- **Estimated Study Completion Date**: July 2021
Psilocybin and LSD have no long-lasting effects in an animal model of alcohol relapse

Marcus W. Meinhardt, Cansu Güngör, Ivan Skorodumov, Lea J. Mertens and Rainer Spanagel

For most psychiatric disorders, including alcohol use disorder (AUD), approved pharmacological treatments are limited in their effectiveness, and new drugs that can easily be translated into the clinic are needed. Currently, great hope lies in the potential of psychedelics to effectively treat AUD. The primary hypothesis is that a single session of psychedelic-guided psychotherapy can restore normal brain function in AUD individuals and thereby reduce the risk of relapse in the long run. Here we applied three different treatment schedules with psilocybin/LSD in order to investigate relapse-like drinking in the alcohol deprivation effect (ADE) model. In contrast to the primary hypothesis, psychedelics had no long-lasting effects on the ADE in male and female rats, neither when administered in a high dosage regime that is comparable to the one used in clinical studies, nor in a chronic microdosing scheme. Only sub-chronic treatment with psilocybin produced a short-lasting anti-relapse effect. However, it is not a translatable treatment option to give psychedelics sub-chronically for relapse prevention. In conclusion, our results in the ADE model do not support the hypothesis that microdosing or high doses of psychedelic reduce relapse behavior. This conclusion has to be confirmed by applying other animal models of AUD. It could also well be that animal models of AUD might be unable to fully capture the therapeutic potential of psychedelic drugs and that only future large-scale clinical trials will be able to demonstrate the efficacy of psychedelics as a new treatment option for AUD.

Neuropsychopharmacology (2020) 45:1316–1322; https://doi.org/10.1038/s41386-020-0694-z
# Study Design

**Study Type**: Interventional (Clinical Trial)

**Estimated Enrollment**: 20 participants

**Allocation**: N/A

**Intervention Model**: Single Group Assignment

**Intervention Model Description**: Open label

**Masking**: None (Open Label)

**Primary Purpose**: Treatment

**Official Title**: Open-Label Proof of Concept Feasibility Study to Explore the Safety, Tolerability and Potential Role of MDMA-Assisted Psychotherapy for the Treatment of Detoxified Patients With Alcohol Use Disorder

**Actual Study Start Date**: April 18, 2018

**Estimated Primary Completion Date**: June 12, 2020

**Estimated Study Completion Date**: June 12, 2020
Cocaine Use Disorder
Psilocybin-facilitated Treatment for Cocaine Use

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.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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</table>
| Cocaine-Related Disorders | Drug: Psilocybin  
Drug: Diphenhydramine | Phase 2 |

Study Design

- **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**: April 2022
- **Estimated Study Completion Date**: April 2022
Methamphetamine Use Disorder
Psilocybin-Enhanced Psychotherapy for Methamphetamine Use Disorder

Brief Summary:
This is a proof-of-concept randomized clinical trial of psilocybin-enhanced psychotherapy versus treatment-as-usual among individuals being treated for methamphetamine use disorder.

<table>
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<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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| Amphetamine-Related Disorders | Drug: Psilocybin  
Behavioral: Treatment-as-usual | Phase 1  
Phase 2 |

Detailed Description:
The trial will take place with individuals admitted to a residential rehabilitation treatment program. The treatment protocol will consist of 4 preparatory therapy visits, 2 psilocybin sessions (25-30mg), and 8 total integration therapy visits. Primary aims assess acceptability, feasibility, and safety with a primary endpoint at the conclusion of the study intervention. An additional aim assesses preliminary efficacy for methamphetamine use disorder and overall functioning at follow-up assessments 60 and 180 days after discharge from the residential treatment program.

Study Design

- **Study Type**: Interventional (Clinical Trial)
- **Estimated Enrollment**: 30 participants
- **Allocation**: Randomized
- **Intervention Model**: Parallel Assignment
- **Masking**: Single (Outcomes Assessor)
- **Masking Description**: Clinical interviewers will be blinded to condition and study timepoint.
- **Primary Purpose**: Treatment
- **Official Title**: Psilocybin-Enhanced Psychotherapy for Methamphetamine Use Disorder
- **Estimated Study Start Date**: January 15, 2022
- **Estimated Primary Completion Date**: December 31, 2023
- **Estimated Study Completion Date**: June 30, 2024
Opioid Use Disorder
Residential Psychedelic (LSD) Therapy for the Narcotic Addict

- 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

Savage et al, 1973
Ibogaine treatment outcomes for opioid dependence from a 12-month follow-up observational study

• 14 patients seeking treatment from ibogaine providers in New Zealand followed for 1 yr

• Significant reduction in SOWS scores post acute treatment

• Abstinence rates post-treatment:
  – 57% at 3 mos
  – 50% at 6 mos
  – 55% at 12 mos (n=11)

Noller et al, 2018
Limitations of ibogaine

• QTc prolongation
• 32 reported deaths from torsade de pointes (TdP)/ventricular arrhythmia
  —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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<td>Recruiting</td>
<td>A Study of Oral <strong>Ibogaine</strong> in <strong>Opioid Withdrawal</strong></td>
<td>• Opiate Withdrawal Syndrome</td>
<td>• Drug: DMX-1002</td>
<td>• MAC Clinical Research Manchester (Early Phase Unit), Neuroscience Centre of Excellence Manchester, Greater Manchester, United Kingdom</td>
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<td>Recruiting</td>
<td>Preliminary Efficacy and Safety of <strong>Ibogaine</strong> in the Treatment of Methadone Detoxification</td>
<td>• Drug Dependence: Drug Use Disorders Opioid Dependence</td>
<td>• Drug: Ibogaine Hydrochloride</td>
<td>• Hospital Universitari Sant Joan Reus, Tarragona, Spain</td>
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<td>3</td>
<td></td>
<td>Not yet recruiting</td>
<td><strong>Ibogaine</strong> in the Treatment of Alcoholism: a Randomized, Double-blind, Placebo-controlled, Escalating-dose, Phase 2 Trial</td>
<td>• Alcoholism</td>
<td>• Drug: Ibogaine Hydrochloride</td>
<td>• Ribeirão Preto Medical School Ribeirão Preto, São Paulo, Brazil</td>
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<td>A Study to Assess <strong>18-Methylocoronaridine (18-MC HCl)</strong> in Healthy Volunteers</td>
<td>• Addiction</td>
<td>• Drug: 18-MC Compound</td>
<td>• Dr. Sam Salman Perth, Australia</td>
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<td>1</td>
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<td>Recruiting</td>
<td>Adjunctive Effects of <strong>Psilocybin</strong> and <strong>Buprenorphine</strong></td>
<td>• Opioid Use Disorder</td>
<td>• Drug: Psilocybin with guided counseling</td>
<td>• University of Wisconsin Madison, Wisconsin, United States</td>
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Tobacco Use Disorder
Pilot Study of Psilocybin in the Treatment of Tobacco Addiction

- Open label
- Psilocybin administered within 15-week smoking cessation program
- Weekly CBT sessions for first 4 weeks
- 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

- Participants
  - 15 participants with nicotine dependence
  - Individuals w/ family or personal history of bipolar disorder, psychotic disorders, and other substance use disorders within past 5 years excluded
  - 2/3 male, average age of 51 years
  - 6 previous quit attempts
Results at 6 months

**Figure 2.** Smoking self-report data. Mean (SEM) of Timeline Follow-back data at intake and 6-month follow-up for the entire study sample, $N=15$ (A), and for participants who tested positive for smoking at 6-month follow-up, $n=3$ (B). 6mo=6-month follow-up. Results shown are for 2-tailed paired t-tests comparing average daily smoking.
Results summary

• 80% participants reported seven-day abstinence at 6 mos
  – 92% had biologically verified abstinence

• 67% participants abstinent at 12 mos

• 60% participants abstinent at 30 mos

Johnson et al, 2014; 2017
Potential treatment mechanism?

- 60% participants met criteria for complete mystical experience
- Cessation correlated with mystical experience measures on session days, as well as ratings of personal meaning and spiritual significance
- Suggests mediating role of mystical experience

Garcia-Romeu et al, 2014
**5-HT2A Agonist Psilocybin in the Treatment of Tobacco Use Disorder**

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<td>Contact PI/Project Leader</td>
<td>JOHNSON, MATTHEW WAYNE</td>
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Questions to consider

• Does the type of therapy matter?
• Can we treat addiction using psychedelics in group settings?
• Can we treat polysubstance use with psychedelics?
• Which patients with addictions are psychedelic treatments inappropriate for?
“Comparing LSD to heroin is like comparing a speck of dust with a mountain. The difference is that heroin helps you to turn from yourself and LSD shows you how to face yourself.”

Savage & McCabe, 1973
Thank you

Contact me at:
Barnetb3@ccf.org
Image sources

- Buprenorphine films: https://highlandscurrent.org/2018/06/15/two-years-of-contraband/
- Psychedelic assisted therapy: https://s3-us-west-1.amazonaws.com/mapscontent/images/training/Charleston+Treatment+Room+Example.png
- Bill Wilson: https://www.guideposts.org/better-living/health-and-wellness/addiction-and-recovery/is-aa-for-alcoholics-only/
- DEA: https://www.dea.gov/sites/default/files/2020-04/Drugs%20of%20Abuse%202020-Web%20Version-508%20compliant-4-24-20_0.pdf
- Meth: https://pittsburgh.cbslocal.com/2020/02/06/meth-ring-busted-in-blair-county/
- Needles: https://magazine.uc.edu/issues/0915/needle-exchange.html
- Cigarettes: https://www.euronews.com/2020/03/15/ireland-bans-menthol-cigarettes-and-rolling-tobacco-starting-may-20
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